Synopsis XM22-04

Name of Sponsor/Company: now owned by Teva	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: XM22 Drug Product	Volume:	
Name of Active Ingredient: glycol-PEGylated-r-metHuG-CSF (INN; Code: XM22)	Page:	
Title of Study: Efficacy and safety of XM22 in patients with non-small cell lung cancer receiving cisplatin/etoposide chemotherapy (multinational, multicenter, randomized, double-blind placebo-controlled study)		
Co-ordinating Investigator: Prof. Igor Mykolayovych Bondarenko Dnipropetrovsk City Multispecialty Clinical Hospital #4, Department of Chemotherapy, Dnipropetrovsk State Medical Academy, Department of Oncology and Medical Radiology, 31 Blyzhnia St., Dnipropetrovsk, 49102, Ukraine. **Investigators:** Please refer to list of investigators (refer to: *Appendix 16.1.4*).		
Study centres: 427 patients were screened at 72 centres in 8 European countries. Patients were randomised in 68 centres (Belarus, Bosnia-Herzegovina, Bulgaria, Poland, Romania, Russia, Serbia, Ukraine).		
Publication (reference): Not applicable		
Studied Period:	Date of first patient enrolled: 10 May 2010 Date of last patient completed:05 April 2011	
Phase of development:	III	
Objectives: **Primary:** The primary objective of this study was demonstration of superiority of XM22 vs. placebo when administered for up to a maximum of four cycles in patients with non-small cell lung cancer receiving cisplatin/etoposide chemotherapy (CTX). The primary endpoint was the incidence of febrile neutropenia (FN) in the first cycle. The secondary objectives of this study were evaluation of efficacy, safety and tolerability of XM22 in comparison to placebo in patients with non-small cell lung cancer receiving cisplatin/etoposide CTX based on the secondary efficacy and safety endpoints and evaluation of pharmacokinetic properties of XM22 in comparison to placebo.		

Methodology: This was a multinational, multicentre, randomised, double-blind, placebo-controlled phase III study. The study was planned for 375 patients with non-small cell lung cancer receiving intravenous (i.v.) cisplatin/etoposide CTX to participate. Patients were to be randomised to treatment with either 6 mg XM22 (n=250) or placebo (n=125). The patients were to undergo a maximum of 4 CTX cycles (21 days per cycle), each cycle beginning with CTX of cisplatin 80 mg/m² i.v. on day 1 and etoposide 120 mg/m² i.v. daily on days 1 to 3. On day 4 in each cycle (i.e. 1 day after the respective last CTX infusion day), patients received a single subcutaneous (s.c.) injection of XM22 or placebo.
Number of patients (planned and analysed): It was planned to randomise 375 patients, 250 to 6 mg XM22 and 125 to placebo. 373 of the 376 patients randomised were treated with randomised study medication: 125 with placebo and 248 with 6 mg XM22. Three of the 376 randomised patients did not receive randomised study medication. Two of the 3 patients died after randomisation before randomised study medication could be administered; the third patient was randomised by mistake (baseline absolute neutrophil count [ANC] $<1.5 \times 10^9$/L) and was not included in the analysis populations.
Diagnosis and main criteria for inclusion: Female or male patients were to have NSCLC stage IIIb/IV receiving cisplatin/etoposide-based, myelosuppressive CTX. Patients were to be CTX-naïve with ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. ECOG performance status was to be ≤2 and cardiac, hepatic and renal function was to be adequate. Individuals with high risk for FN with regard to the cisplatin/etoposide CTX according to the assessment of the investigator were excluded. Risk factors were age >65 years, low performance status, poor nutritional status and liver, renal or cardiovascular disease.
Test product, dose and mode of administration, batch number: XM22 was supplied in pre-filled syringes containing 0.6 mL for s.c. injection. Patients were to receive a single dose of 6 mg as a subcutaneous injection once per CTX treatment cycle. Batch numbers XM22: XM22-04/01, XM22-04/03, XM22-03/02, XM22-03/05, XM22-04/02, XM22-04/04
Duration of treatment: Patients were treated for 12 weeks. Thereafter the patients were observed for adverse events for 30 days after the last administration of study medication.
Reference therapy, dose and mode of administration, batch number: Placebo was supplied in 0.6 mL pre-filled syringes for s.c. injection. Patients were to receive a single dose of placebo as a subcutaneous injection once per CTX treatment cycle. Batch numbers placebo: XM22-04/01, XM22-04/03, XM22-04/02, XM22-04/04.

Criteria for evaluation:

Primary endpoint for efficacy: The primary efficacy endpoint was the incidence of FN in the first CTX cycle.

Secondary endpoints for efficacy:

- Incidence of febrile neutropenia (FN) in cycles 2, 3, and 4 and across all cycles.
- Duration of severe neutropenia (DSN). Severe neutropenia was defined as grade 4 neutropenia with an ANC $<0.5 \times 10^9$/L.
- Incidence of severe neutropenia, defined as grade 4 (ANC $<0.5 \times 10^9$/L). The incidence of severe neutropenia is equivalent to the frequency of ANC nadir $<0.5 \times 10^9$/L.
- Duration of very severe neutropenia (DVSN) (ANC $<0.1 \times 10^9$/L), measured in days.
- Incidence of very severe neutropenia (ANC $<0.1 \times 10^9$/L). The incidence of very severe neutropenia is the same as the frequency of ANC nadir $<0.1 \times 10^9$/L.
- Depth of ANC nadir. The patient's lowest ANC in each cycle was to be determined.
- Time to ANC nadir, defined as the time in days from CTX administration until the occurrence of the ANC nadir.
- Time to ANC recovery, defined as the time in days from CTX administration until the patient's ANC increased to $\geq 2.0 \times 10^9$/L after the expected nadir.
- Time to ANC recovery from ANC nadir, defined as difference in days between the day of the occurrence of ANC nadir to the first day after ANC nadir with an ANC value $\geq 1.5 \times 10^9$/L.
- Time in days in hospital and time in the Intensive Care Unit due to FN or connected infections.
- Incidence of treatment with i.v. antibiotics due to FN or connected infections, defined as the number of patients receiving i.v. antibiotics per cycle and across all cycles.
- Percentage of actually delivered vs. scheduled cumulative CTX dose (for both cisplatin and etoposide) per patient.
- Proportion of patients with CTX doses reduced, omitted, or delayed
- Number of days of delay of CTX
- Overall quality of life, as assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3) and the EORTC QLQ-LC13.

- Incidence of patients requiring prophylactic open treatment.

Safety

- Incidence of adverse events (AEs).
- AEs of special interest
- Changes in safety laboratory parameters.
- Changes in vital signs, physical examination and body weight.
- Electrocardiogram (ECG) (sub-study)
- Assessment of injection site reactions.
- Immunogenicity (development of antibodies against study drug).
- Mortality
- Frequency of culture-confirmed infections.
- Frequency of neutropenic fever.
- Number of transfusions and/or use of erythropoietin or erythropoietin releasing agents.

Other

- Pharmacokinetics in a subset of patients.
- CD34+ cell mobilisation in a subset of patients.

Statistical methods: All efficacy analyses were performed with the data of the Intent-to-treat (ITT) population, i.e. all patients who were randomised to one of the treatment groups and the According-to-protocol (ATP) population, which consisted of all patients from the ITT population without a major protocol violation. The primary population for the analysis of efficacy in superiority trial was the ITT population. The robustness of the results in the ITT population were supported by the ATP population.

The primary objective was the demonstration of superiority of XM22 vs. placebo in patients with non small cell lung cancer.

The primary efficacy endpoint was defined as the incidence of FN in CTX cycle 1.

For the analysis of the primary efficacy endpoint, a logistic regression analysis was fitted including randomised treatment, region (Rest of Europe, Russia, Ukraine) sex and body weight class (≤60, >60 to ≤75 and >75 [kg]) as fixed factors and with the last ANC value measured prior to CTX treatment (baseline ANC) as covariate. The model should allowed for possible overdispersion.

No adjustment for type I error was applied to the secondary efficacy endpoints, so all secondary analyses should be interpreted in an exploratory manner. Where applicable, for secondary efficacy endpoints for which regression analyses were planned in the study protocol, statistical models with the same explanatory variables as in the analysis of the main endpoint

were estimated.

Demographic and baseline characteristics, AEs and other safety endpoints were presented as descriptive statistics (continuous variables) or frequency tables (categorical variables).

Summary – Conclusions

The demographic and baseline characteristics were comparable across both treatment groups. Mean (± standard deviation [SD]) age was comparable in both groups (58.7 (± 8.5) years for placebo vs. 58.2 (± 8.5) years for XM22). Only a small but comparable proportion of the patients in each treatment group were women (16.0% placebo, 12.0% XM22).

Efficacy Results:

Primary Endpoint

The primary objective of this study was the demonstration of superiority of XM22 versus placebo when administered for up to a maximum of four cycles in patients with non-small cell lung cancer receiving cisplatin/etoposide CTX. The primary endpoint was the incidence of febrile neutropenia in the first cycle.

The incidence of FN in cycle 1 was lower in the XM22 group (2.4%) compared to the placebo group (5.6%), with an odds ratio of 0.39 (95% CI: 0.121, 1.260) (ITT population). Although the incidence of FN in the XM22 group was less than half that in the placebo group, the difference was not statistically significant, with p=0.1151. The study therefore failed to meet its primary efficacy endpoint.

The statistical methodology used for the primary analysis ensured that the power of the statistical analysis would be about 90% if the placebo excess risk for FN was in the range of 6% to 9% (actual incidence therefore 7% to 10%) and the actual incidence rate for XM22 was at most 1%. The actual incidence of FN in this study were lower than anticipated for placebo based on the results of published lung cancer studies using the same CTX combination with the same or similar cisplatin and etoposide dosages. The lower than expected incidence of FN under placebo treatment is probably due to the exclusion of patients with a high risk of FN from this study and a less strict definition of FN in the published studies than the one used in this study. This study was not powered to demonstrate a significant difference for the observed incidences of FN.

Secondary Endpoints

All p-values reported for the comparison of treatment groups concerning the secondary efficacy endpoints are raw and unadjusted p-values of explorative tests on differences between treatments.

The incidence of FN was lower in the XM22 group in cycles 3 and 4; the higher incidence in cycle 2 was due to FN in a single patient.

The DSN in cycle 1 is a commonly used primary endpoint in studies with granulocyte colony-stimulating factors (G-CSFs). The DSN in cycle 1 was shorter in the XM22 group (mean±SD:

0.6±1.1 days) than in the placebo group (2.3±2.5 days). Poisson regression analysis (XM22 - placebo) yielded a 95% CI of -2.089 to -1.232 with p<0.0001, indicating considerable shortening of DSN in the XM22 group. In addition, in cycle 1 the majority (67.9%) of XM22-treated did not experience severe neutropenia, whereas only 40.8% of placebo-treated patients were free of severe neutropenia.

The DSN in cycles 2, 3 and 4 was consistently shorter in the XM22 treatment group compared to placebo, with p<0.0001 in each case. Of note, in each of cycles 2 to 4 around 80% of XM22-treated patients experienced no severe neutropenia at all, whereas only around 40% of placebo patients were free of severe neutropenia.

The incidence of severe neutropenia over all cycles was much lower in the XM22 group compared to the placebo group (41.4% vs. 80.0%; p<0.0001). The incidence of severe neutropenia was much lower in the XM22 group compared to the placebo group in each cycle (cycle 1: 32.1 vs. 59.2%, cycle 2: 16.7 vs. 52.4%, cycle 3: 13.8 vs. 51.1%, cycle 4: 14.8 vs. 55.6%, p<0.0001 in each case). Similarly, the incidence of very severe neutropenia was lower in the XM22 group compared to the placebo group in each cycle. The mean DVSN was shorter in the XM22 group compared to the placebo group in each cycle.

The mean ANC nadir in cycle 1 was higher for the XM22 group (1.60 ± SD 1.64), with p<0.0001. The ANC nadir in both treatment groups was lowest (i.e. worst) in cycle 1. In the XM22 group, the ANC nadir increased to a mean value above 2.5 x 10^9/L in cycles 2 to 4, whereas in the placebo group the mean ANC nadir remained below 1.0 x 10^9/L in cycles 2 to 4. In cycles 2, 3 and 4, the mean ANC nadir had higher absolute values (i.e. better values) in the XM22 group compared to the placebo group (2.8 vs. 0.8, 2.8 vs. 0.8, and 2.6 vs. 0.7 x 10^9/L), with p<0.0001 in each case. The time to ANC nadir was shorter in the XM22 treatment group compared to placebo in each cycle.

The time to ANC recovery was shorter in the XM22 group compared to the placebo group in each cycle, with p<0.0001 in each case; a shorter time to ANC recovery is better for a patient. Similarly, the time to ANC recovery from ANC nadir was shorter in the XM22 group compared to the placebo group in each cycle, with p<0.0001 in each case.

The analysis of efficacy variables in subgroups revealed consistent treatment differences across the subgroups.

In the ITT population, 5 patients in the placebo group (4 in cycle 1, 1 in cycle 3) and 3 patients in the XM22 group (1 in each of cycles 1, 3 and 4) were hospitalised due to FN or connected infection. In cycle 1, the higher incidence of hospitalisation due to FN in the placebo group compared to the XM22 group (3.2 vs. 0.4%) had p<0.05. All received antibiotics and the duration of hospitalisation ranged from 2 to 20 days with no time spent in the ICU.

The majority of patients in both treatment groups received their planned chemotherapy dose in each cycle, with only 0.9 to 3.3% of placebo patients and 1.1 to 2.3% of XM22 patients having CTX dose reduced or treatments omitted.

The proportion of patients with delays in the administration of CTX was higher for the placebo

group in each of cycles 2 to 4, with $p<0.05$ in each case. The higher proportion of patients with delays in the placebo group was due to a higher proportion of patients with ANC < 1.5 x 10^9/L in the placebo group compared to the XM22 group.

Quality of life changes over the course of the study were comparable in the XM22 and placebo treatment groups.

For all efficacy analyses, the results in the ATP population were consistent with those in the ITT population demonstrating the robustness of the results.

Pharmacokinetics and CD34+ cell mobilisation

In cycle 1, mean serum concentrations of XM22 reached a maximum about 48 h after dosing and returned to approximately pre-dose values by 240 h. As expected, XM22 concentrations were around zero for placebo-treated patients.

In cycle 4, the mean serum concentrations reached a maximum at around 24 h and returned to pre-dose values by 240 h. Overall, mean serum concentrations in cycle 4 were lower than in cycle 1. As neutrophil-mediated clearance is the primary mechanism of elimination of XM22, faster elimination of XM22 is expected in cycle 4 due to neutrophil recovery following the previous cycles of G-CSF treatment.

The PK profile of XM22 observed in lung cancer patients in this study was consistent with that in breast cancer patients, based on a comparison with the XM22 PK data from studies XM22-02 and XM22-03 (data on file).

In summary, the CD34+ cell count results show an effect of 6 mg XM22 on CD34+ cell mobilisation in the first CTX cycle.

Safety Results (Safety population):

TEAEs were experienced by 115 (92.0%) patients in the placebo group and by 221 (89.1%) patients in the XM22 group. The most commonly affected preferred terms (PTs) were alopecia, anaemia, nausea, neutropenia, thrombocytopenia, asthenia, vomiting, and leukopenia. All of these TEAEs are known to be associated with administration of the CTX component drugs. Nausea and thrombocytopenia are also listed as adverse reactions to Neulasta®.

Frequencies of most PTs were generally comparable between the treatment groups. The only PTs that differed in frequency by ≥5% between the treatment groups were alopecia (33.6% placebo, 40.7% XM22), neutropenia (35.2%, 20.6%), asthenia (18.4%, 11.3%), and hypokalaemia (2.4%, 8.1%). The differences for alopecia and asthenia are not considered to be clinically relevant. Prevention or reduction of neutropenia is the expected primary pharmacological effect of XM22.

Severe TEAEs were reported in 59 (47.2%) placebo patients and 104 (41.9%) XM22 patients.

9 (7.2%) patients treated with placebo and 31 (12.5%) patients treated with XM22 died in this study. With few exceptions, the TEAEs leading to death were manifestations of the underlying condition (NSCLC) or respiratory AEs. The most frequent PTs for TEAEs leading to death

were non-small cell lung cancer (0.8% placebo, 2.4% XM22), disease progression (0%, 2.0%), and cardio-respiratory arrest (0%, 1.2%). The higher overall frequency of TEAEs leading to death in the XM22 group appears to be attributable primarily to a higher incidence of events reported as disease progression. Disease progression was reported as an AE leading to death and/or cause of death in 2 (1.6%) patients in the placebo group as compared to 14 (5.6%) patients in the XM22 group. Thorough examination by the Sponsor of the individual data for all patients who died suggested that the deaths reported in the XM22 group have diverse aetiologies that do not currently indicate a relationship to study medication, but rather a relationship to the underlying cancer and/or other underlying conditions. Only one TEAE leading to death was assessed by the investigator as related to study medication (XM22, cardio-respiratory arrest, "unlikely" relationship). The death rate of 12.5% observed in the XM22 group is not unexpected in a population of NSCLC patients receiving cisplatin/etoposide, as considerably higher death rates at 3 months have been reported in the literature for this patient population.

Serious TEAEs were reported in 22 (17.6%) placebo patients and in 58 (23.4%) XM22 patients. The most frequent serious TEAEs were anaemia (1.6%, 3.2%), non-small cell lung cancer (0.8%, 3.2%), and disease progression (0%, 2.4%).

The overall incidence of bone-pain-related symptoms was low and similar in both treatment groups (8 [6.4%] placebo patients, 21 [8.5%] XM22 patients). Bone-pain-related symptoms were generally mild or moderate, non-serious, and did not lead to discontinuation from the study in the XM22 group.

Diarrhoea-like symptoms were reported in 4 (3.2%) placebo patients and in 7 (2.8%) XM22 patients (all cases of the PT diarrhoea). None of the AEs in diarrhoea-like symptoms led to discontinuation of study participation and none were serious; With one exception in the XM22 group, all were mild (in the XM22 group) or moderate in severity (in the placebo group).

Overall, results for laboratory safety variables, vital signs (blood pressure and heart rate), body weight, physical examination, infections, febrile neutropenia and blood transfusions and injection site reactions did not give rise to any safety concerns.

ECG monitoring was performed at baseline (within 24 h before start of CTX in cycle 1), on day 5 (24 h after study drug administration) in cycles 1 and 4, and at the end of study visit. The ECG data in this study revealed no clear effect of XM22 on heart rate, AV nodal conduction as measured by PR interval duration, cardiac depolarisation as measured by QRS duration or morphology. There was also no clear signal of an effect on cardiac repolarisation. Hence this trial does not provide any signal that XM22 has any cardiac safety liability as determined by ECG data.

Conclusion

The primary endpoint in this study was the incidence of febrile neutropenia in the first cycle. Although the incidence of febrile neutropenia in the XM22 group was less than half that in the placebo group (2.4 vs. 5.6%), the difference was not statistically significant, with p=0.1151. The FN incidence in the placebo group of this study was lower than expected based on the results of published lung cancer studies using the same chemotherapy combination with the same or similar cisplatin and etoposide dosages. This could have been caused by the exclusion of patients with a high risk of FN from this study and a less strict definition of FN in the published studies than the one used in this study. This study was not powered to demonstrate a significant difference for the FN incidences observed. Nevertheless, the odds ratio for FN in cycle 1 of 0.39 is in line with published results for pegfilgrastim and filgrastim.

The DSN in cycle 1 is a commonly used primary endpoint in studies with G-CSFs. The DSN in cycle 1 was considerably shorter in the XM22 group (mean±SD: 0.6±1.1 days) than in the placebo group (2.3±2.5 days), p<0.0001.

The results for all other neutropenia-related secondary variables consistently indicated that treatment with XM22 was superior to placebo.

The safety profile of XM22 was consistent with the known safety profile of G-CSFs.

Date of report

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