Clinical trial results:
A Randomised, Multi-Centre, Assessor-Blinded, Active-Controlled, Parallel Group, Equivalence Phase III Study Comparing the Safety and Efficacy of USV Pegfilgrastim and Neulasta® in Breast Cancer Patients Undergoing Myelosuppressive Chemotherapy

Summary

EudraCT number	2015-000266-64
Trial protocol	HU BG
Global end of trial date	21 February 2017

Results information

Result version number	v1 (current)
This version publication date	08 March 2018
First version publication date	08 March 2018

Trial information

Trial identification

Sponsor protocol code	PEGF/USV/P3/003

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	USV PRIVATE LIMITED
Sponsor organisation address	ARVIND VITHAL GANDHI CHOWK, BSD MARG, GOVANDI, MUMBAI, India, 400088
Public contact	Dr. Esmail Samiwala, USV Private Limited, Arvind Vithal Gandhi Chowk, BSD Marg, Govandi, Mumbai 400088, India, +91 22 25561197, esmail.samiwala@usv.in
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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	21 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 February 2017
Global end of trial reached?	Yes
Global end of trial date	21 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of USV Pegfilgrastim compared to Neulasta® with respect to the mean duration of severe neutropenia (DSN) defined as the mean number of days with Grade 4 neutropenia [absolute neutrophil count (ANC) less than 0.5 × 109/L], during Cycle 1 of the chemotherapy treatment.

Protection of trial subjects:

Before initiating this clinical study, the investigator/institution obtained the written and dated approval/favourable opinion from the appropriately constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the Clinical Study Protocol, Investigational Drug Brochure, written Informed Consent Form, and any other written information provided to subjects.
The study was carried out in compliance with the Clinical Study Protocol and the principles of Good Clinical Practice (GCP), as per standard operating procedures (SOP) and in accordance with the International Council for Harmonisation (ICH) ICH E6 GCP, the EU Clinical Trials Directive 2001/20/EC, the principles of the accepted version of the World Medical Association Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR) and as per all applicable local regulatory guidelines.

Background therapy:

All eligible subjects received a maximum of 6 cycles of TAC chemotherapy (docetaxel 75 mg/m2, doxorubicin 50 mg/m2, cyclophosphamide 500 mg/m2) during the treatment period.

Evidence for comparator:

Selected reference product (comparator) for this study was EU-licensed Neulasta®. Neulasta® is a colourless solution intended for s.c. injection commercially available as prefilled syringes.

Actual start date of recruitment	21 October 2015
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	Romania: 15
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Georgia: 133
Country: Number of subjects enrolled	Serbia: 23
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	Russian Federation: 20
Worldwide total number of subjects	248
EEA total number of subjects	26

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)	216
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Total 254 subjects were enrolled (172 in USV Pegfilgrastim and 82 in Neulasta arm). Subjects were randomised in a ratio of 2:1 to receive either USV Pegfilgrastim or EU-licensed Neulasta® (active control treatment) in a country stratified manner. A total of 6 subjects, discontinued the study before receipt of first dose of IMP.

Pre-assignment

Screening details:

A total of 296 subjects from 31 centres were screened for inclusion into the study of which 42 subjects were classified as screen failures. Forty-two subjects (16.5%) were considered as screen failures.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was assessor blinded trial. The allocated treatment was disclosed only to the unblinded study staff. There were separate blinded and unblinded study teams in each study site. The unblinded team member(s) were responsible for the receipt, accountability, preparation, and administration of the study treatment (pegfilgrastim treatment). The assessor(s) –the prinprincipal investigator and other co-investigators participating in the subject assessments were blinded to the treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	USV PEGFILGRASTIM

Arm description:

The subjects who met eligibility criteria were randomized to one of the two arms. Subjects randomized to USV Pegfilgrastim were to receive USV Pegfilgrastim in all 6 chemotherapy cycles. Out of 248 subjects who received at least one dose of Pegfilgrastim, 166 were in USVPegfilgrastim group, 152 completed treatment period and 147 completed follow up period.

Arm type	Experimental
Investigational medicinal product name	USV Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

USV Pegfilgrastim is a clear colourless sterile solution supplied in a single-dose pre-filled sterile syringe, each containing 6 mg (based on protein content) of pegfilgrastim in 0.6 mL solution for subcutaneous injection. The treatment with USV Pegfilgrastim was administered by the unblinded team member on Day 2 of each chemotherapy cycle (at least 24 hour after administration of chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection per cycle.

Arm title	Neulasta

Arm description:

82 subjects were randomized and received at least one dose of EU-licensed Neulasta®. 78 subjects in this arm completed the treatment period and 77 subjects completed the follow up period. The treatment with Neulasta® (EU-licensed comparator) was administered by the unblinded team member on Day 2 (D2) of each chemotherapy cycle (at least 24h after administration of chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection per cycle.

Arm type	Active comparator

Investigational medicinal product name	EU-licensed Neulasta
Investigational medicinal product code	
Other name	Pegfilgrastim
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

A single dose 6mg/mL pre-filled syringe of EU-licensed Neulasta® was administered for each chemotherapy cycle, as a subcutaneous injection on day 2 of each chemotherapy cycle (at least 24h after chemotherapy).

Number of subjects in period 1	USV PEGFILGRASTIM	Neulasta
Started	166	82
Completed	147	77
Not completed	19	5
Physician decision	1	1
Consent withdrawn by subject	15	4
Adverse event, non-fatal	3	-

Baseline characteristics

Reporting groups	
Reporting group title	USV PEGFILGRASTIM
Reporting group description:	
The subjects who met eligibility criteria were randomized to one of the two arms. Subjects randomized to USV Pegfilgrastim were to receive USV Pegfilgrastim in all 6 chemotherapy cycles. Out of 248 subjects who received at least one dose of Pegfilgrastim, 166 were in USVPegfilgrastim group, 152 completed treatment period and 147 completed follow up period.	
Reporting group title	Neulasta
Reporting group description:	
82 subjects were randomized and received at least one dose of EU-licensed Neulasta®. 78 subjects in this arm completed the treatment period and 77 subjects completed the follow up period. The treatment with Neulasta® (EU-licensed comparator) was administered by the unblinded team member on Day 2 (D2) of each chemotherapy cycle (at least 24h after administration of chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection per cycle.	

Reporting group values	USV PEGFILGRASTIM	Neulasta	Total
Number of subjects	166	82	248
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			
Age in years			
Units: years			
arithmetic mean	52.4	53.4	
standard deviation	± 11.26	± 11.02	-
Gender categorical Units: Subjects			
Female	166	82	248
Male	0	0	0

End points

End points reporting groups

Reporting group title	USV PEGFILGRASTIM

Reporting group description:

The subjects who met eligibility criteria were randomized to one of the two arms. Subjects randomized to USV Pegfilgrastim were to receive USV Pegfilgrastim in all 6 chemotherapy cycles. Out of 248 subjects who received at least one dose of Pegfilgrastim, 166 were in USVPegfilgrastim group, 152 completed treatment period and 147 completed follow up period.

Reporting group title	Neulasta

Reporting group description:

82 subjects were randomized and received at least one dose of EU-licensed Neulasta®. 78 subjects in this arm completed the treatment period and 77 subjects completed the follow up period. The treatment with Neulasta® (EU-licensed comparator) was administered by the unblinded team member on Day 2 (D2) of each chemotherapy cycle (at least 24h after administration of chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection per cycle.

Primary: Mean duration of severe neutropenia (Grade 4), defined as the number of days in which the subject had an ANC < 0.5 × 10^9/L during Cycle 1 of chemotherapy.

End point title	Mean duration of severe neutropenia (Grade 4), defined as the number of days in which the subject had an ANC < 0.5 × 10^9/L during Cycle 1 of chemotherapy.

End point description:

The main efficacy endpoint was defined as the mean number of days of Grade 4 neutropenia (ANC below 0.5 x 10^9/L) during the first treatment cycle. The primary analysis of the duration of severe neutropenia in Cycle 1 consisted in testing equivalence of USV Pegfilgrastim and Neulasta®. The Least-square means (LSMeans) were estimated within a general linear model framework (using proc genmod in SAS), accounting for treatment arm, and applying a log link. LS Mean difference and 95% Confidence Interval (CI) between the two treatment arms was then back-transformed by exponentiation, resulting in a ratio of means and its 95% CI. Equivalence was concluded if the 95% CI of the ratio of means was entirely contained in the interval [0.65, 1.55].

End point type	Primary

End point timeframe:

First Chemotherapy cycle

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: LSM				
least squares mean (standard deviation)	1.58 (± 1.207)	1.65 (± 1.231)		

Statistical analyses

Statistical analysis title	Statistical Analysis of Primary endpoint

Statistical analysis description:

The DSN in Cycle 1 was the primary endpoint for the comparative assessment of efficacy of USV

Pegfilgrastim to Neulasta®. Severe neutropenia was defined as occurrence of ANC below 0.5 x 109/L. Equivalence was concluded if the 95% CI of the ratio of least-square means of DSN for the two treatment arms was entirely contained in the interval [0.65-1.55].

Comparison groups	USV PEGFILGRASTIM v Neulasta
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	LSM Ratio
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.18

Notes:

[1] - Equivalence was concluded if the 95% CI of the ratio of least-square means of DSN for the two treatment arms was entirely contained in the interval [0.65-1.55].

Secondary: Mean duration of severe neutropenia (DSN) during Cycles 2

End point title	Mean duration of severe neutropenia (DSN) during Cycles 2

End point description:

Duration of Severe Neutropenia (Days) in Cycle 2-6 was analyzed. For each cycle, least square Means (95% Cl) of Treatment Arms and their Ratio, Estimated within a Generalized Linear Model Accounting for the Treatment Effect (FAS)

End point type	Secondary

End point timeframe:

Cycle 2

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: LSM of Duration of severe Neutropenia				
least squares mean (confidence interval 95%)	0.96 (0.79 to 1.17)	0.99 (0.76 to 1.29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of severe nuetropenia Cycle 4

End point title	Mean Duration of severe nuetropenia Cycle 4

End point description:

Duration of Severe Neutropenia (Days) in Cycle 4: Least-Square Means (95% Cl) of Treatment Arms and their Ratio, Estimated within a Generalized Linear Model Accounting for the Treatment Effect (FAS)

End point type	Secondary

End point timeframe:

Cycle 4

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Least Square Mean				
least squares mean (confidence interval 95%)	1.03 (0.84 to 1.26)	0.98 (0.73 to 1.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of severe neutropenia Cycle 3

End point title	Mean Duration of severe neutropenia Cycle 3

End point description:

Duration of Severe Neutropenia (Days) in Cycle 3: Least-Square Means (95% CI) of Treatment Arms and their Ratio, Estimated within a Generalized Linear Model Accounting for the Treatment Effect (FAS)

End point type	Secondary

End point timeframe:

Cycle 4

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Least Square Mean				
least squares mean (confidence interval 95%)	0.89 (0.73 to 1.07)	1.01 (0.79 to 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean duration of severe neutropenia Cycle 5

End point title	Mean duration of severe neutropenia Cycle 5

End point description:

Duration of Severe Neutropenia (Days) in Cycle 5: Least-Square Means (95% CI) of Treatment Arms and their Ratio, Estimated within a Generalized Linear Model Accounting for the Treatment Effect (FAS)

End point type	Secondary

End point timeframe:

Cycle 5

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Least square Mean				
least squares mean (confidence interval 95%)	0.92 (0.75 to 1.12)	1.0 (0.76 to 1.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean duration of severe neutropenia cycle 6

End point title	Mean duration of severe neutropenia cycle 6

End point description:

Duration of Severe Neutropenia (Days) in Cycle 6: Least-Square Means (95% CI) of Treatment Arms and their Ratio, Estimated within a Generalized Linear Model Accounting for the Treatment Effect (FAS)

End point type	Secondary

End point timeframe:

Cycle 6

End point values	USV PEGFILGRASTIM	Neulasta		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	82		
Units: Least Square Mean				
least squares mean (confidence interval 95%)	1.12 (0.9 to 1.38)	1.09 (0.81 to 1.47)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were assessed from randomization to end of study period

Adverse event reporting additional description:

Adverse events were reported by the subjects

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	USV PEGFILGRASTIM

Reporting group description:

The subjects who met eligibility criteria were randomized to one of the two arms. Subjects randomized to USV Pegfilgrastim were to receive USV Pegfilgrastim in all 6 chemotherapy cycles. Out of 248 subjects who received at least one dose of Pegfilgrastim, 166 were in USVPegfilgrastim group, 152 completed treatment period and 147 completed follow up period.

Reporting group title	Neulasta

Reporting group description:

82 subjects were randomized and received at least one dose of EU-licensed Neulasta®. 78 subjects in this arm completed the treatment period and 77 subjects completed the follow up period. The treatment with Neulasta® (EU-licensed comparator) was administered by the unblinded team member on Day 2 (D2) of each chemotherapy cycle (at least 24h after administration of chemotherapy) and consisted of a single 6 mg subcutaneous (s.c.) injection per cycle.

Serious adverse events	USV PEGFILGRASTIM	Neulasta	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 166 (5.42%)	3 / 82 (3.66%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastasis to central nervous system	Additional description: Serious Adverse Event during Follow up period		
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral T-cell lymphoma unspecified	Additional description: SAE during follow up period		
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral infarction			
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (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			
Agranulocytosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 166 (3.61%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 82 (1.22%)	
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			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Breast abscess			
subjects affected / exposed	1 / 166 (0.60%)	0 / 82 (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: 5 %

Non-serious adverse events	USV PEGFILGRASTIM	Neulasta	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 166 (98.80%)	82 / 82 (100.00%)	
Nervous system disorders			
Dizziness	Additional description: AE during treatment period		
subjects affected / exposed	36 / 166 (21.69%)	15 / 82 (18.29%)	
occurrences (all)	54	46	
Headache	Additional description: AE during treatment period		
subjects affected / exposed	46 / 166 (27.71%)	18 / 82 (21.95%)	
occurrences (all)	80	25	
Blood and lymphatic system disorders			
Anaemia	Additional description: AEs in Treatment Period)		
subjects affected / exposed	15 / 166 (9.04%)	9 / 82 (10.98%)	
occurrences (all)	47	30	
Febrile neutropenia	Additional description: AEs during treatment period		
subjects affected / exposed	9 / 166 (5.42%)	2 / 82 (2.44%)	
occurrences (all)	9	2	
Leukocytosis	Additional description: AE during treatment period		
subjects affected / exposed	6 / 166 (3.61%)	5 / 82 (6.10%)	
occurrences (all)	34	28	
leukopenia	Additional description: AE during treatment period		
subjects affected / exposed	74 / 166 (44.58%)	36 / 82 (43.90%)	
occurrences (all)	364	184	
Neutropenia	Additional description: AE during treatment period		
subjects affected / exposed	130 / 166 (78.31%)	63 / 82 (76.83%)	
occurrences (all)	788	427	
Thrombocytopenia	Additional description: AE during treatment period		
subjects affected / exposed	25 / 166 (15.06%)	8 / 82 (9.76%)	
occurrences (all)	93	31	
General disorders and administration site conditions			
Asthenia	Additional description: AE during treatment period		
subjects affected / exposed	35 / 166 (21.08%)	18 / 82 (21.95%)	
occurrences (all)	65	30	
Fatigue	Additional description: AE during treatment period		

subjects affected / exposed	21 / 166 (12.65%)	12 / 82 (14.63%)	
occurrences (all)	31	32	
Injection site reaction	Additional description: AE during treatment period		
subjects affected / exposed	16 / 166 (9.64%)	8 / 82 (9.76%)	
occurrences (all)	72	32	
Gastrointestinal disorders			
Abdominal pain	Additional description: AE during treatment period		
subjects affected / exposed	9 / 166 (5.42%)	2 / 82 (2.44%)	
occurrences (all)	11	2	
Abdominal pain upper	Additional description: AE during treatment period		
subjects affected / exposed	12 / 166 (7.23%)	9 / 82 (10.98%)	
occurrences (all)	12	14	
Diarrhoea	Additional description: AE during treatment period		
subjects affected / exposed	33 / 166 (19.88%)	20 / 82 (24.39%)	
occurrences (all)	38	24	
Nausea	Additional description: AE during treatment period		
subjects affected / exposed	79 / 166 (47.59%)	38 / 82 (46.34%)	
occurrences (all)	206	158	
Vomiting	Additional description: AE during treatment period		
subjects affected / exposed	17 / 166 (10.24%)	7 / 82 (8.54%)	
occurrences (all)	21	11	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: AE during treatment period		
subjects affected / exposed	62 / 166 (37.35%)	30 / 82 (36.59%)	
occurrences (all)	69	32	
Musculoskeletal and connective tissue disorders			
Bone pain	Additional description: AE during treatment period		
subjects affected / exposed	54 / 166 (32.53%)	27 / 82 (32.93%)	
occurrences (all)	473	165	
Spinal pain	Additional description: AE during treatment period		
subjects affected / exposed	13 / 166 (7.83%)	8 / 82 (9.76%)	
occurrences (all)	24	40	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported