MDS-004 Study: REVLIMID® (lenalidomide) versus Placebo in Myelodysplastic Syndromes with Deletion (5q) Abnormality

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1. EXECUTIVE SUMMARY

- MDS-004 was a randomized, double-blind, placebo-controlled Phase III study that compared the efficacy of 2 different dose regimens of REVLIMID (5 mg daily every 28 days and 10 mg daily Days 1-21 every 28 days) to placebo in red blood cell (RBC) transfusion-dependent Low- or Int-1 risk MDS with del(5q) , with or without additional cytogenetic abnormalities. Primary endpoint of the study was RBC transfusion independence (RBC-TI) of at least 26 weeks. *MDS-004 was **not** designed to compare lenalidomide 5 mg to lenalidomide 10 mg.*
- RBC-TI ≥ 26-weeks rates were 41.3% in the lenalidomide 5-mg arm and 56.1% in the lenalidomide 10-mg arm compared to 5.9% in the placebo arm (*P<.001*)
- Median time to RBC-TI with lenalidomide was rapid with 3.3 weeks in the 5-mg arm and 4.3 weeks in the 10-mg arm
    - 95% of patients treated with lenalidomide with RBC-TI for ≥ 26 weeks, achieved RBC-TI by approximately 12 weeks
- Median increase in hemoglobin (Hb) was 5.1 g/dL in the lenalidomide 5-mg arm and 6.3 g/dL in the lenalidomide 10-mg arm compared to 2.3 g/dL in the placebo arm
- Cytogenetic remission (complete + partial) rates were 17.4% in the lenalidomide 5-mg arm and 41.5% in the lenalidomide 10-mg arm compared to 0% in the placebo arm (*P<.001*)
- Both lenalidomide 5mg and 10 mg doses were generally well-tolerated
    - Rates of Grade 3 or 4 neutropenia, thrombocytopenia, leukopenia, and anemia were similar in lenalidomide 5 mg (74%, 33%, 13, and 6%, respectively) and 10 mg arms (75%, 41%, 9, and 3%, respectively) and higher compared to the placebo arm (15%, 2%, 0%, and 9%, respectively). Neutropenia and thrombocytopenia were managed with dose reduction or interruption, and supportive care
    - Rates of deep vein thrombosis (DVT) were 1% in the lenalidomide 5-mg arm, 6% in the lenalidomide 10-mg arm, and 2% in the placebo arm. DVT was managed with dose interruption and anticoagulation
    - Rates of discontinuation due to adverse events were 16% in the lenalidomide 5-mg arm, 9% in the lenalidomide 10-mg arm, and 5% in the placebo arm
- Rates of AML progression were similar across all 3 arms (Log rank *P=.6474*) with 9% in the placebo arm as of a median follow-up of 18.5 months, 10% in the lenalidomide 5-mg arm as of a median follow-up of 13.7 months, and 7% in the lenalidomide 10-mg arm as of a median follow-

up of 19.3 months. Cumulative incidence of AML progression among lenalidomide-treated patients was 7.7% at 2 years measured from the time of randomization.

2. BACKGROUND

In December 2005, the Food and Drug Administration (FDA) approved REVLIMID® (lenalidomide) for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk MDS associated with deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities (Revlimid Prescribing Information, January 2009). This approval was based on clinical findings from an open label, single-arm, multi-center Phase II study of 148 patients treated with lenalidomide 10 mg once daily or 10 mg for 21 days every 28 days (List et al. 2006). The study was not designed nor powered to prospectively compare the efficacy of the 2 dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity. Red blood cell transfusion independence (RBC-TI) (defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period) occurred in 99 (67%) patients, 90% of whom achieved their transfusion benefit by completion of 3 months in the study. Median duration of RBC-TI was 44 weeks (range of 0 to > 67 weeks). The dose of REVLIMID was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of patients and a second dose reduction or interruption due to adverse events was required in 50 (33.8%) patients.

The MDS-004 study was initiated prior to FDA approval of REVLIMID in del(5q) MDS and in response to recommendation by FDA to run a randomized clinical trial with REVLIMID in MDS. Although MDS-004 was not requested as a formal post approval commitment trial, the results from this ongoing study were requested by the FDA as a post approval commitment in the 2005 approval letter.

3. SUMMARY OF CLINICAL EXPERIENCE

MDS-004 was a randomized, double-blind, placebo-controlled, multi-center, Phase III study conducted in Europe and Israel that compared the efficacy of 2 different dose regimens of lenalidomide (5 mg every 28 days and 10 mg Days 1-21 every 28 days) to placebo in red blood cell (RBC) transfusion-dependent (defined as no consecutive 56 days within the last 112 days without RBC transfusion) Low- or Int-1 risk MDS with del(5q), with or without additional cytogenetic abnormalities (Fenaux et al. 2009b; Fenaux et al. 2009a). MDS-004 was **not** powered to compare REVLIMID 5 mg to 10 mg. Patients were excluded from study enrollment with absolute neutrophil count (ANC) < 500 cells/uL and/or platelet count < 25,000/uL.

3a. Study Design

The primary endpoint of MDS-004 was the absence of RBC transfusions for at least 26 consecutive weeks on treatment and an increase in hemoglobin (Hb) of >1 g/dL from baseline. *Note: RBC transfusion independence (TI) of at least 26 consecutive weeks is a more stringent MDS 004 protocol-specified measure of TI than that of the International Working Group (IWG) definition, which requires the absence of RBC transfusions for 8 consecutive weeks.* Some of the secondary endpoints of MDS-004 included erythroid response, duration of RBC-TI, cytogenetic response (each assessed per IWG 2000 criteria), time to AML progression (according to FAB classification), and adverse events (assessed per NCI-CTCAE v 3.0).

The study included a pre-randomization phase, a double-blind phase, and an open-label phase. Prior to randomization, patients were stratified according to IPSS risk and cytogenetic complexity. Patients were then randomized in a double-blind fashion to 1 of 3 arms:

- Lenalidomide 5 mg daily per 28-day cycle
- Lenalidomide 10 mg daily Days 1-21 per 28-day cycle
- Placebo

Response was assessed at 16 weeks in the double-blind and open-label phases. Patients who achieved at least a minor erythroid response in the double-blind phase continued with double-blind treatment for up to 52 weeks or until relapse or progression. Responders initially randomized to placebo who experienced relapse or disease progression prior to Week 52 of the double-blind phase were permitted to cross over to lenalidomide 5 mg daily. Non-responders at Week 16 of the double-blind phase discontinued double-blind treatment and entered the open-label phase of the study for a maximum of 3 years (including time spent in the double-blind phase), receiving lenalidomide 5 mg daily if double-blind treatment was placebo, lenalidomide 10 mg if double-blind treatment was lenalidomide 5 mg, or off study if double-blind treatment was lenalidomide 10 mg. Responders at Week 52 during the double-blind phase were allowed to continue their assigned double-blind treatment in the open-label phase. *The open label phase of MDS-004 is on-going*.

Final data from the double-blind phase in addition to some data from the open-label phase (i.e., duration of RBC TI , and progression to AML) of MDS-004 were presented at the Annual Meeting of the American Society of Hematology (ASH) in December 2009 (Fenaux et al. 2009a).

3b. Efficacy Results

Baseline characteristics were well-balanced across the 3 arms except there was a higher proportion of patients with RAEB MDS subtype in the lenalidomide 5 mg and lenalidomide 10 mg arms compared to the placebo arm (15% and 12% vs. 6%, respectively) (Table 1).

Table 1. Baseline Patient and Disease Characteristics: MDS-004 (mITT Population)

	Placebo (n = 51)	Lenalidomide 5 mg (n = 46)	Lenalidomide 10 mg (n = 41)
Median age, yrs (range)	70 (39–85)	66 (40–86)	68 (36–84)
Female, %	80	78	68
Median time since diagnosis, yrs (range)	2 (0–14)	3 (0–17)	3 (0–15)
Median transfusion burden, units per 8 wks (range)	6 (4–12)	6 (1–28)	6 (2–12)
FAB type, %			
RA	69	67	68
RARS	16	11	20
RAEB	6	15	12
Other	10	7	0
IPSS category, %			
Low-risk	55	39	49
Int-1-risk	45	61	51
Karyotype, %			
Isolated del(5q)	73	76	78
del(5q) + 1 abnormality	22	15	10
del(5q) + ≥ 2 abnormalities	6	9	12
ANC 0.5-1.0 × 10^9/L, %	6	22	10
Platelets 25-50 × 10^9/L, %	0	2	0

Key: **ANC**=absolute neutrophil count; **FAB**=French-American-British; **INT**=intermediate; **IPSS**=International Prognostic Scoring System; **mITT**=modified intent-to-treat; **RA**=refractory anemia; **RAEB**=refractory anemia with excess blasts; **RARS**=refractory anemia with ringed sideroblasts; **WKS**=weeks; **YRS**=years
Adapted from: Fenaux 2009 ASH Oral Presentation

All efficacy analyses were performed using a modified intent-to-treat (mITT) population which included 138 randomized patients as of a data cut-off of June 26, 2008 with centrally-confirmed diagnosis and RBC transfusion-dependent anemia who received at least 1 dose of study drug. The most common reason for being excluded from the mITT population in MDS-004 was inadequate BM specimen for central review. The RBC-TI ≥ 26-week rate was also identified using an intent-to-treat (ITT) analysis which included all 205 randomized patients. *The primary endpoint of RBC-TI ≥ 26 weeks was determined using both mITT and ITT populations because a sizeable number of randomized patients were excluded from the mITT population*.

Results were consistent between the mITT and ITT populations (Table 2). Median time to RBC-TI was approximately 1 cycle among patients treated with 5 and 10 mg of lenalidomide. Of the patients who achieved RBC-TI for ≥ 26 weeks, 50%, 75% and 95% did so by approximately 4, 6, and 12 weeks, respectively. Achievement of RBC-TI for ≥ 26 weeks was not affected by age, gender, FAB classification, IPSS risk, time from diagnosis, cytogenetic complexity, baseline platelet counts, or number of cytopenias at baseline.

Table 2. Efficacy Results: MDS-004 (mITT and ITT Populations)

Efficacy Variable	Placebo		Lenalidomide 5 mg		Lenalidomide 10 mg	
	mITT (n=51)	ITT (n=67)	mITT (n=46)	ITT (n=69)	mITT (n=41)	ITT (n=69)
Primary Endpoint						
Median RBC-TI ≥ 26 wks (protocol), %	6	6	41*	33*	56*	54*
Secondary Endpoints						
Median RBC-TI ≥ 8 wks (IWG), %	8	8	50*	48*	61*	61*
Median (95% CI) Duration TI ≥ 26 wks, wks	NE (9-NE)		NE (52-NE)		106 (83-NE)	
Median Time to TI ≥ 26 wks, wks	0.3 (0.3-24.1)		3.3 (0.3-12.3)		4.3 (0.3-14.7)	
Median Maximum Hb increase, g/dL	2.3		5.1**		6.3***	
Cytogenetic Response^, %						
CR	0		10.9***		24.4*	
PR	0		6.5		17.1	
CR+PR	0		17.4*		41.5*	

**P<.001* vs. placebo; *** P< .05* vs. placebo; ****P=.01* vs. placebo

^ Assessed by standard cytogenetics and fluorescent in situ hybridization (FISH) with CR defined as absence of chromosome 5q31 abnormality and PR defined as reduction of abnormality by > 50%

Key: **CI**=confidence interval; **CR**=complete response; **Hb**=hemoglobin; **ITT**=intent-to-treat; **IWG**=International Working group; **mITT**=modified intent-to-treat; **NE**=not estimable; **PR**=partial response; **RBC-TI**=red blood cell transfusion independent; **TI**=transfusion independence; **wks**=weeks

Adapted from: Fenaux 2009 ASH Oral Presentation and Abstract

3c. Safety Results

All safety analyses, including progression to AML, were performed using all 205 randomized patients who received at least 1 dose of study drug. Safety was similar in lenalidomide 10 mg and lenalidomide 5 mg arms (Table 3). Neutropenia and thrombocytopenia were manageable with dose interruption, dose reduction and supportive care. Deep vein thromboses were managed per MDS-004 protocol (i.e., study drug interruption and anticoagulation therapy).

Table 3. Most Common Grade 3 or 4 Adverse Events: MDS-004 (Safety Population)

	Placebo (n = 67)	Lenalidomide 5 mg (n = 69)	Lenalidomide 10 mg (n = 69)
Grade 3 or 4 adverse events (≥ 5% of patients in any group)			
Patients with ≥ 1 event, n (%)	29 (43)	62 (90)	65 (94)
Neutropenia	10 (15)	51 (74)	52 (75)
Thrombocytopenia	1 (2)	23 (33)	28 (41)
Leukopenia	0 (0)	9 (13)	6 (9)
Anemia	6 (9)	4 (6)	2 (3)
Deep vein thrombosis	1 (2)	1 (1)	4 (6)
Adverse events leading to, n (%)			
Discontinuation	3 (5)	11 (16)	6 (9)
Dose reduction	0 (0)	36 (52)	40 (58)
Dose interruption	4 (6)	19 (28)	28 (41)

Adapted from: Fenaux et al ASH 2009 Oral Presentation

Time to AML progression was measured from randomization (not from diagnosis) and includes data from the open-label phase. Rates of AML progression were similar across all 3 arms (Log rank

P=.6474) with 9% (6 out of 67 patients) in the placebo arm as of a median follow-up of 18.5 months, 10% (7 out of 69 patients) in the lenalidomide 5-mg arm as of a median follow-up of 13.7 months, and 7% (5 out of 69 patients) in the lenalidomide 10-mg arm as of a median follow-up of 19.3 months. *The placebo arm included patients who crossed-over from placebo to lenalidomide 5 mg daily if, during the double-blind phase, they were nonresponders at 16 weeks.* Median time to AML progression from the initial study dose was 9.3, 5.9, and 3.1 months in the lenalidomide 5 mg, lenalidomide 10 mg, and placebo arms, respectively (Fenaux et al. 2009b). The cumulative incidence of AML progression among lenalidomide-treated patients was 7.7% at 2 years measured from the time of randomization (Fenaux et al. 2009a). *Note: median time from diagnosis to study entry was 2 years for placebo and 3 years for both lenalidomide arms.*

The investigators of the MDS-004 study concluded that both doses of lenalidomide were generally well tolerated and resulted in significant RBC-TI and cytogenetic responses, with lenalidomide 10 mg associated with better RBC-TI and cytogenetic responses than the 5-mg dose, with comparable safety profile in the del(5q) population In addition, there were no trends to suggest an increase in AML progression with lenalidomide compared to the untreated del(5q) population as of a June 26, 2008 cut-off. Furthermore, these data support the use of lenalidomide 10 mg daily as a starting dose in the del(5q) population, with dose reduction or interruption as needed.

4. REFERENCES

1. Fenaux P, Giagounidis A, Selleslag D, et al. RBC transfusion independence and safety profile of lenalidomide 5 or 10 mg in patients with low- or int-1-risk MDS with del(5q): Results from a randomized Phase III trial (MDS-004) [oral]. *Oral presented at: Annual Meeting and Exposition of the American Society of Hematology* 2009a; December 5-8; New Orleans, LA.
2. Fenaux P, Giagounidis A, Selleslag D, et al. RBC transfusion independence and safety profile of lenalidomide 5 or 10 mg in pts with low- or int-1-risk MDS with del5q: Results from a randomized Phase III trial (MDS-004) [abstract]. *Proceedings of the 51st Annual Meeting and Exposition of the American Society of Hematology* 2009b; December 5-8; New Orleans, LA: Abstract #0944.
3. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *New England Journal of Medicine* 2006; 355(14): 1456-65.
4. Revlimid (lenalidomide) Prescribing Information. Summit, NJ: Celgene Corporation; January 2009.