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REVIEW

Clinical efficacy and safety of XM01, a biosimilar recombinant human erythropoietin, in the management of anemia

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Abstract: In this third paper of a series of three reviews on approved biosimilar erythropoietins, we review the evidence about the clinical efficacy and safety of XM01 (epoetin theta). XM01 was developed as a stand-alone product but is considered clinically as a biosimilar. As in the preceding reviews, clinical efficacy is assessed as a function of therapeutic equivalence of biosimilar versus reference product and, in the cancer setting, also superiority over placebo; while safety is evaluated in terms of immunogenicity, venous thromboembolism and mortality. Four studies on patients with chronic kidney disease and three studies on oncology patients are reviewed. In the renal setting, these include two randomized controlled trials on hemoglobin maintenance in hemodialysis and predialysis patients; as well as two open-label extension studies in these populations that also include Phase II patients. Studies in the cancer setting include three randomized controlled trials; in patients with solid tumors receiving platinum-based chemotherapy, in patients with either solid tumors or hematological malignancies receiving non-platinum based chemotherapy, and in patients with hematological malignancies undergoing antineoplastic therapy. Based on the available data, the clinical and safety outcomes of treatment with XM01 are likely to be similar to those of the comparator product NeoRecormon® and superior over placebo. Both XM01 and NeoRecormon® can be considered interchangeable in the management of anemia in the approved indications. Patients transferred from reference product to biosimilar can be expected to show the same efficacy and safety outcomes. There is no evidence for the interchangeability of XM01 with other biosimilar or originator erythropoietins. In keeping with EMA guidance about traceability, it is recommended that clinicians document the product prescribed by its commercial name, especially when switching patients from originator to biosimilar or vice versa.

Keywords: biosimilars, biosimilar pharmaceuticals, efficacy, safety, erythropoietin, recombinant proteins

Introduction

This is the third paper in a series of reviews[1,2] of biosimilar erythropoietins for *Biosimilars*. This article reviews the clinical efficacy and safety of XM01 (epoetin theta; Teva Pharmaceutical Industries Ltd, Petah, Tikva, Israel). The European Medicines Agency (EMA) approved this product on July 23, 2009 and it is marketed as Eporatio® but is also known as Biopoin® and Ratioepo®.

Epoetin theta was developed as a stand-alone product, and is not technically considered to be a biosimilar by some[3] but for practical purposes it is regarded as such by others,[4] and is considered clinically to be a biosimilar for purposes of this review. In the renal setting XM01 is approved for the treatment of symptomatic anemia associated with chronic renal failure in adult patients. In the cancer setting XM01 is indicated for

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the treatment of symptomatic anemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy (Table 1). Contraindications for XM01 as specified on the EMA label, and are listed in Table 2. See our previous reviews for details on scope and approach.[1,2]

Clinical studies

Overview

The late-stage clinical development program of XM01 submitted to the EMA[5] included two Phase III hemoglobin (Hb) maintenance studies in 270 chronic kidney disease (CKD5) patients on hemodialysis with prior erythropoiesis-stimulating agent (ESA) treatment (study XM01-07);[6] and one study in 288 patients with CKD5 not receiving dialysis (predialysis) with prior ESA treatment (study XM01-06);[7] an open extension safety study of trials XM01-04 and XM01-06 involving 289 patients on subcutaneous (SC) XM01 (study XM01-08); and another open extension safety study of trial XM01-05 involving 124 patients on intravenous (IV) XM01 (study XM01-09).[5] In the oncology setting, the clinical development program included a Phase III, randomized, placebo- and active- controlled, double-blind, parallel-group study in 223 cancer patients with solid tumors receiving platinum-containing chemotherapy (study XM01-21);[8] one Phase III, randomized, placebo-controlled, double-blind, parallel-group study in 186 patients with solid tumors or non-myeloid hematological malignancies receiving non-platinum chemotherapy (study XM01-22);[9] and one Phase III, randomized, placebo-controlled, double-blind, parallel-group study in 177 patients with low grade non- Hodgkin's lymphoma, chronic lymphocytic leukemia or multiple myeloma (study XM01-23).[5] The indication is at best tangential to the label (Table 1).

Studies XM01-04 and XM01-05, patients from which were followed in open-extension Phase III studies XM01-08 and XM01-09, are not reviewed here separately.

Study XM01-23 was stopped prematurely due to slow recruitment and because the indication was removed from the ESA label. Because of the indication issue it is not included in this present review.

Table 1 Therapeutic indications for XM01 as approved by the EMA

Chronic renal insufficiency	Treatment of symptomatic anemia associated with chronic renal failure
Cancer	Treatment of symptomatic anemia in cancer patients with non-myeloid malignancies receiving chemotherapy

Note: data obtained from the European Medicines Agency (EMA).[5]

Table 2 Contraindications for XM01 as specified by the EMA

Hypersensitivity to the active substance or to any of the excipients
Uncontrolled hypertension

Note: data obtained from the European Medicines Agency (EMA).[5]

In the European public assessment reports (EPAR) document, safety for the renal studies was reported as an aggregate across studies, not by individual study. The articles reporting on some of these studies provided only general statements about safety. Because of this lack of by-study safety data, this present review can only provide summary safety data across renal studies.

Renal studies

Study XM01-07: Hb maintenance in patients with chronic renal failure on hemodialysis and with prior ESA treatment

Methods

The primary objective of study XM01-07[5,6] was to compare the efficacy of IV treatment with XM01 versus NeoRecormon® (Amgen Inc, Thousand Oaks, CA, USA) in hemodialysis patients with renal anemia who previously were on stable Hb maintenance therapy with NeoRecormon IV. The intent was to document the therapeutic equivalence of XM01 IV relative to NeoRecormon IV in this population.

The study was designed as a multicenter, randomized, controlled, double-blind, comparative, parallel-group, non-inferiority, Phase III study. Hemodialysis patients were allocated in a 2:1 scheme to XM01 IV or NeoRecormon IV and treated for 26 weeks following a run-in period of 2 weeks. The main Hb parameter of interest was the mean Hb concentration of weeks 0 through 2 and the mean Hb concentration of weeks 15 through 26; the latter being the efficacy evaluation period (EEP). During the baseline period patients were administered NeoRecormon at the same dose and frequency as before entering the study. For patients randomized to the XM01 arm, there was a 1:1 dose conversion from NeoRecormon. Patients were treated with XM01 or NeoRecormon for 24 weeks.

The primary endpoint of interest to this study was the increase in mean Hb levels from baseline to end of treatment. Relevant secondary endpoints, which were evaluated during the EEP only, included the percentage of Hb values per patient within the target interval; the percentage of patients with Hb values within the target interval at each week during the EEP; and the number of patients requiring blood transfusions during the treatment period. The target interval for Hb values was defined as $\pm$1 g/dL of baseline and $\geq$9.5 to $\leq$12.0 g/dL.

Patients

The sample consisted of male and female adult patients who had been on hemodialysis for at least 6 months, receiving hemodialysis sessions two or three times a week with concurrent administration of NeoRecormon IV and maintenance of stable Hb for at least 3 months prior to the baseline period. Stable Hb was defined as at least four measurements within the last 8 weeks within the target interval for Hb level, with the difference between the highest and lowest values <2 g/dL. Also, serum ferritin had to be >100 µg/L or transferrin saturation >20%.

A total of 347 patients were screened, of whom 180 were randomized to the XM01 and 90 to the NeoRecormon arm. The according-to-protocol (ATP) population was the primary population for efficacy analyses and included 147 patients in the XM01 arm and 68 patients in the NeoRecormon arm. As detailed in Table 3, the two treatment arms were similar in terms of sex, age, weight, reason of chronic renal failure, and duration of prior treatment with epoetin.

Efficacy

Primary and secondary efficacy endpoints are summarized in Table 4. The analysis of covariance (ANCOVA) estimated difference in mean Hb from baseline to the EEP in both arms was −0.01 g/dL ($P > 0.05$ [not significant (ns)]). The 95% confidence interval (CI) of −0.24 to 0.21 was within the predefined equivalence range of ±1.0 g/dL. The percentage of Hb values per patient within the target range during each week in the EEP was statistically similar in both treatment arms, as was the percentage of patients with Hb values within the target range. The number of patients in each treatment arm requiring a blood transfusion was not significantly different.

Table 3 Patient characteristics in study XM01-07

Characteristic	XM01 (n = 180)	Epoetin beta (n = 90)
Male, n (%)	103 (57.2)	50 (55.6)
Age, years (M ± SD)	61.0 ± 14.4	60.9 ± 12.2
Weight, kg (M ± SD)	69.0 ± 13.3	71.9 ± 13.3
Years since first dialysis, n (%)		
0–3 years	97 (53.9)	47 (52.2)
4–10 years	64 (35.6)	37 (41.1)
≥11 years	19 (10.6)	6 (6.7)
Years since first treatment with epoetin, n (%)		
0–3 years	111 (61.7)	52 (57.8)
4–10 years	56 (31.1)	32 (35.6)
≥11 years	5 (2.8)	2 (2.2)
Reason for renal failure, n (%)*		
Chronic glomerulonephritis	43 (23.9)	17 (18.9)
Hypertension	39 (21.7)	21 (23.3)
Diabetes mellitus	29 (16.1)	22 (24.4)
Chronic pyelonephritis	28 (15.6)	16 (17.8)
Unknown source	25 (13.9)	10 (11.1)

Notes: *Multiple mentions per patient are possible. Data obtained from Gertz et al.[6]
Abbreviations: M, mean; SD, standard deviation.

Study XM01-06: Hb maintenance in patients with chronic kidney disease not receiving dialysis (predialysis) and with prior ESA treatment

Methods

The primary aim of study XM01-06[5,7] was to compare the efficacy of SC treatment with XM01 and NeoRecormon in predialysis patients with renal anemia who previously were on stable Hb maintenance therapy with NeoRecormon IV. The goal was to assess the therapeutic equivalence of XM01 SC relative to NeoRecormon SC in this population. Predialysis was operationalized as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 within the 3 months prior to screening.

The design and endpoints of this study were identical to those of study XM01-07, with the exception of the population studied (predialysis versus hemodialysis) and the route of administration (SC versus IV).

Patients

The sample consisted of male and female adults with chronic renal failure not yet receiving dialysis; specifically, patients with an eGFR <60 mL/min/1.73 m^2 within the 3 months prior. Patients had to show evidence of stable Hb prior to the baseline period: at least four measurements within the last 8 weeks within the target Hb interval, with the difference between the highest and lowest values <2 g/dL. Also, serum ferritin had to be >100 µg/L or transferrin saturation >20%. The target interval for Hb values was defined as ±1 g/dL of baseline and ≥9.5 to ≤12.0 g/dL.

A total of 373 patients were screened and 193 were subsequently randomized to the XM01 SC and 95 to the NeoRecormon SC arm. The ATP population was the primary population for efficacy analyses and included 158 patients in the XM01 arm and 79 patients in the NeoRecormon arm. As detailed in Table 5, the two treatment arms were similar in terms of sex, age, weight, reason of chronic renal failure, and time since first treatment with epoetin.

Efficacy

Primary and secondary efficacy endpoints are summarized in Table 6. The ANCOVA estimated difference in mean Hb from baseline to the EEP in both arms was −0.01 g/dL

Table 4 Efficacy endpoints in study XM01-07

	XM01 ATP (n = 150)	Epoetin beta ATP (n = 74)	XM01 ITT (n = 180)	Epoetin beta ITT (n = 90)	*P*
Hb concentration at baseline (g/dL) (M ± SD)	10.86 ± 0.62	10.83 ± 0.59	10.87 ± 0.65	10.87 ± 0.67	ns
Hb concentration during EEP period (g/dL) (M ± SD)	10.66 ± 0.89	10.66 ± 0.92	10.60 ± 0.98	10.66 ± 1.05	ns
Difference in mean Hb (g/dL)	–0.01		–0.08		
95% CI	–0.24 to 0.21		–0.30 to 0.14		
Change from baseline to EEP (g/dL) (M ± SD)	–0.21 ± 0.82	–0.17 ± 0.96	–0.27 ± 0.88	–0.20 ± 0.99	ns
Blood transfusions during EEP period			7	4	ns

Note: data obtained from Gertz et al.[6]
Abbreviations: M, mean; SD, standard deviation; CI, confidence interval; ns, not significant; ATP, according-to-protocol; ITT, intention-to-treat; EEP, efficacy evaluation period; Hb, hemoglobin.

($P > 0.05$, ns). The 95% CI of –0.20 to 0.22 was within the predefined equivalence range of ±1.0 g/dL. The percentage of Hb values per patient within the target range during each week in the EEP was statistically similar in both treatment arms, as was the percentage of patients with Hb values within the target range. Only one patient treated with XM01 and none administered NeoRecormon required a blood transfusion. This difference was statistically non-significant.

Study XM01-08: long-term efficacy and safety of once- versus thrice-weekly XM01 SC in patients with chronic renal failure not yet receiving dialysis

Methods

Patients enrolled in studies XM01-04 (Phase II study)[5] and XM01-06 (maintenance Phase III study)[7] were invited to participate in an open extension study in which all patients were treated with XM01 SC, including those previously randomized to the NeoRecormon SC arm. The duration was 24 weeks for all patients following the original studies. The objective was to compare the efficacy and safety of once- versus thrice-weekly SC injections of XM01 at the same total weekly dose.

The primary endpoint of interest to this review was the time-adjusted area under the curve for hemoglobin (AUC-Hb) during the EEP (weeks 25 to 36, 12 weeks). Relevant secondary endpoints were the percentage of Hb values within the target interval during the EEP, percentage of patients with Hb values within the therapeutic range during the EEP, within-patient variance in Hb levels during the EEP, measured values of Hb, and the number of blood transfusions.

Patients

The sample consisted of male and female predialysis patients who had completed the double-blind treatment period of studies XM01-04[5] and XM01-06.[7] Of the 289 patients who enrolled in the study, 95 patients completed the study in the once-weekly arm and 82 patients in the thrice-weekly arm. Baseline demographic characteristics were similar across

Table 5 Patient characteristics in study XM01-06

Characteristic	XM01 (n = 193)	Epoetin beta (n = 95)
Male, n (%)	92 (47.7)	59 (62.1)
Age, years (M ± SD)	64.1 ± 13.1	61.7 ± 15.7
Weight, kg (M ± SD)	74.6 ± 15.3	75.2 ± 17.3
Years since first diagnosis of renal anemia, n (%)		
0–3 years	134 (69.4)	68 (71.6)
4–10 years	42 (21.8)	21 (22.1)
≥11 years	6 (3.1)	0 (0.0)
No data available	11 (5.7)	6 (6.3)
Years since first treatment with epoetin, n (%)		
0–3 years	191 (99.0)	95 (100.0)
4–10 years	2 (1.0)	0 (0.0)
Reason of renal failure, n (%)*		
Chronic glomerulonephritis	66 (34.2)	27 (28.4)
Hypertension	42 (21.8)	19 (20.0)
Diabetes mellitus	31 (16.1)	22 (23.2)
Chronic pyelonephritis	34 (17.6)	15 (15.8)
Unknown source	19 (9.8)	11 (11.6)

Notes: *Multiple mentions per patient are possible. Data obtained from Gertz et al.[7]
Abbreviations: M, mean; SD, standard deviation.

Table 6 Efficacy endpoints in study XM01-06

	XM01 ATP (n = 159)	Epoetin beta ATP (n = 81)	*P*
Hb concentration at baseline (g/dL) (M ± SD)	10.88 ± 0.59	10.93 ± 0.61	ns
Hb concentration during EEP period (g/dL) (M ± SD)	11.07 ± 0.94	11.08 ± 0.82	ns
Difference in mean Hb (g/dL)	0.01		
95% CI	–0.20 to 0.22		
Change from baseline to EEP (g/dL) (M ± SD)	0.19 ± 0.80	0.15 ± 0.73	ns

Note: data obtained from Gertz et al.[7]
Abbreviations: M, mean; SD, standard deviation; CI, confidence interval; ns, not significant; ATP, according-to-protocol; EEP, efficacy evaluation period; Hb, hemoglobin.

treatment groups in terms of the time since first diagnosis of renal failure and of renal anemia, and reasons for renal failure. Demographic characteristics of patients enrolled in study XM01-08 were not provided and it cannot be ascertained whether or not both arms differed in any of these variables.

Efficacy

Primary and secondary endpoints are summarized in Table 7. The difference in time adjusted AUC-Hb during the EEP between XM01 SC once weekly and thrice weekly was –0.17 g/dL ($P > 0.05$, ns). The 95% CI of –0.40 to 0.06 was within the predefined equivalence range of +1.0 g/dL. The percentage of patients who experienced Hb outside the target range of 9.5–12.5 g/dL was stated to be similar in both study arms during the EEP, however, counts or percentages are not reported. Both treatment arms are stated to be similar in the percentages of patients with Hb values within the therapeutic range (9.5–12.0 g/dL) during the EEP in the ATP and intention-to-treat (ITT) population, but again, no data are reported. In addition, within-patient standard deviation and variability in Hb levels in the ITT population during the EEP was stated to be similar for both arms, but again without statistical evidence presented. Hb values slightly decreased in both arms during the first 12 weeks on-study, but here too no statistical evidence is reported. Mean of Hb of patients enrolled in study XM01-04 was higher than patients enrolled in study XM01-06 (12.2 g/dL versus 11.0 g/dL, respectively).

Table 7 Efficacy endpoints in study CSR XM01–08

	XM01 once weekly	XM01 thrice-weekly	*P*
Time adjusted AUC-Hb at baseline (g/dL) (M ± SD)	11.012 ± 0.902	11.039 ± 0.878	ns
Time adjusted AUC-Hb during EEP period (g/dL) (M ± SD)	10.728 ± 0.829	10.908 ± 0.960	ns
Difference in mean time adjusted AUC-Hb (g/dL)	–0.17		
95% CI	–0.40 to 0.06		
Blood transfusions	2	2	ns
Percentage of Hb values within the target interval during the EEP	No statistical evidence reported		
Percentage of patients with Hb values within the therapeutic range during the EEP	No statistical evidence reported		
Within-patient variance in Hb levels during the EEP	No statistical evidence reported		
Measured values of Hb	No statistical evidence reported		

Note: data obtained from the European Medicines Agency (EMA).[5]
Abbreviations: M, mean; SD, standard deviation; CI, confidence interval; AUC-Hb, area under the curve for hemoglobin; EEP, efficacy evaluation period; ns, not significant.

However, patients from XM01-04 had higher mean Hb values than patients from study XM01-06, but this was attributable to differences in starting dose and Hb at baseline. Four patients required a blood transfusion, two patients in both arm during the study (ATP population). Blood transfusion was not required in both arms during EEP.

Study XM01-09: long-term efficacy and safety of XM01 IV in hemodialysis patients

Methods

Patients enrolled in studies XM01-05 (Phase II study)[5] were invited to participate in an open extension study in which all patients were treated with XM01 IV, including those previously randomized to the NeoRecormon IV arm. The duration was 36 weeks for all patients following the original studies. The objective was to evaluate the long-term efficacy and safety of XM01 IV.

The primary endpoint of interest to this review was the assessment of the safety profile of XM01 IV. Relevant secondary endpoints were the time-adjusted AUC-Hb during the study period, percentage of Hb values per patient within the therapeutic range, the time course and the change from baseline of Hb values, and the number of blood transfusions.

Patients

The sample consisted of male and female dialysis patients who had completed the double-blind treatment period of Phase II study XM01-05.[5] Of the 124 patients who enrolled in the study, 109 patients completed the study. Characteristics of patients enrolled in study XM01-09 were not reported.

Efficacy

Primary and secondary endpoints are summarized in Table 8. The mean of time adjusted AUC-Hb during the study was stated to be within the therapeutic range during the study period, however, no data are presented in the EPAR. Due to the high starting dose of XM01 in study XM01-05, the mean percentage of Hb values per patient within the therapeutic range increased; however, no statistical evidence is presented.

Table 8 Efficacy endpoints in study CSR XM01-09

	XM01 IV
Time-adjusted AUC-Hb	No statistical evidence reported
Percentage of Hb values per patient within the therapeutic range	No statistical evidence reported
The time course and the change from baseline of Hb values	No statistical evidence reported
Blood transfusion	4

Note: data obtained from the European Medicines Agency (EMA).[5]
Abbreviations: AUC-Hb, area under the curve for hemoglobin; IV, intravenous.

Mean Hb values were high at the beginning of this study, and then Hb values decreased and stayed stable during the study; however, again, no statistical evidence is reported. Four patients required a blood transfusion; three patients needed only one blood transfusion and one patient needed two blood transfusions.

Aggregate safety data for renal studies

No patients developed significant anti-erythropoietin antibodies, hence there were no cases of pure red cell aplasia. Eight patients on XM01 experienced an arteriovenous fistula thrombosis event in the Phase II and III studies (no breakdown data provided), and one patient experienced an arteriovenous fistula thrombosis event in follow-up extension study XM01-09. A total of 21 patients taking XM01 died during the Phase II and III studies: one death was assessed as unlikely related to XM01 and the other deaths were assessed as unrelated to XM01. Additional safety data have been summarized elsewhere.[10]

Cancer studies

Study XM01-21: efficacy and safety of XM01 SC in anemic patients with solid tumors receiving platinum-containing chemotherapy

Methods

The primary objectives of this study were to demonstrate the superiority of XM01 SC compared to placebo SC in terms of efficacy, and to compare the efficacy and safety profile of XM01 SC with that of NeoRecormon SC in patients with solid tumors receiving platinum-containing chemotherapy.[5,8]

This study was designed as a multicenter, randomized, placebo- and active-controlled, double-blind Phase III study. Only the person administering study medication was unblinded. Patients were randomized in a 1:1:1 ratio to treatment with XM01, NeoRecormon, or placebo.

The primary endpoint of interest to this review was the number of patients with a complete Hb response. This was defined as an increase in Hb of ≥2 g/dL from baseline without the benefit of a transfusion within the previous 4 weeks. Relevant secondary endpoints were the number of patients having a complete Hb response with the initial dose, the number of patients having a partial Hb response (defined as increase of ≥1 g/dL from baseline), and the number of patients receiving transfusions.

Patients

The sample consisted of male and female adult patients diagnosed with a solid tumor and anemia attributed to platinum-based chemotherapy. Anemia was defined as an Hb concentration ≤11 g/dL Exclusion criteria were patients with head and neck tumors, uncontrolled severe hypertension, and patients receiving concomitant radiotherapy.

A total of 223 patients were randomized to treatment with either XM01 (n = 76), NeoRecormon (n = 73) or placebo (n = 74). Table 9 presents the demographic and baseline characteristics of the 3 treatment groups; all of them were statistically comparable. There were no relevant differences between treatment groups with regard to medical history, prior or concomitant medications, blood transfusions prior to study entry, concomitant diseases, tumor types and on-study chemotherapies.

Efficacy

Primary and secondary endpoints are summarized in Table 10. The number of patients with a complete Hb response was significantly higher in the XM01 group compared to the placebo group ($P < 0.0001$). The baseline Hb adjusted odds ratio of achieving complete Hb response was 8.06 (95% CI = 3.89–17.63). There were no statistically significant differences in complete Hb response between the XM01 and NeoRecormon arms ($P > 0.05$, ns). The proportion of patients who had a complete Hb response without changing the starting dose was significantly higher in the XM01 group than in the placebo group ($P = 0.0012$). As to partial Hb response, the responder rate was higher among patients treated with XM01 than those given placebo ($P < 0.0001$). More patients in the placebo group than in the XM01 group received blood transfusions ($P = 0.0433$).

Safety

None of the patients participating in the study developed neutralizing anti-epoetin antibodies to XM01

Table 9 Patient characteristics in study XM01-21

Characteristic	XM01 (n = 76)	Placebo (n = 74)	Epoetin beta (n = 73)
Male, n (%)	30 (39.5)	19 (25.7)	22 (30.1)
Age, years (M ± SD)	53.7 ± 10.3	56.0 ± 10.9	57.3 ± 10.5
Weight, kg (M ± SD)	66.1 ± 13.2	66.0 ± 13.7	69.0 ± 14.6
Most common tumor types, n (%)*			
Ovarian epithelial cancer	14 (18.4)	20 (27.0)	21 (28.8)
Gastric cancer	6 (7.9)	7 (9.5)	5 (6.8)
Lung squamous cell carcinoma	4 (5.3)	7 (9.5)	5 (6.8)
Breast cancer	6 (7.9)	6 (7.9)	3 (4.1)
Ovarian epithelial cancer metastatic	6 (7.9)	3	6 (7.9)

Notes: *Multiple mentions per patient are possible. Data obtained from Tjulandin et al.[8]
Abbreviations: M, mean; SD, standard deviation.

Table 10 Efficacy endpoints in study CSR XM01-21

	XM01	Placebo	Epoetin beta
Baseline Hb [g/dL] (M ± SD)	9.6 ± 1.1	9.4 ± 1.2	9.5 ± 0.8
Complete Hb response, n (%)	50 (65.8)	15 (20.3)	52 (71.2)
Treatment (XM01 vs placebo)			
P-value	<0.0001		
Odds ratio (95% CI)	8.06 (3.89 to 17.63)		
Complete Hb response without dose adjustment [n (%)]	26 (34.2)	8 (10.8)	29 (39.7)
Treatment (XM01 vs placebo)			
P-value	0.0012		
Odds ratio (95% CI)	4.24 (1.84 to 10.76)		
Partial Hb response without blood transfusion [n (%)]	69 (90.8)	37 (50)	66 (90.4)
Treatment (XM01 vs placebo)			
P-value	<0.0001		
Odds ratio (95% CI)	9.80 (4.19 to 26.00)		
Patients received blood transfusions [n (%)]	8 (10.5)	18 (24.3)	9 (12.3)
Treatment (XM01 vs placebo)			
P-value	0.0433		
Odds ratio (95% CI)	0.38 (0.14 to 0.95)		

Note: data obtained from Tjulandin et al.[8]
Abbreviations: M, mean; SD, standard deviation; CI, confidence interval; Hb, hemoglobin; vs, versus.

or NeoRecormon. No specific VTEs were reported during the study. Twenty-one of the patients in this study (5 XM01, 12 placebo, 4 NeoRecormon) died during the study period. The most frequent reason for death was disease progression. For one patient treated with NeoRecormon the causal relationship of the death was assessed as unclassifiable by the investigator. The remaining deaths were not suspected to be related to treatment with XM01 or NeoRecormon. Additional safety data have been summarized elsewhere.[10]

Study XM01-22: efficacy and safety of XM01 SC in anemic patients with solid tumors or non-myeloid hematological malignancies receiving non-platinum chemotherapy

Methods

The primary objectives of this study were to demonstrate the superiority of XM01 SC compared to placebo SC in terms of efficacy, and to compare the safety profile of XM01 SC with that of placebo in patients with solid tumors or non-myeloid malignancies receiving non-platinum chemotherapy.

This study was designed as a multicenter, randomized, double-blind Phase III study. Patients were randomized in a 1:1 ratio to either treatment with XM01 or treatment with placebo.

As in study XM01-21, the primary endpoint of interest was the number of patients with a complete Hb response – defined as an increase in Hb of ≥2 g/dL from baseline without the benefit of a transfusion within the previous 4 weeks. Relevant secondary endpoints were the number of patients having a complete Hb response with the initial dose, the number of patients having a partial Hb response (defined as increase of ≥1 g/dL from baseline), and the number of patients receiving transfusions.

Patients

The sample consisted of male and female adult patients diagnosed with a solid tumor or non-myeloid hematological tumor and experiencing anemia induced by non-platinum-based chemotherapy. Exclusion criteria were any other primary hematologic disorder that would cause anemia, patients with head and neck tumors, uncontrolled severe hypertension and patients receiving concomitant radiotherapy. A total of 186 patients were randomized to treatment with either XM01 (n = 95) or placebo (n = 91). As detailed in Table 11, the demographics and baseline characteristics of the two treatment arms were comparable. There were no relevant differences between treatment groups with regard to medical history, prior or concomitant medications, blood transfusions prior to study entry, concomitant diseases, tumor types and on-study chemotherapies.

Efficacy

Primary and secondary endpoints are summarized in Table 12. The number of patients with a complete Hb response was significantly higher in the XM01 arm than in the placebo arm ($P < 0.0001$). The baseline Hb adjusted odds ratio of achieving a complete Hb response following treatment with XM01 was 7.94 (95% CI = 4.18–15.63). The proportion of patients who had a complete Hb response without changing the starting dose was significantly higher in the XM01 group than in the placebo group ($P < 0.0001$). Partial Hb response was achieved in more XM01-treated than in placebo-treated patients ($P = 0.0025$). More patients

Table 11 Patient characteristics in study XM01-22

Characteristic	XM01 (n = 95)	Placebo (n = 91)
Male, n (%)	30(31.6)	34 (37.4)
Age, years (M ± SD)	56.9 ± 14.7	55.8 ± 14.3
Weight, kg (M ± SD)	67.4 ± 15.2	68.6 ± 14.1
Most common malignancies, n (%)*		
Multiple myeloma	19 (20.0)	17 (18.7)
Breast cancer	16 (16.8)	17 (18.7)
Chronic lymphoma leukemia	5 (5.3)	7 (7.7)
Gastric cancer	6 (6.3)	3 (3.3)

Notes: *Multiple mentions per patient are possible. Data obtained from Tjulandin et al.[9]
Abbreviations: M, mean; SD, standard deviation.

Table 12 Efficacy endpoints in study XM01-22

	XM01	Placebo
Baseline Hb [g/dL] (M ± SD)	9.2 ± 1.3	9.1 ± 1.3
Complete Hb response, n (%)	69 (72.6)	23 (25.3)
Treatment (XM01 vs placebo)		
P-value	<0.0001	
Odds ratio (95% CI)	7.944 (4.182 to 15.632)	
Complete Hb response without dose adjustment [n (%)]	43 (45.3)	9 (9.9)
Treatment (XM01 vs placebo)		
P-value	<0.0001	
Odds ratio (95% CI)	7.728 (3.590 to 18.285)	
Partial Hb response without blood transfusion [n (%)]	61.5 (82.1)	56 (61.5)
Treatment (XM01 vs placebo)		
P-value	<0.0025	
Odds ratio (95% CI)	2.841 (1.462 to 5.694)	
Patients received blood transfusions [n (%)]	13 (13.7)	25 (25.3)
Treatment (XM01 vs placebo)		
P-value	0.0277	
Odds ratio (95% CI)	0.352 (0.133 to 0.868)	

Note: data obtained from Tjulandin et al.[9]
Abbreviations: M, mean; SD, standard deviation; CI, confidence interval; Hb, hemoglobin; vs, versus.

in the placebo group than in the XM01 group received blood transfusions ($P = 0.0277$).

Safety

None of the patients included in the study developed neutralizing anti-epoetin antibodies to XM01. No specific VTEs were reported. Eleven of the patients in this study (6 XM01, 5 placebo) died during the study period. The most frequent reason for death was disease progression. None of the deaths were suspected to be related to treatment. Additional safety data have been summarized elsewhere.[10]

Comments

The studies reviewed here provide adequate evidence about the therapeutic equivalence of the IV and SC formulations of XM01 relative to originator NeoRecormon and the superiority over placebo. This therapeutic equivalence was demonstrated in the renal (hemodialysis and predialysis) and oncology (platinum and non-platinum chemotherapy-induced anemia) settings.

In the renal settings, the comparative trial design of studies XM01-07 and XM01-06 permitted direct inferences about the therapeutic equivalence of XM01 relative to NeoRecormon in maintaining Hb levels in patients with chronic kidney disease requiring (XM01-07) or not yet requiring (XM01-06) hemodialysis. These studies showed that Hb levels did not differ significantly between XM01- and NeoRecormon-treated patients and did not shift significantly when therapy would be changed from originator to XM01.

In the oncology setting, studies XM01-21 and XM01-22 showed the superiority of XM01 over placebo in patients treated with platinum and non-platinum-based chemotherapy. Study XM01-21 also documented the therapeutic equivalence of XM01 relative to NeoRecormon.

As XM01 was submitted as an independent application and not as an application for a "similar biological medicinal product", the EMA disallowed any extrapolations from the indications of other approved epoetins. Hence the approved indications for XM01 are not as broad as those for HX575[1] and SB309.[2] In the renal setting, the XM01 is approved for the treatment of symptomatic anemia associated with chronic renal failure in adults but not children. XM01 is not approved for the indications of increasing the yield of autologous blood from patients in a predonation program or for reducing the exposure to allogeneic blood transfusion in adults prior to major elective orthopedic surgery. In the oncology setting, XM01 is indicated for the treatment of symptomatic anemia in cancer patients with non-myeloid malignancies receiving chemotherapy.

It was striking that many efficacy and safety statements about XM01 were included in the EPAR for which no statistical evidence was presented. While we would like to believe that a regulatory approval document such as an EPAR is similar to a top-tier peer-reviewed publication in terms of rigor of reporting, the reporting methods in the XM01 EPAR would not meet standard journal publication criteria.

Based on the available data, in routine clinical practice the clinical and safety outcomes of treatment with XM01 can be expected to be similar to those of NeoRecormon. Both products can be considered interchangeable in the approved indications: patients transferred from NeoRecormon XM01 are likely to show the same efficacy and safety outcomes.

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Disclosure

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