Sponsor

Sandoz GmbH

Generic Drug Name

Filgrastim

Trial Indication(s)

Neutropenia in breast cancer patients on myelosuppressive chemotherapy

Protocol Number

EP06-302

Protocol Title

A randomized, double-blind, parallel-group, multi-center Phase III study comparing the efficacy and safety of EP2006 and Neupogen® in breast cancer patients treated with myelosuppressive chemotherapy

Clinical Trial Phase

III

Study Start/End Dates

26 Dec 2011 to 17 Jun 2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a randomized, double-blind, parallel-group, multi-center Phase III study.

Centers

25 centers in 6 countries: Russia (10), Ukraine (6), Hungary (6), Latvia (1), Slovakia (1), Czech Republic (1)

Objectives:

Primary objective:

- The primary objective of the study was to assess the efficacy of EP2006 compared to Neupogen® (US-licensed) with respect to the mean duration of severe neutropenia (DSN), defined as the number of consecutive days with grade 4 neutropenia (absolute neutrophil count [ANC] less than 0.5 × 109/L), during Cycle 1 of the neoadjuvant or adjuvant TAC regimen (Taxotere® [docetaxel 75 mg/m2] in combination with Adriamycin® [doxorubicin 50 mg/m2] and Cytoxan® [cyclophosphamide 500 mg/m2]) in breast cancer patients.

Test Product (s), Dose(s), and Mode(s) of Administration

Test: EP2006 solution provided in vials with the strength of 480 mcg in 1.6 mL (concentration: 300 mcg filgrastim per 1.0 mL) was administered by subcutaneous injection with a daily dose of 5 mcg/kg body weight.

Reference: Neupogen® (US-licensed) provided in commercially available vials with the strength of 480 mcg in a nominal fill volume of 1.6 mL (concentration: 300 mcg filgrastim per 1.0 mL) administered by subcutaneous injection with a daily dose of 5 mcg/kg body weight.

Statistical Methods

The following hypotheses were tested at a one-sided significance level of 2.5% (μ denotes the mean DSN under Neupogen® and EP2006, respectively): H 0: μ Neupogen (Groups 3+4) - μ EP2006 (Groups 1+2) ≤ -1 day H 1: μ Neupogen (Groups 3+4) - μ EP2006 (Groups 1+2) > -1 day The primary efficacy endpoint was analyzed using an analysis of co-variance (ANCOVA) with the factors ‘treatment group’ and ‘kind of chemotherapy’ (strata: adjuvant, neoadjuvant) and the covariate ‘baseline ANC’. Groups 1 and 2 and Groups 3 and 4, respectively, were combined to calculate a one-sided 97.5% confidence interval (CI) for the difference in mean DSN

between the two combined treatment groups in Cycle 1. The decision of non-inferiority was based on the lower limit of the two-sided 95% CI (which is equivalent to the lower one-sided 97.5% CI). Non-inferiority of EP2006 was to be concluded if the lower limit of the two-sided 95% CI was larger than -1 day. No test for the assumption of normality was performed. The robustness of the ANCOVA was assumed based on simulation results for 3 to 5 point ordinal outcomes scale (Sullivan and D'Agostino 2003). The DSN was expected to have a similar ordinal outcome scale. The primary analysis of the main efficacy endpoint was based on the PP set which constitutes the most conservative approach for a non-inferiority assessment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Patients with histologically proven breast cancer, eligible for neoadjuvant or adjuvant myelosuppressive chemotherapy.
- Women ≥ 18 years of age.
- Estimated life expectancy of more than six months.

Exclusion criteria:

- Previous or concurrent malignancy except non-invasive non-melanoma skin cancer, in situ carcinoma of the cervix, or other solid tumor treated curatively, and without evidence of recurrence for at least ten years prior to study entry.
- Any serious illness or medical condition that may interfere with safety, compliance, response to the products under investigation and their evaluation.

Participant Flow Table

Primary reason for premature treatment and study discontinuations (all randomized patients)

Primary reason	EP N=54 n (%)	EPNEU N=55 n (%)	NEUEP N=55 n (%)	NEU N=54 n (%)	Total N=218 n (%)
For treatment discontinuation					
Withdrawal by subject	5 (55.6)	3 (50.0)	3 (42.9)	2 (28.6)	13 (44.8)
Lost to follow up	0 (0.0)	0 (0.0)	1 (14.3)	1 (4.3)	2 (6.9)
Death	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Physician decision	1 (11.1)	1 (16.7)	3 (42.9)	0 (0.0)	5 (17.2)
Other	2 (22.2)	2 (33.3)	0 (0.0)	4 (57.1)	8 (27.6)
For withdrawal from study					
Withdrawal by subject	4 (33.3)	3 (42.9)	3 (37.5)	2 (33.3)	12 (36.4)
Lost to follow up	1 (8.3)	1 (14.3)	2 (25.0)	1 (16.7)	5 (15.2)
Death	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)
Other	6 (50.0)	3 (42.9)	3 (37.5)	3 (50.0)	15 (45.5)

Baseline Characteristics

Demographics - total, FAS population (EP, EPNEU, NEUEP, NEU)

	Descriptive statistics / Count (%)				
	EP (N=53)	EPNEU (N=54)	NEUEP (N=55)	NEU (N=52)	Total (N=214)
Age [years]					
Mean	51.5	47.5	49.7	46.9	48.9
Median	53.0	48.5	50.0	46.5	50.0
SD	11.16	11.64	11.05	10.91	11.26
Min	24	26	26	23	23
Max	74	73	71	76	76
n	53	54	55	52	214
Ethnicity					
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.5)
Not Hispanic or Latino	53 (100.0)	54 (100.0)	55 (100.0)	51 (98.1)	213 (99.5)
Race					
White	53 (100.0)	54 (100.0)	55 (100.0)	52 (100.0)	214 (100.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Demographics - total, PP population (EP, EPNEU, NEUEP, NEU)

	Descriptive statistics / Count (%)				
	EP (N=50)	EPNEU (N=51)	NEUEP (N=52)	NEU (N=51)	Total (N=204)
Age [years]					
Mean	51.4	47.8	49.7	46.9	49.0
Median	53.0	50.0	50.0	47.0	50.0
SD	11.28	11.50	11.37	11.02	11.34
Min	24	26	26	23	23
Max	74	73	71	76	76
n	50	51	52	51	204
Ethnicity					
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.5)
Not Hispanic or Latino	50 (100.0)	51 (100.0)	52 (100.0)	50 (98.0)	203 (99.5)
Race					
White	50 (100.0)	51 (100.0)	52 (100.0)	51 (100.0)	204 (100.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Summary of Efficacy

Primary Outcome Result(s)

Primary efficacy variable (DSN) in Cycle 1 (PP set)

		EP+EPNEU (EP2006) N=101	**NEUEP+NEU (Neupogen®) N=103**
DSN in Cycle 1 (days)	n	101	103
	Mean	1.17	1.20
	SD	1.11	1.02
	Range	0-4	0-4
		N (%)	**N (%)**
DSN categories	0-2 days	92 (91.1)	92 (89.3)
	≥ 3 days	9 (8.9)	11 (10.7)

DSN = duration of severe neutropenia Note: Percentages are based on those patients with an available assessment (missing patients are not included) within the respective group.[1] From ANCOVA with factors treatment group and kind of chemotherapy and the covariate baseline absolute neutrophil count

Summary of Safety

Safety Results

TEAEs occurring in 2% of the patients or more – all treatment groups (SAF set)

Primary system organ class Preferred term	EP N=53 number of patients (% of patients) number of events	EPNEU N=54	NEUEP N=55	NEU N=52	Total N=214
Patients with at least one AE	52 (98.1) 618	52 (96.3) 509	52 (94.5) 577	50 (96.2) 623	206 (96.3) 2327
Blood and lymphatic system disorders	12 (22.6) 57	12 (22.2) 59	10 (18.2) 31	14 (26.9) 56	48 (22.4) 203
Anemia	6 (11.3) 10	5 (9.3) 9	4 (7.3) 6	11 (21.2) 24	26 (12.1) 49
Neutropenia	5 (9.4) 21	7 (13.0) 18	6 (10.9) 20	6 (11.5) 22	24 (11.2) 81
Leukopenia	4 (7.5) 21	4 (7.4) 12	2 (3.6) 3	3 (5.8) 9	13 (6.1) 45
Febrile neutropenia	3 (5.7) 3	5 (9.3) 5	1 (1.8) 1	1 (1.9) 1	10 (4.7) 10
Gastrointestinal disorders	35 (66.0) 172	37 (68.5) 140	38 (69.1) 177	38 (73.1) 193	148 (69.2) 682
Nausea	29 (54.7) 103	33 (61.1) 95	32 (58.2) 116	37 (71.2) 149	131 (61.2) 463
Vomiting	9 (17.0) 27	10 (18.5) 22	10 (18.2) 21	9 (17.3) 19	38 (17.8) 89
Diarrhea	5 (9.4) 8	11 (20.4) 14	13 (23.6) 21	8 (15.4) 11	37 (17.3) 54
Abdominal pain	3 (5.7) 8	2 (3.7) 2	4 (7.3) 7	3 (5.8) 6	12 (5.6) 23
Abdominal pain upper	2 (3.8) 3	0 (0.0) 0	5 (9.1) 10	2 (3.8) 2	9 (4.2) 15
Stomatitis	3 (5.7) 3	3 (5.6) 3	0 (0.0) 0	2 (3.8) 4	8 (3.7) 10
Dyspepsia	2 (3.8) 2	1 (1.9) 1	2 (3.6) 2	0 (0.0) 0	5 (2.3) 5
General disorders and administration site conditions	36 (67.9) 154	37 (68.5) 144	42 (76.4) 176	37 (71.2) 151	152 (71.0) 625
Asthenia	20 (37.7) 66	28 (51.9) 98	32 (58.2) 111	28 (53.8) 101	108 (50.5) 376
Fatigue	17 (32.1) 52	9 (16.7) 17	11 (20.0) 38	13 (25.0) 38	50 (23.4) 145
Pyrexia	6 (11.3) 9	3 (5.6) 8	1 (1.8) 1	1 (1.9) 2	11 (5.1) 20
Hyperthermia	2 (3.8) 13	1 (1.9) 6	1 (1.8) 2	1 (1.9) 8	5 (2.3) 29
Hypothermia	0 (0.0) 0	3 (5.6) 6	1 (1.8) 14	1 (1.9) 1	5 (2.3) 21
Edema peripheral	2 (3.8) 2	2 (3.7) 2	1 (1.8) 1	0 (0.0) 0	5 (2.3) 5

Primary system organ class Preferred term	EP N=53 number of patients (% of patients) number of events	EPNEU N=54	NEUEP N=55	NEU N=52	Total N=214
Investigations	4 (7.5) 7	3 (5.6) 5	4 (7.3) 5	6 (11.5) 9	17 (7.9) 26
Alanine aminotransferase increased	2 (3.8) 2	1 (1.9) 1	1 (1.8) 1	1 (1.9) 1	5 (2.3) 5
Gamma-glutamyltransferase increased	2 (3.8) 3	1 (1.9) 1	0 (0.0) 0	2 (3.8) 3	5 (2.3) 7
Metabolism and nutrition disorders	9 (17.0) 22	5 (9.3) 10	5 (9.1) 8	13 (25.0) 33	32 (15.0) 73
Decreased appetite	8 (15.1) 21	4 (7.4) 8	3 (5.5) 6	13 (25.0) 32	28 (13.1) 67
Musculoskeletal and connective tissue disorders	20 (37.7) 55	24 (44.4) 57	27 (49.1) 78	22 (42.3) 71	93 (43.5) 261
Bone pain	13 (24.5) 33	20 (37.0) 46	19 (34.5) 60	19 (36.5) 60	71 (33.2) 199
Arthralgia	3 (5.7) 8	4 (7.4) 4	6 (10.9) 8	3 (5.8) 3	16 (7.5) 23
Myalgia	2 (3.8) 5	3 (5.6) 4	3 (5.5) 5	3 (5.8) 4	11 (5.1) 18
Musculoskeletal pain	5 (9.4) 6	1 (1.9) 2	2 (3.6) 3	1 (1.9) 3	9 (4.2) 14
Nervous system disorders	10 (18.9) 30	8 (14.8) 8	9 (16.4) 11	6 (11.5) 7	33 (15.4) 56
Headache	3 (5.7) 6	3 (5.6) 3	2 (3.6) 2	1 (1.9) 1	9 (4.2) 12
Dizziness	3 (5.7) 8	0 (0.0) 0	3 (5.5) 4	1 (1.9) 1	7 (3.3) 13
Neuropathy peripheral	2 (3.8) 2	2 (3.7) 2	1 (1.8) 1	2 (3.8) 2	7 (3.3) 7
Peripheral sensory neuropathy	3 (5.7) 3	0 (0.0) 0	2 (3.6) 2	1 (1.9) 1	6 (2.8) 6
Toxic neuropathy	1 (1.9) 1	0 (0.0) 0	2 (3.6) 2	2 (3.8) 2	5 (2.3) 5
Skin and subcutaneous tissue disorders	41 (77.4) 62	44 (81.5) 48	43 (78.2) 69	43 (82.7) 75	171 (79.9) 254
Alopecia	41 (77.4) 43	44 (81.5) 45	43 (78.2) 46	43 (82.7) 44	171 (79.9) 178
Erythema	5 (9.4) 15	2 (3.7) 3	6 (10.9) 19	6 (11.5) 23	19 (8.9) 60
Vascular disorders	4 (7.5) 12	6 (11.1) 16	4 (7.3) 4	4 (7.7) 11	18 (8.4) 43
Flushing	1 (1.9) 3	3 (5.6) 10	0 (0.0) 0	2 (3.8) 7	6 (2.8) 20
Hot flush	2 (3.8) 3	1 (1.9) 1	1 (1.8) 1	1 (1.9) 1	5 (2.3) 6

Serious Adverse Events by System Organ Class

SAEs – all treatment groups (SAF set)

Primary system organ class Preferred term	EP N=53 number of patients (% of patients)	EPNEU N=54 number of events	NEUEP N=55	NEU N=52
Number of patients with any event	5 (9.4)	6	4 (7.4)	4	1 (1.8)	1	2 (3.8)	3
Blood and lymphatic system disorders	3 (5.7)	4	4 (7.4)	4	1 (1.8)	1	2 (3.8)	2
Febrile neutropenia*	3 (5.7)	3	4 (7.4)	4	1 (1.8)	1	1 (1.9)	1
Anemia	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.9)	1
Leukopenia	1 (1.9)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Gastrointestinal disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.9)	1
Diarrhea	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.9)	1
Vascular disorders	2 (3.8)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Embolism	1 (1.9)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hypertensive crisis	1 (1.9)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

*There was one further FN, which however was not reported as SAE.

One death due to thromboembolism of the pulmonary artery (coded as Preferred Term: embolism) was reported.

Other Relevant Findings

Not Applicable

Date of Clinical Trial Report

19 Dec 2013