XM02, the First Biosimilar G-CSF, is Safe and Effective in Reducing the Duration of Severe Neutropenia and Incidence of Febrile Neutropenia in Patients with Small Cell or Non-small Cell Lung Cancer Receiving Platinum-Based Chemotherapy

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Background: Recombinant granulocyte colony-stimulating factors such as Neupogen are used to treat chemotherapy-induced neutropenia. The aim of the study was to show that a new granulocyte colony-stimulating factor, XM02, is as safe and effective as Neupogen in the treatment of chemotherapy-induced neutropenia in patients with small cell or non-small cell lung cancer.

Patients and methods: A total of 240 patients receiving platinum-based chemotherapy were randomized in cycle 1 to treatment with daily injections (subcutaneous 5 μg/kg/d) of XM02 ($n = 160$) or Filgrastim Neupogen ($n = 80$) for at least 5 days and a maximum of 14 days. In subsequent cycles, all patients received XM02.

Results: The mean duration of severe neutropenia was 0.5 and 0.3 days in cycle 1 for XM02 and Filgrastim, respectively. In the analysis of covariance for duration of severe neutropenia in cycle 1, the estimated treatment difference "XM02 minus Filgrastim" was 0.157 days, with 95% confidence level (−0.114 days, 0.428 days), which was included in the prespecified equivalence range (−1, 1). There was no statistically significant difference of the end point incidence of febrile neutropenia in cycle 1 between XM02 and Filgrastim ($p = 0.2347$). The adverse event profile was similar between XM02 and Filgrastim.

Conclusion: XM02 demonstrated similar efficacy and safety profile as the reference medication Filgrastim in cycle 1. In conclusion, treatment with XM02 is beneficial in ameliorating severe neutropenia and febrile neutropenia in lung cancer patients receiving myelosuppressive chemotherapy. XM02 is safe and well tolerated in the doses applied in this study.

Key Words: Lung cancer, Chemotherapy, G-CSF, Neutropenia, XM02.

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Cancer chemotherapy frequently leads to neutropenia, which affects more than one in three patients receiving chemotherapy for cancer. Patients with severe neutropenia (absolute neutrophil count (ANC) $<0.5 \times 10^9$/L) are at high risk to develop potentially life-threatening infections. Recombinant granulocyte colony-stimulating factors (G-CSFs) are effective pharmaceutical substances and are successfully applied to treat chemotherapy-induced neutropenia.[1]

Natural human G-CSF is a glycoprotein composed of a single polypeptide chain of 174 or 177 amino acids.[2,3] The bacterially synthesized nonglycosylated recombinant methionyl form of human G-CSF (r-metHuG-CSF) has been approved under the generic name Filgrastim and is marketed under the trade name Neupogen (Amgen Inc., Thousand Oaks, CA).

BioGeneriX AG has clinically developed XM02, a nonglycosylated r-metHuG-CSF expressed in *Escherichia coli* for intravenous (i.v.) and subcutaneous (s.c.) administration in the treatment of chemotherapy-induced neutropenia as biosimilar to the reference Filgrastim Neupogen. The manufacturing process was developed by Sicor Biotech.

The primary aim of the study was to show efficacy and safety of XM02 compared with Filgrastim in the treatment of chemotherapy-induced neutropenia in patients with lung cancer.

PATIENTS AND METHODS

Patients

Between December 2004 and December 2005, patients with lung cancer requiring chemotherapy participated at 47 centers in 11 countries. The study was approved by local institutional review boards and ethics committees. Male and female patients ≥18 years of age with small cell or non-small cell lung cancer were eligible to participate if they signed and dated written informed consent, were planned/eligible to

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receive a platinum-based myelosuppressive chemotherapy, were chemotherapy-naive or had received no more than one previous chemotherapy regimen, had Eastern Cooperative Oncology Group performance status ≤2, an ANC $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and adequate hepatic, cardiac, and renal function for the chosen chemotherapy-regimen.

METHODS

This was a multinational, multicenter, randomized, controlled phase-III study. A total of 240 patients were randomized to treatment with either XM02 ($n = 160$) or Filgrastim ($n = 80$) in the first chemotherapy cycle. In the subsequent cycles, all patients received XM02. The patients underwent a maximum of 6 chemotherapy cycles (3 or 4 weeks per cycle, depending on the chemotherapy protocol), each cycle beginning with a chemotherapy infusion on Day 1. In each cycle, 24 hours after the last chemotherapy infusion, the patients received daily s.c. injections of 5 μg/kg/d (based on actual body weight) XM02 or Filgrastim (Filgrastim in the first cycle only) for at least 5 days and a maximum of 14 days according to the Summary of Product Characteristics of Neupogen.[4] If a chemotherapy protocol required chemotherapy infusions during the cycle, simultaneous administration of study drug on these days was at the discretion of the investigator. Study drug had to be stopped when an ANC of $\geq 10 \times 10^9$/L after nadir was reached. Blood samples for the determination of the ANC were taken within 24 hours before chemotherapy and then daily starting on Day 2 (in cycles 2–6 starting on Day 5) until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9$/L. Body temperature (axillary) was measured with a standardized device daily until Day 15, or longer until ANC reached $\geq 2.0 \times 10^9$/L.

Endpoints and Definitions

Efficacy endpoints included the duration of severe neutropenia (DSN) in cycles 1 and 4, defined as the number of days with grade 4 neutropenia with an ANC $< 0.5 \times 10^9$/L, the incidence of observed febrile neutropenia (FN) (observed FN defined as body temperature of >38.5°C for more than 1 hour and ANC $< 0.5 \times 10^9$/L, both measured on the same day) and of protocol defined FN (intake of systemic antibiotics) by cycle and across all cycles, the depth of ANC nadir in cycles 1 and 4, and the time to ANC recovery in cycles 1 and 4. Safety assessment was based on adverse events (AEs), laboratory parameters, physical examinations, and vital signs.

Statistical Methods

All safety analyses were summarized using descriptive statistics. In addition, the incidence of AEs was compared for XM02 versus Filgrastim using Fisher exact test (two-sided *p*-values). The Wilcoxon test was used to compare changes of safety laboratory parameters from baseline between the two active groups.

Analysis of covariance was applied for DSN, ANC nadir, and time to ANC recovery. All analyses of efficacy endpoints were done without alpha-adjustment and were interpreted as descriptive/exploratory analyses. Incidences of FN were compared between XM02 and Filgrastim by means of the Cochran-Mantel-Haenszel test.

The primary objective of the study was to demonstrate safety of XM02 in patients with lung cancer. The sample size of 240 patients appeared to be sufficient to meet this objective and was not determined by means of statistical sample size calculations. Nevertheless, with 240 patients the probability of observing at least one case of a specific AE, which has a true incidence rate of 0.5% was approximately 70%, and it was approximately 91% if the true incidence rate is 1%.

RESULTS

Of the 240 randomized patients, 219 patients (91.3%) completed cycle 1 and 115 patients (47.9%) prematurely terminated the study, 41 (17.1%) because of progression of underlying disease, 21 (8.8%) withdrew consent, 20 (8.3%) due to AEs, 12 (5.0%) because of death, and 6 (2.5%) due to noncompliance; 15 patients (6.3%) prematurely terminated the study due to other reasons. Overall, the patients were exposed to study drug for a median of 49.0 days (range, 2.0–84.0 days). Median duration within the cycles was 10.0 to 11.5 days (range, 2–15 days). The majority of patients (48.8%) received a chemotherapy combination of cisplatin + etoposide. Other frequently applied chemotherapy combinations were cisplatin + gemcitabine (15.3%), carboplatin + vinorelbine (8.3%), carboplatin + etoposide (7.4%), carboplatin + gemcitabine (6.2%), carboplatin + paclitaxel (6.2%), and cisplatin + vinorelbine (5.4%). The treatment groups were similar with regard to disposition, and study drug and chemotherapy exposure. Demographic, baseline, and disease characteristics are summarized in Table 1.

Efficacy

Results are summarized in Table 2 for the full analysis set.

Duration of Severe Neutropenia

In the full analysis set, mean DSN was 0.5 and 0.3 days in cycle 1 for XM02 and Filgrastim, respectively, and 0.4 and 0.3 days in cycle 4 after the switch from Filgrastim to XM02 in the reference group. In the analysis of covariance for DSN in cycle 1, the estimated treatment difference "XM02 minus Filgrastim" was 0.157 days, with 95% confidence interval (−0.114 days, 0.428 days), which was included in the prespecified equivalence range (−1, 1).

Febrile Neutropenia

In cycle 1, incidences of observed or protocol defined FN were 15.0% for XM02 and 8.8% for Filgrastim ($p = 0.2347$), and in cycle 4, after switch from Filgrastim to XM02 in the reference group, incidences were 4.3% and 3.3% ($p = 0.9036$), respectively. Across all cycles, the incidence of observed or protocol defined FN was 33.1% and 23.8% in the XM02 and Filgrastim/XM02 groups, respectively.

Absolute Neutrophil Count

In cycle 1 in both treatment groups, mean ANC values increased after Day 2, reaching a maximum on Day 5 and then decreased to a nadir on Day 11 (Day 12 for Filgrastim group). Thereafter, mean values increased again, reaching a maximum on Day 14. On Day 21, mean values approached those observed on Day 1 in both treatment groups. The ANC

TABLE 1. Patient Characteristics—Safety Set

	XM02 (n = 158)	Neupogen[a] (n = 79)
Gender (N [%])		
Male	127 (80.4%)	61 (77.2%)
Female	31 (19.6%)	18 (22.8%)
Age (yr)		
Mean	58.8	58.1
SD	8.8	10.1
Median	58.5	59.0
Range	34–78	34–78
Race (N [%])		
Caucasian	149 (94.3%)	76 (96.2%)
Hispanic	8 (5.1%)	3 (3.8%)
Other	1 (0.6%)	0 (0.0%)
Body mass index (kg/m²)		
Mean	23.99	24.41
SD	4.22	4.17
Median	23.50	24.20
Range	16.0–39.6	16.4–36.4
Cancer type (N [%])		
Small cell	26 (16.5%)	13 (16.5%)
Non-small cell	132 (83.5%)	66 (83.5%)
Cancer stage (N [%])		
Limited (small cell)	6 (3.8%)	2 (2.5%)
Extensive (small cell)	20 (12.7%)	11 (13.9%)
Stage 3 (non small cell)	54 (34.2%)	22 (27.8%)
Stage 4 (non small cell)	78 (49.4%)	44 (55.7%)
Prior therapy (N [%])		
Chemotherapy (yes)	21 (13.3%)	12 (15.2%)
Radiation therapy (yes)	20 (12.7%)	7 (8.9%)
ECOG before cycle 1 (N [%])		
Status 0	29 (18.4%)	19 (24.1%)
Status 1	100 (63.3%)	43 (54.4%)
Status 2	29 (18.4%)	17 (21.5%)

Body mass index calculated as body weight/(height)².
[a] Patients in this group received Neupogen in cycle 1 and XM02 afterward.
ECOG, Eastern Cooperative Oncology Group.

TABLE 2. Results of Efficacy Endpoints

Treatment Group Full Analysis Set (n)	XM02 (n = 160)	Neupogen[a] (n = 80)
Mean DSN (days)		
Cycle 1	0.5	0.3
Cycle 4	0.4	0.3
Mean ANC nadir (10^9/L)		
Cycle 1	2.1	2.9
Cycle 4	2.3	3.2
Mean time to ANC recovery (days)		
Cycle 1	6.3	4.5
Cycle 4	6.4	4.5
Incidence of FN (%)[b]		
Cycle 1	15.0	8.8
Across all cycles	33.1	23.8

[a] Patients in this group received Neupogen in cycle 1 and XM02 afterward (including in cycle 4).
[b] Observed or protocol defined FN.
DSN, duration of severe neutropenia; ANC, absolute neutrophil count; FN, febrile neutropenia.

profile was similar in cycles 2 to 6. The ANC profile of patients receiving chemotherapy of myelotoxic potency category "platinum/etoposide" (mean DSN under this treatment regimen was 0.5 days) is shown in Figure 1.

In cycle 1, mean ANC nadir values were 2.1×10^9/L in the XM02 group and 2.9×10^9/L in the Filgrastim group. In cycle 4, after switch from Filgrastim to XM02 in the reference group, mean ANC nadir values were 2.3×10^9/L and 3.2×10^9/L in the XM02 and Filgrastim/XM02 groups, respectively.

In cycle 1, mean time to ANC recovery was 6.3 days in the XM02 group and 4.5 days in the Filgrastim group. In cycle 4, after switch from Filgrastim to XM02 in the reference group, mean time to ANC recovery was 6.4 days and 4.5 days in the XM02 and Filgrastim/XM02 groups, respectively.

Adverse Events

In the course of the study, 223 patients (94.1%) experienced a total of 2215 treatment emergent AEs (TEAEs). Of these, 203 were considered as severe in 95 patients (40.1%). There were 112 serious AEs (SAEs) in 72 patients (30.4%), and 31 patients (13.1%) discontinued the study due to a TEAE. There were 22 patients with TEAEs with outcome death (9.3%) during the study observation period, i.e., until 30 days after end of study. All deaths were considered not to be related to the study drug. One patient died on Day 17 in cycle 1 from an afebrile sepsis, 13 days after start of treatment with XM02. The patient had received a 3-day chemotherapy regimen with cisplatin and etoposide. The patient developed severe neutropenia on Day 10 with a nadir ANC value of 0.2×10^9/L on Day 11. On Day 15, 1 day before the patient developed first symptoms (disorientation and weakness), the patient's ANC was 13.5×10^9/L, and the last measured value on Day 17 was 32.3×10^9/L. The patient had no clinical signs of sepsis, in particular no fever.

Overall, commonly reported TEAEs were nausea (in 49.8% of patients), anemia (38.8%), and vomiting (35.9%). Most often reported drug-related AEs were anemia (2.1%), myalgia (2.1%), back pain (2.1%), and headache (2.1%). In general, drug-related AEs occurred early in the study, i.e., they were reported within 20 days after study start, or within 6 days after start of a cycle. Possibly drug-related AEs in cycle 1 are displayed in Table 3. The AE profile was similar between the XM02 and Filgrastim/XM02 groups.

No distinct changes were observed in the course of the study for laboratory parameters, physical examination findings, or vital signs, and there were no clinically relevant differences between the treatment groups with regard to these variables.

DISCUSSION

The primary aim of this study was to demonstrate safety and efficacy of XM02 when administered for up to a maximum of six chemotherapy cycles in patients with lung cancer. A total of 237 patients in a heterogeneous patient

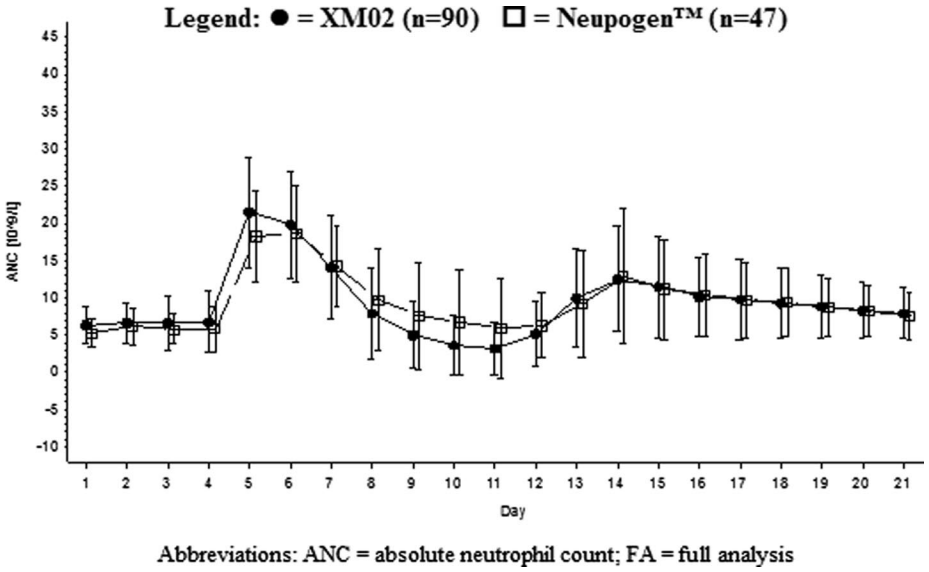

FIGURE 1. Mean (±SD) of absolute neutrophil counts in cycle 1. Full analysis (FA) set—patients receiving chemotherapy of myelotoxic potency category etoposide.

TABLE 3. Possibly Drug Related Adverse Events Cycle 1

Treatment Group	XM02 (n = 158)			Filgrastim (n = 79)		
Safety Set (n)						
System Organ Class Preferred Term	*N*	%	*E*	*N*	%	*E*
Musculoskeletal and connective tissue disorders	7	4.4	7	3	3.8	3
Back pain	2	1.3	2	2	2.5	2
Myalgia	2	1.3	2	1	1.3	1
Bone pain	2	1.3	2	0	0.0	0
Musculoskeletal pain	1	0.6	1	0	0.0	0
General disorders and administration site conditions	5	3.2	7	3	3.8	4
Pyrexia	3	1.9	3	1	1.3	2
Fatigue	1	0.6	1	1	1.3	1
Asthenia	1	0.6	2	0	0.0	0
Chest pain	1	0.6	1	0	0.0	0
Injection site pain	0	0.0	0	1	1.3	1
Gastrointestinal disorders	4	2.5	4	0	0.0	0
Abdominal pain	1	0.6	1	0	0.0	0
Gastrointestinal disorder	1	0.6	1	0	0.0	0
Nausea	1	0.6	1	0	0.0	0
Vomiting	1	0.6	1	0	0.0	0
Nervous system disorders	3	1.9	3	1	1.3	1
Headache	3	1.9	3	1	1.3	1
Skin and subcutaneous tissue disorders	1	0.6	1	2	2.5	3
Rash	0	0.0	0	1	1.3	2
Eczema	1	0.6	1	0	0.0	0
Rash pruritic	0	0.0	0	1	1.3	1
Investigations	2	1.3	2	1	1.3	1
Body temperature increased	1	0.6	1	1	1.3	1
Aspartate aminotransferase increased	1	0.6	1	0	0.0	0
Blood and lymphatic system disorders	2	1.3	2	0	0.0	0
Thrombocythaemia	1	0.6	1	0	0.0	0
Thrombocytopenia	1	0.6	1	0	0.0	0
Metabolism and nutrition disorders	1	0.6	1	0	0.0	0
Hyponatraemia	1	0.6	1	0	0.0	0
Vascular disorders	1	0.6	1	0	0.0	0
Thrombophlebitis	1	0.6	1	0	0.0	0

N = number of patients exposed to study drug or number of patients affected by TEAEs.
% = 100 × (*N* affected/*N* exposed).
E = number of events for the *N* patients. Adverse events were coded using MedDRA 7.1.

population were exposed to XM02 in the course of the study. XM02 demonstrated similar efficacy and safety profile as the reference medication Filgrastim.

The most often reported drug-related TEAEs in this study were myalgia, back pain, anemia, and headache. Bone and muscle pain are known adverse drug reactions to G-CSFs, however, occurring with a higher incidence than seen in this study.

Of the observed deaths, none were related to study drug but primarily to progression/refractoriness of underlying disease and—to a smaller extent—to AEs of applied chemotherapy. These data reflect the clinical course of patients with advanced non-small cell lung cancer and an overall rather dismal prognosis. The overall mortality observed (9.3%) in this study was in the expected range.[5,6] One patient died of an afebrile sepsis, no other patients died of FN or infections.

The incidence of observed or protocol defined FN in cycle 1 was 15.0% and 8.8% in the XM02 and Filgrastim groups, respectively. In a study conducted by Timmer-Bonte et al.,[7] the incidence of FN in cycle 1 of lung cancer chemotherapy was 10% in patients treated with antibiotics + G-CSF.

In a study in 348 breast cancer patients published by del Giglio et al.[8] comparing XM02 and Filgrastim versus placebo in cycle 1 in a homogenous population receiving docetaxel 75 mg/m^2/doxorubicin 60 mg/m^2 chemotherapy equivalence of XM02 versus Filgrastim and superiority versus placebo was clearly demonstrated with a DSN in cycle 1 of 1.1, 1.1, and 3.8 days in the XM02, Filgrastim, and placebo group, respectively. In the same study, the incidence of FN in cycle 1 was 12.1, 12.5, and 38.1% under XM02, Filgrastim, and placebo, respectively. Another study in the same development program was conducted by Engert et al.[9] in 92 non-Hodgkin-lymphoma patients comparing XM02 and Filgrastim in the first cycle of cyclophosphamide-hydroxydaunomycin-oncovin-prednisolon or rituximab cyclophosphamide-hydroxydaunomycin-oncovin-prednisolon chemotherapy. In this study, there was a trend to better efficacy results in the XM02 group compared

with the Filgrastim group with a DSN of 0.5 days (XM02) and 0.9 days (Filgrastim) and an incidence of FN of 11.1% (XM02) and 20.7% (Filgrastim) in cycle 1.

These inconsistent results on the incidence of FN in the three studies in breast cancer, lung cancer, and non-Hodgkin-lymphoma representing the complete XM02 development program in cancer patients will be further investigated in a meta-analysis on the incidence of FN in cycle 1 (manuscript in preparation).

For patients receiving XM02 or Filgrastim, the ANC values distinctly increased after start of treatment, reaching a maximum on Day 5, and then decreased to a nadir around Day 11. Thereafter, ANC values increased again, reaching a maximum on Day 14. On Day 21, mean values returned to values as observed on Day 1. Holmes et al.[1] reported the same biphasic ANC profile under treatment with Filgrastim.

The benefit of the biosimilar G-CSF XM02 may be improved cost-effectiveness associated with a similar safety and efficacy profile compared with the reference product.

In conclusion, treatment with XM02 is beneficial in ameliorating severe neutropenia and FN in lung cancer patients receiving myelosuppressive chemotherapy. XM02 is safe and well tolerated in the doses applied in this study.

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