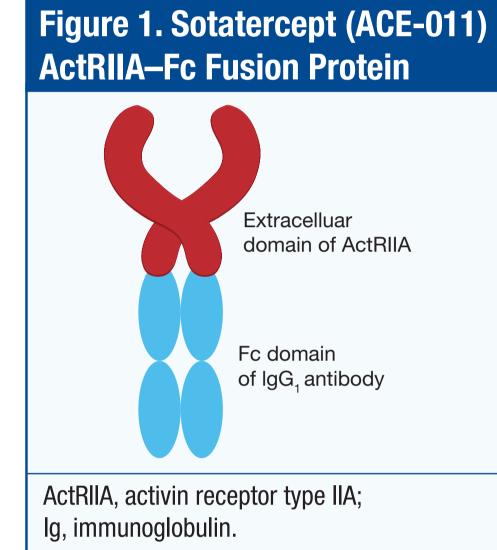
An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

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BACKGROUND

- Anemia, a hallmark of myelodysplastic syndromes (MDS), is challenging to treat, particularly after failure of erythropoiesisstimulating agents (ESAs)¹
- Sotatercept (ACE-011):
- Is a novel and first-in-class activin type IIA receptor fusion protein² (Figure 1) that acts on late-stage erythropoiesis to increase the release of mature erythrocytes into circulation^{3,4}
- Inhibits SMAD2/3 signaling³
 Acts via a mechanism distinct from erythropoietin
- Sotatercept stimulated erythropoiesis and significantly increased hemoglobin (Hb) levels in healthy volunteers,⁵ supporting its clinical development for the treatment of anemia in patients with lower-risk MDS



OBJECTIVE

 To determine a safe, tolerable, and effective dose of sotatercept in patients with anemia and International Prognostic Scoring System (IPSS)-defined Low- or Intermediate (Int)-1-risk MDS or non-proliferative chronic myelomonocytic leukemia (CMML)⁶

METHODS

Study Design

- This is a phase 2, open-label, dose-finding study; interim data are presented
- Patients received subcutaneous sotatercept at dose levels 0.1, 0.3, 0.5, or 1.0 mg/kg once every 3 weeks (Figure 2)

MDS, myelodysplastic syndromes; OS, overall survival; q3w, every 3 weeks; SC, subcutaneous

Key Eligibility Criteria

- IPSS-defined Low- or Int-1-risk MDS or non-proliferative CMML (white blood cell count < 13,000/µL)
- Anemia (defined as Hb level ≤ 9.0 g/dL requiring transfusion of ≥ 2 units of red blood cells [RBCs] in the 84 days prior to enrollment)
- No response, loss of response, or low chance of response to ESAs (reflected by serum erythropoietin > 500 mIU/mL)

Study Endpoints

- The primary efficacy endpoint was rate of erythroid hematologic improvement (HI-E) as defined by modified International Working Group (IWG) 2006 criteria⁷
- Secondary endpoints included rate of achievement of RBCtransfusion independence (TI) ≥ 56 days and safety

RESULTS

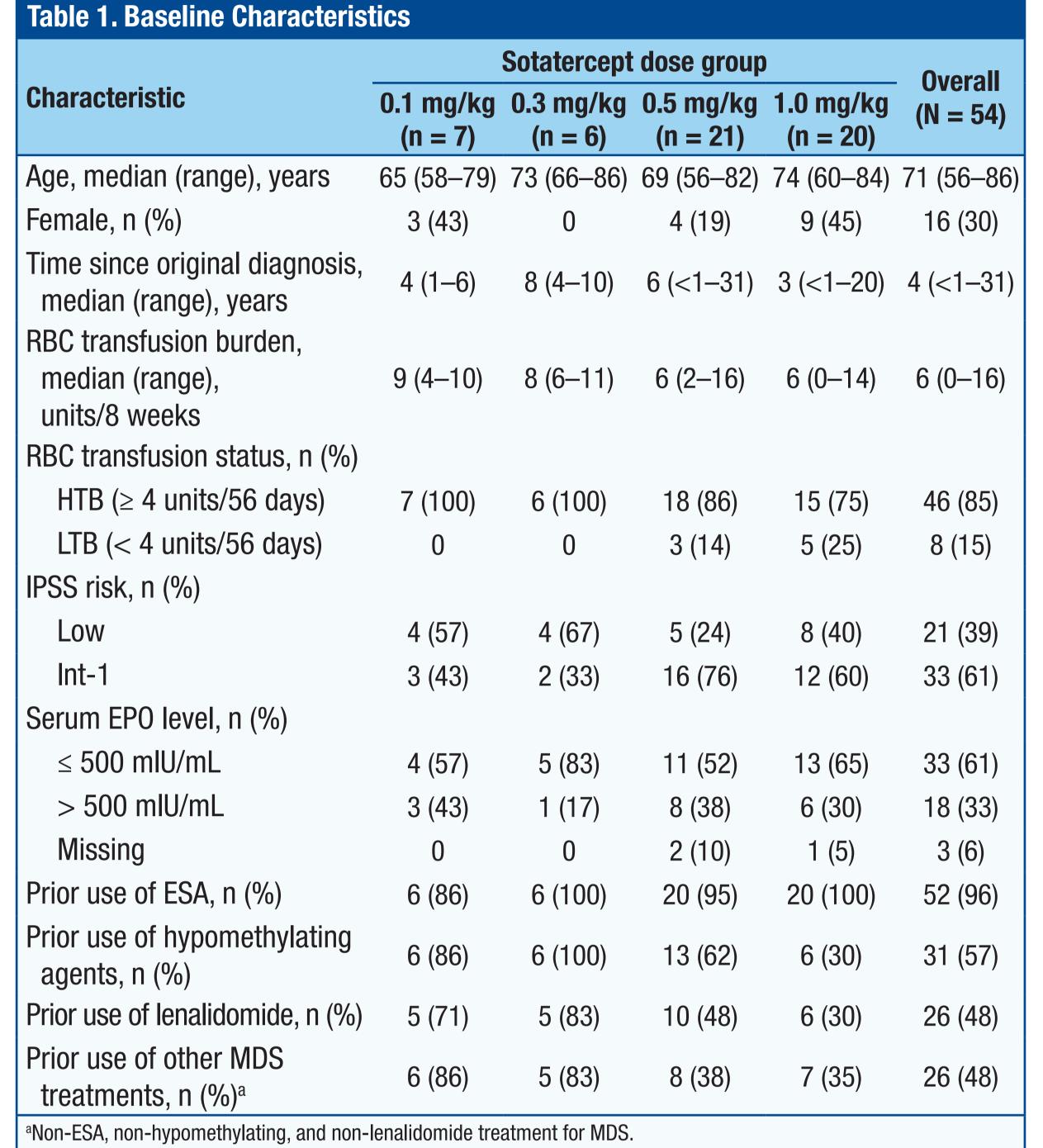
Baseline Characteristics

- As of May 22, 2014, a total of 54 MDS patients were enrolled
- Baseline characteristics are presented in Table 1
- 46 of 54 patients (85%) had a RBC transfusion burden of
 ≥ 4 units/56 days (high transfusion burden; HTB)
- 8 of 54 patients (15%) had a RBC transfusion burden of
 4 units/56 days (low transfusion burden; LTB)

Efficacy

- Of 53 patients evaluable for efficacy, HI-E (modified IWG 2006 criteria) was achieved in 24 patients (45%):
- 0.1 mg/kg: 0 patients (0%)
- 0.3 mg/kg: 4 patients (67%)0.5 mg/kg: 8 patients (40%)
- 1.0 mg/kg: 12 patients (60%)
- 1 patient in the 0.5 mg/kg dose group was excluded from efficacy analysis due to protocol violation

Figure 2. Study Design Part 1: Dose finding Sotatercept 0.1 mg/kg SC q3w Enroll ≤ 20 evaluable patients per dose level Sotatercept 0.3 mg/kg SC q3w Response Assess MDS Continue failure and OS Discontinue very 6 months up to Sotatercept 0.5 mg/kg SC q3w response 24 months after 5-8 following No response cycles of first treatmen Sotatercept 1.0 mg/kg SC q3w treatment Sotatercept 2.0 mg/kg SC q3w Part 2: Recommended dose (as determined by steering committee) in Part 1 carried over into Part 2 with enrollment of 15 additional patients



EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HTB, high transfusion burden; Int, Intermediate; IPSS, International Prognostic Scoring System; LTB, low transfusion burden; MDS, myelodysplastic syndromes; RBC, red blood cell.

HTB Patients

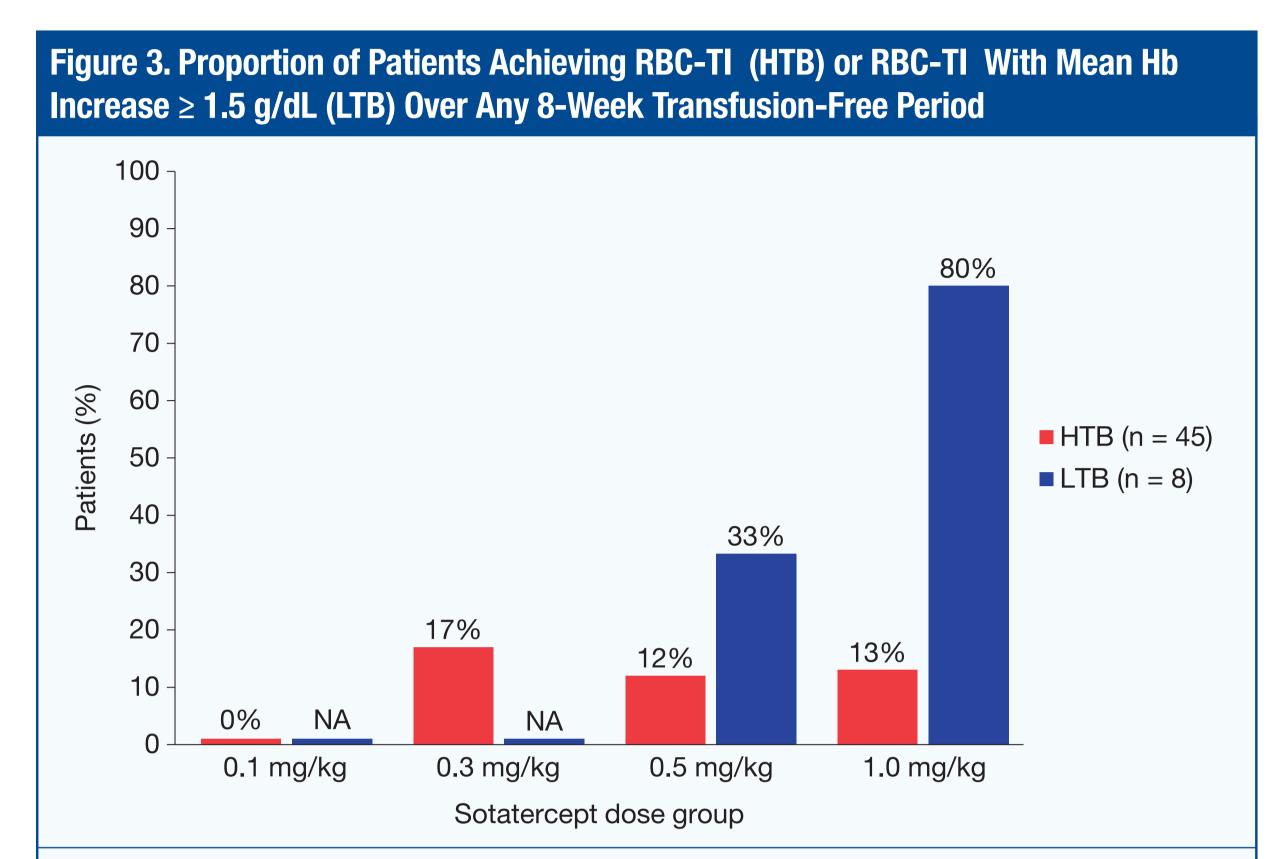
presented in Figure 4

- 19 of 45 HTB patients (42%) responded with a reduction in transfusion burden of ≥ 4 RBC units/56 days (Table 2)
- Duration of transfusion response appeared to be dose dependent
- 5 HTB patients (11%) achieved RBC-TI ≥ 56 days (Figure 3)
 An example of RBC-TI ≥ 56 days achieved in an individual HTB patient in the sotatercept 1.0 mg/kg dose group is
- Duration of RBC-TI ranged from 59 to 345+ days

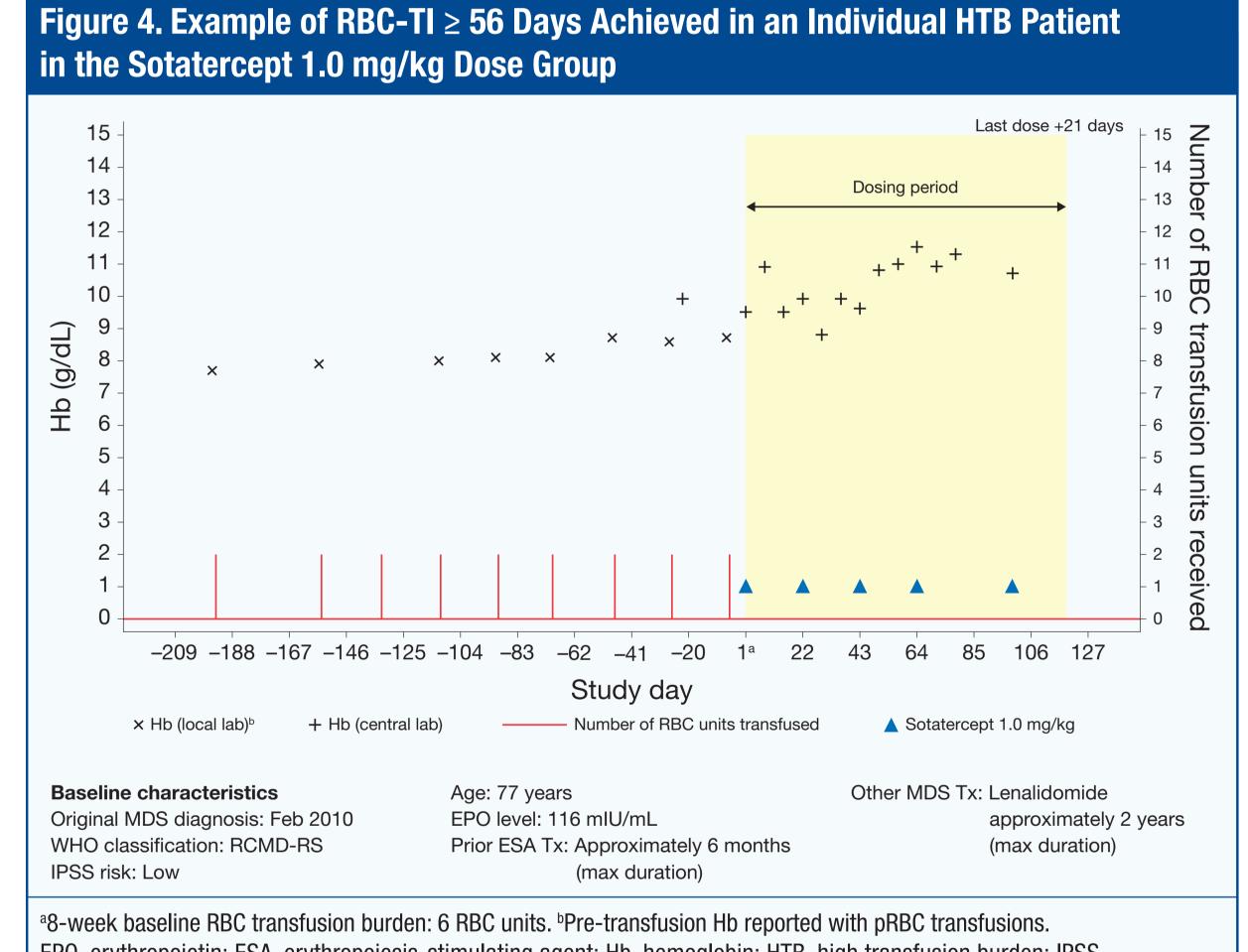
	Sotatercept dose group				Overall
	0.1 mg/kg (n = 7)	0.3 mg/kg (n = 6)	0.5 mg/kg (n = 17)	1.0 mg/kg (n = 15)	(N = 45)
Transfusion burden reduction ≥ 4 RBC units/56 days, n (%)	0	4 (67)	7 (41)	8 (53)	19 (42)
Duration of longest response, median (range), days	NA	68 (62–144)	150 (83–345+)	88 (62–154+)	106 (62–345+)
RBC-TI ≥ 56 days, n (%)	0	1 (17)	2 (12)	2 (13)	5 (11)

LTB Patients

- Over any 8-week transfusion-free period, 5 of 8 patients (63%) achieved both a mean Hb increase ≥ 1.5 g/dL sustained for ≥ 56 days and RBC-TI ≥ 56 days (Figure 3)
 Maximum mean Hb increases ranged from 1.9 to 4.4 g/dL
- Duration of RBC-TI ranged from 76 to 233+ days
- Patients with Hb levels > 11.0 g/dL were subject to dose delay as per protocol, which may have impacted duration of Hb increase



Hb, hemoglobin; HTB, high transfusion burden; LTB, low transfusion burden; NA, not applicable; RBC-TI, red blood cell transfusion independence.



^a8-week baseline RBC transfusion burden: 6 RBC units. ^bPre-transfusion Hb reported with pRBC transfusions. EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HTB, high transfusion burden; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; pRBC, packed RBC; RBC, red blood cell; RBC-TI, RBC transfusion independence; RCMD-RS, refractory cytopenia with multilineage dysplasia and ring sideroblasts; Tx, treatment; WHO, World Health Organization.

Changes in Platelet and Neutrophil Levels

- Overall, increases in platelet levels of $\geq 30 \times 10^9/L$ were observed for 7 of 11 patients with baseline platelet levels $< 100 \times 10^9/L$
 - Baseline platelet counts were missing for 2 patients
- Overall, increases in absolute neutrophil count (ANC) of $\geq 0.5 \times 10^9/L$ were observed in 5 of 5 patients with baseline ANC of $< 1.0 \times 10^9/L$
- Analysis of ANC and platelet hematologic improvement is ongoing

Safety

- Sotatercept was generally well tolerated (Table 3)
- 3 patients discontinued due to treatment-emergent adverse events considered suspected related to sotatercept: 1 patient with grade 2 hemolytic anemia; 1 patient with grade 3 hypertension; and 1 patient with grade 2 muscle weakness in the 0.3, 0.5, and 1.0 mg/kg dose groups, respectively

Table 3. Treatment-Emergent Adverse Events (TEAEs) Considered Suspected Related to Sotatercept Sotatercept dose group TEAE, n (%) Sotatercept dose group 0.1 mg/kg (n = 7) 0.3 mg/kg (n = 21) 1.0 mg/kg (n = 20) Overall (N = 54) Patients with \geq 1 TEAE 2 (29) 3 (50) 6 (29) 9 (45) 20 (37) TEAEs occurring in \geq 5% of patients Fatigue/asthenia* 0 0 3 (14) 4 (20) 7 (13) Headache 0 1 (17) 2 (10) 2 (10) 5 (9) Decreased appetite 0 0 2 (10) 2 (10) 4 (7) Nausea 0 0 3 (14) 1 (5) 4 (7) Dyspnea 0 0 2 (10) 1 (5) 3 (6)

b1 patient had grade 3 pain in both thighs; 1 patient had grade 3 hypertension; 1 patient had transformation to acute leukemia approximately 5.5 months after study treatment discontinuation (baseline WHO subtype: RAEB-1, end-of-treatment WHO subtype: RAEB-2). The investigator could not rule out a contributory role of sotatercept. RAEB, refractory anemia with excess blasts; WHO, World Health Organization.

CONCLUSIONS

Grade 3–4 TEAEs

- Sotatercept was well tolerated in lower-risk MDS patients at the dose levels tested
- Sotatercept showed promising evidence of clinical activity in both HTB and LTB lower-risk MDS patients who were anemic and previously treated with ESAs, lenalidomide, hypomethylating agents, and/or other MDS therapies
- In LTB patients, erythroid responses with sustained mean Hb level increases of ≥ 1.5 g/dL were observed in the majority of patients in the absence of RBC transfusions ≥ 56 days
- These data support further exploration of higher sotatercept dose levels; longer-term treatment is ongoing in both HTB and LTB lower-risk MDS patients

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