A Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Lower-Risk Myelodysplastic Syndromes or Non-Proliferative Chronic Myelomonocytic Leukemia and Anemia Requiring Transfusion

Rami Komrokji[1], Guillermo Garcia-Manero[2], Lionel Ades[3], Abderrahmane Laadem[4], Bond Vo[4], Thomas Prebet[5], Aspasia Stamatoullas[6], Thomas Boyd[7], Jacques Delaunay[8], David P. Steensma[9], Mikkael A. Sekeres[10], Odile Beyne-Rauzy[11], Jun Zou[4], Kenneth M. Attie[12], Matthew L. Sherman[12], Pierre Fenaux[3], Alan F. List[1]

[1]Department of Malignant Hematology, Moffitt Cancer Center, Tampa, FL, USA; [2]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [3]Service d'Hématologie Séniors, Hôpital St-Louis, Université Paris 7, Paris, France; [4]Celgene Corporation, Summit, NJ, USA; [5]Département d'Onco-Hématologie, Institut Paoli Calmettes, Marseille, France; [6]Service d'Hématologie, Centre Henri Becquerel, Rouen, France; [7]North Star Lodge Cancer Center, Yakima Valley Memorial Hospital, Yakima, WA, USA; [8]Service d'Hématologie Clinique, CHU de Nantes – Hôtel Dieu, Nantes, France; [9]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [10]Hematology and Oncology, Leukemia Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [11]Département d'Hématologie – Médecine Interne, Centre Hospitalier Universitaire Purpan Pavillion de Médecines, Toulouse, France; [12]Acceleron Pharma, Cambridge, MA, USA

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Faculty Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Celgene Corporation	X	X	X					

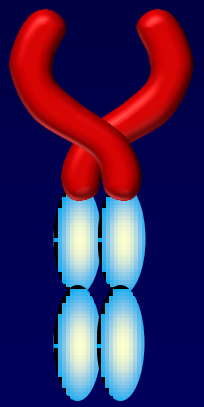
Off-Label Product Use

Will you be presenting or referencing off-label or investigational use of a therapeutic product?		
	No	
X	Yes, please specify:	Sotatercept (ACE-011) is an investigational agent being assessed for efficacy and safety in myelodysplastic syndromes

Background

- **Anemia, a hallmark of MDS, is challenging to treat, particularly after failure of ESAs[1]**
- **Sotatercept (ACE-011):**
  - **Is a novel and first-in-class ActRIIA fusion protein that acts on late-stage erythropoiesis to increase maturation and release of erythrocytes into circulation[2–4]**
  - **Inhibits SMAD2/3 signaling[3]**
  - **Acts via a mechanism distinct from EPO**

Sotatercept (ACE-011)
ActRIIA–Fc fusion protein



Extracellular domain of ActRIIA

Fc domain of IgG_1 antibody

ActRIIA, activin type IIA receptor fusion protein; EPO, erythropoietin; ESAs, erythropoiesis-stimulating agent; Ig, immunoglobulin.

1. Fenaux P, Adès L. Blood. 2013;121:4280-6.
2. Iancu-Rubin C, et al. Exp Hematol. 2013;41:155-66.
3. Carrancio S, et al. Br J Haematol. 2014;165:870-82.
4. Dussiot M, et al. Nat Med. 2014;20:398-407.

Background

- **Sotatercept stimulated erythropoiesis and significantly increased Hb levels in healthy volunteers,[1] supporting its clinical development for the treatment of anemia in patients with lower-risk MDS**

Hb, hemoglobin.

1. Sherman ML, et al. J Clin Pharmacol. 2013;53:1121-30.

Objective

- **To determine a safe, tolerable, and effective dose of sotatercept in anemic patients with IPSS[1] Low or Int-1-risk MDS or non-proliferative CMML[a]**

[a]No CMML patients recruited to-date; data presented are for MDS patients only.

CMML, chronic myelomonocytic leukemia; Int, intermediate;
IPSS, International Prognostic Scoring System.

1. Greenberg P, et al. Blood. 1997;89:2079-88.

Methods

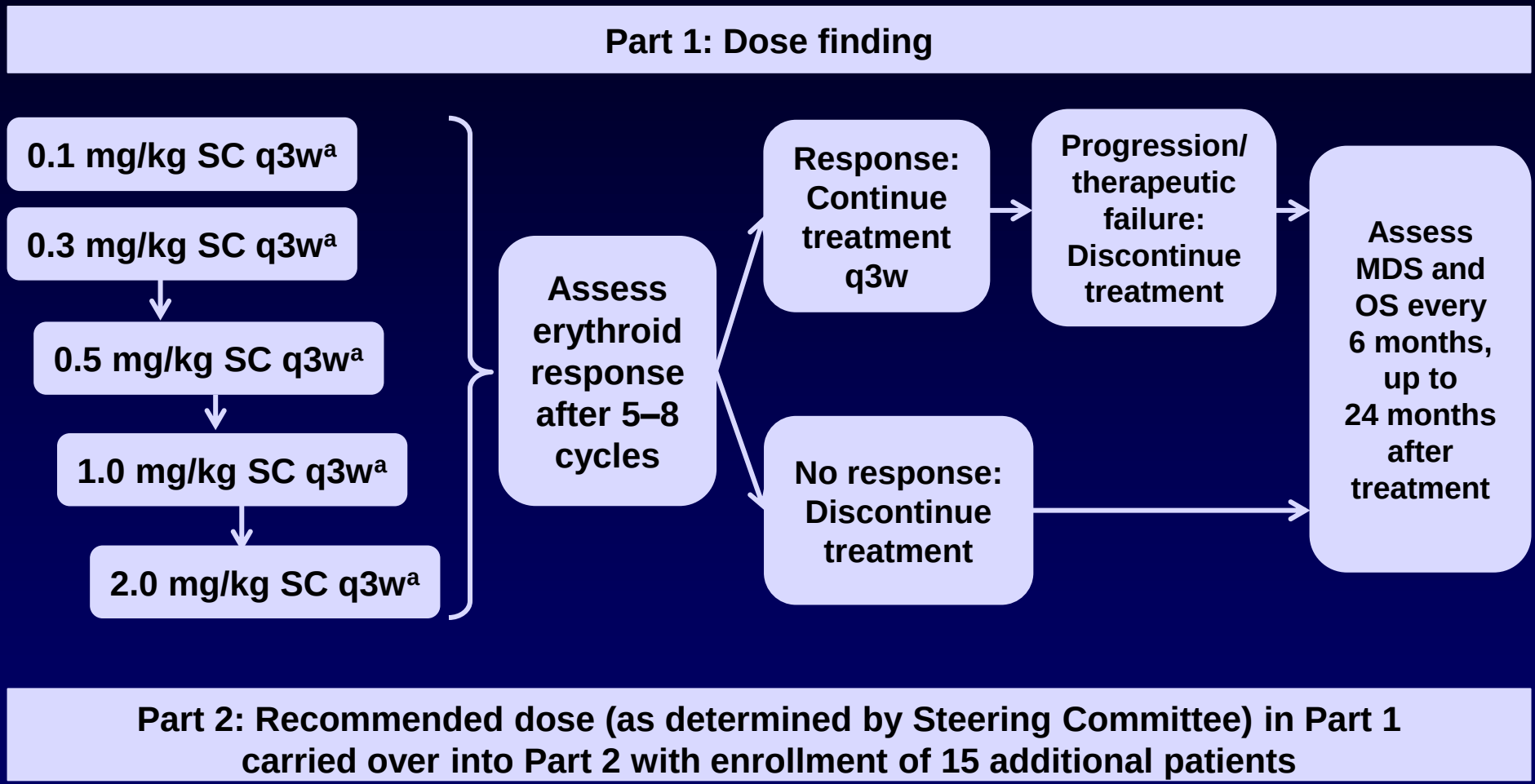
- This is an ongoing phase 2, open-label, dose-finding study
- Patients received SC sotatercept at dose levels 0.1, 0.3, 0.5, 1.0, or 2.0 mg/kg every 3 weeks
- Data as of February 4, 2015
- ClinicalTrials.gov Identifier: NCT01736683

SC, subcutaneous.

Methods: Eligibility Criteria

- **Eligible patients had:**
  - **IPSS-defined Low or Int-1-risk MDS**
  - **Anemia (defined as Hb level ≤ 9.0 g/dL requiring transfusion of ≥ 2 units of RBCs in the 12 weeks prior to enrollment)**
  - **No response, loss of response, or low chance of response to ESAs (reflected by serum EPO level > 500 mIU/mL)**
- **Those with a baseline RBC transfusion burden ≥ 4 units/8 weeks were classed as high-transfusion burden (HTB) patients**
- **Those with a baseline RBC transfusion burden < 4 units/8 weeks were classed as low-transfusion burden (LTB) patients**

Methods: Study Design



[a]Max of 20 evaluable patients enrolled per dose level.
OS, overall survival; q3w, every 3 weeks.

Methods: Study Endpoints

- **Efficacy was assessed by HI-E (defined using modified IWG 2006 criteria[1]):**
  - **HTB patients: reduction in RBC transfusion burden of ≥ 4 units/8 weeks**
  - **LTB patients: mean Hb increase ≥ 1.5 g/dL sustained for ≥ 8 weeks**
- **Secondary endpoints included rate of RBC transfusion independence (RBC-TI) ≥ 8 weeks and safety**
  - **Adverse events were graded according to NCI-CTCAE version 4.0**

HI-E, erythroid hematologic improvement; IWG, International Working Group; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

1. Cheson BD, et al. Blood. 2006;108:419-25.

Results: Baseline Characteristics

Characteristic	Sotatercept dose group					Overall (N = 59)
	0.1 mg/kg (n = 7)	0.3 mg/kg (n = 6)	0.5 mg/kg (n = 21)	1.0 mg/kg (n = 20)	2.0 mg/kg (n = 5)	
Age, median (range), years	65 (58–79)	73 (66–86)	69 (56–82)	74 (60–84)	73 (47–81)	71 (47–86)
Female, n (%)	3 (43)	0	4 (19)	9 (45)	4 (80)	20 (34)
Time since MDS diagnosis, median (range), years	4 (1–6)	8 (4–10)	6 (< 1–31)	3 (< 1–20)	2 (< 1–5)	4 (< 1–31)
RBC transfusion burden, median (range), units/8 weeks	9 (4–10)	8 (6–11)	6 (2–16)	6 (0–10)	4 (3–8)	6 (0–16)
RBC transfusion status, n (%)						
HTB (≥ 4 units/8 weeks)	7 (100)	6 (100)	18 (86)	15 (75)	4 (80)	50 (85)
LTB (< 4 units/8 weeks)	0	0	3 (14)	5 (25)	1 (20)	9 (15)
IPSS risk, n (%)						
Low	4 (57)	4 (67)	5 (24)	7 (35)	0	20 (34)
Int-1	3 (43)	2 (33)	16 (76)	13 (65)	5 (100)	39 (66)

Results: Baseline Characteristics

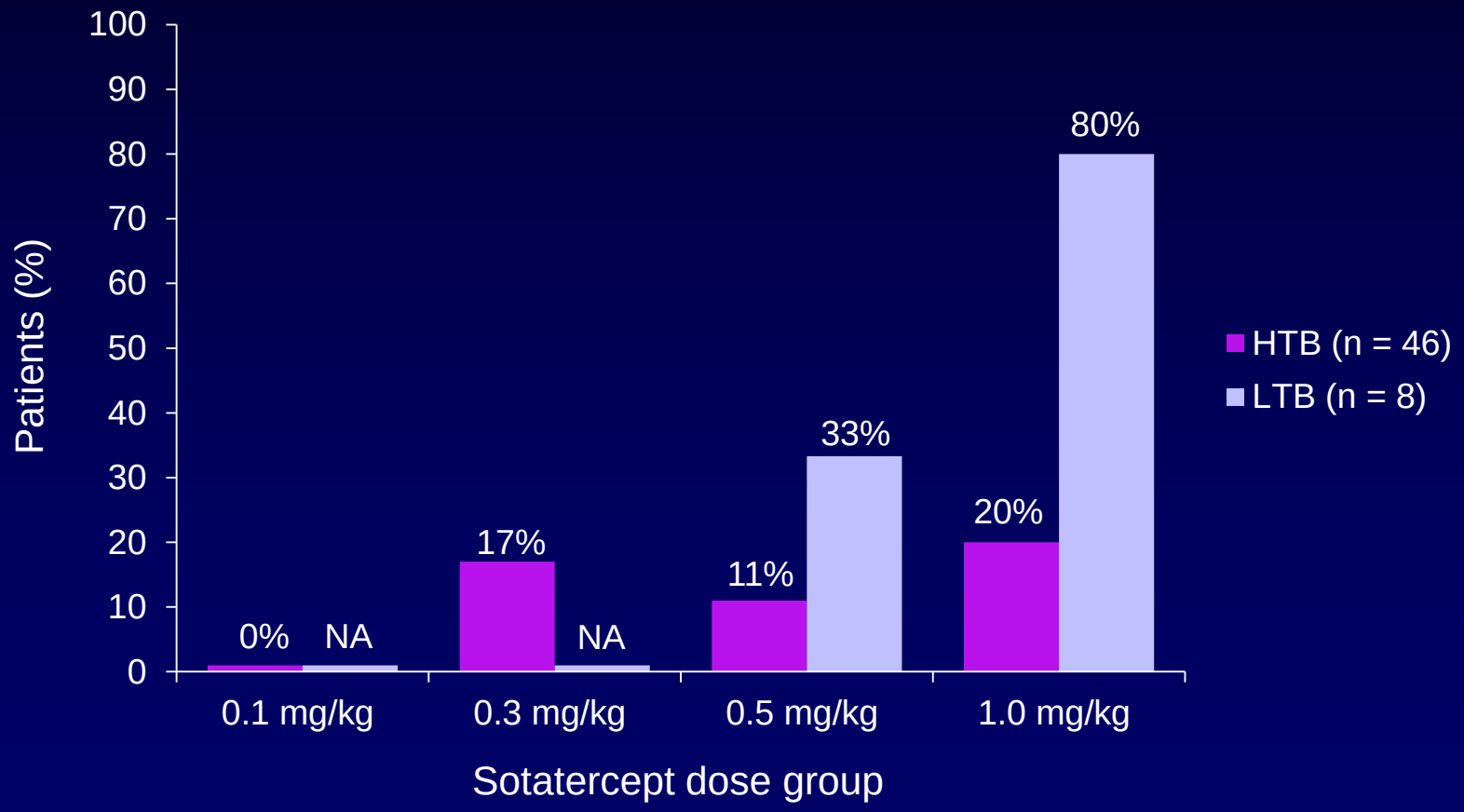
Characteristic	Sotatercept dose group					Overall (N = 59)
	0.1 mg/kg (n = 7)	0.3 mg/kg (n = 6)	0.5 mg/kg (n = 21)	1.0 mg/kg (n = 20)	2.0 mg/kg (n = 5)	
Serum EPO level, n (%)						
≤ 500 mIU/mL	4 (57)	5 (83)	11 (52)	13 (65)	2 (40)	35 (59)
> 500 mIU/mL	3 (43)	1 (17)	8 (38)	6 (30)	1 (20)	19 (32)
Missing	0	0	2 (10)	1 (5)	2 (40)	5 (9)
Prior use of ESA, n (%)	6 (86)	6 (100)	20 (95)	20 (100)	4 (80)	56 (95)
Prior use of hypomethylating agents, n (%)	6 (86)	6 (100)	13 (62)	6 (30)	0	31 (53)
Prior use of lenalidomide, n (%)	5 (71)	5 (83)	10 (48)	6 (30)	1 (20)	27 (46)
Prior use of other MDS treatments, n (%)	6 (86)	5 (83)	8 (38)	7 (35)	0	26 (44)

Results: Overall

- **Of 54 patients evaluable for efficacy, 24 (44%) achieved HI-E:**
  - **Sotatercept 0.1 mg/kg: 0 of 7 patients**
  - **Sotatercept 0.3 mg/kg: 4 of 6 patients (67%)**
  - **Sotatercept 0.5 mg/kg: 10 of 21 patients (48%)**
  - **Sotatercept 1.0 mg/kg: 10 of 20 patients (50%)**
- **Efficacy results for sotatercept 2.0 mg/kg dose group are not included due to limited data**

Results: Overall

Achievement of RBC-TI in HTB patients or RBC-TI with mean Hb increase ≥ 1.5 g/dL in LTB patients over any 8-week period



NA, not applicable.

Results: HTB Patients

- **HI-E was achieved in 40% of HTB patients in the sotatercept 1.0 mg/kg dose group**

	Sotatercept dose group			
	0.1 mg/kg (n = 7)	**0.3 mg/kg (n = 6)**	**0.5 mg/kg (n = 18)**	**1.0 mg/kg (n = 15)**
HI-E (RBC transfusion burden reduction ≥ 4 units/8 weeks), n (%)	0	4 (67)	9 (50)	6 (40)
Duration of longest response, median (range), days	NA	68 (62–173)	107 (56–540+)	123 (62–353+)
RBC-TI ≥ 8 weeks, n (%)	0	1 (17)	2 (11)	3 (20)
Duration of RBC-TI ≥ 8 weeks, days	NA	124	154, 540+	59, 78, 353+

Results: LTB Patients

- Of 8 LTB patients, 5 (63%) achieved RBC-TI ≥ 8 weeks and a mean Hb increase of ≥ 1.5 g/dL sustained for ≥ 8 weeks
  - Median duration of RBC-TI was 367+ days (range 175–472+ days)
- Among responders, mean Hb increases ranged from 1.7 to 3.6 g/dL; median Hb increase was 2.0 g/dL
  - Patients with Hb levels > 11.0 g/dL were subject to dose delay per protocol, which may have impacted assessment of duration of Hb increase

Results: HI-E by RS Status

- **HI-E was achieved in 56% of RS-positive (defined as ≥ 15% RS) and 20% of RS-negative (defined as < 15% RS) patients in the sotatercept 1.0 mg/kg dose group**

RS status[a]	HI-E by sotatercept dose group and RS status, n/N (%)			
	0.1 mg/kg	0.3 mg/kg	0.5 mg/kg	1.0 mg/kg
RS-positive[b]	0/6	4/4 (100)	5/9 (56)	5/9 (56)
RS-negative[c]	0/1	0/2	0/2	1/5 (20)

[a]RS status is from baseline, where available; RS status was unknown for 16 patients.
[b]Defined as ≥ 15% RS.
[c]Defined as < 15% RS.

RS, ring sideroblasts.

Results: Changes in Platelet Level and ANC

- **Increases in platelet levels of ≥ 30 × 10^9/L were observed for 7 of 11 patients with baseline platelet levels < 100 × 10^9/L**
- **Increases in ANC of ≥ 0.5 × 10^9/L were observed in all patients (5 of 5) with a baseline ANC of < 1.0 × 10^9/L**

ANC, absolute neutrophil count.

Results: Common Adverse Events

	Sotatercept dose group					Overall (N = 59)
	0.1 mg/kg (n = 7)	0.3 mg/kg (n = 6)	0.5 mg/kg (n = 21)	1.0 mg/kg (n = 20)	2.0 mg/kg (n = 5)	
Patients with ≥ 1 TEAE	6 (86)	3 (50)	20 (95)	19 (95)	4 (80)	52 (88)
TEAEs ≥ 10% of patients						
Fatigue/asthenia[a]	0	1 (17)	10 (48)	12 (60)	1 (20)	24 (41)
Peripheral edema	2 (29)	2 (33)	4 (19)	4 (20)	0	12 (20)
Diarrhea	0	2 (33)	5 (24)	3 (15)	2 (40)	12 (20)
Nausea	0	1 (17)	4 (19)	4 (20)	1 (20)	10 (17)
Constipation	0	1 (17)	6 (29)	2 (10)	0	9 (15)
Vomiting	0	1 (17)	2 (10)	3 (15)	0	6 (10)
Decreased appetite	0	0	3 (14)	3 (15)	0	6 (10)
Pain in extremity	0	1 (17)	2 (10)	3 (15)	0	6 (10)
Headache	3 (43)	1 (17)	2 (10)	2 (10)	1 (20)	9 (15)
Dizziness	1 (14)	2 (33)	1 (5)	1 (5)	1 (20)	6 (10)
Cough	1 (14)	1 (17)	2 (10)	5 (25)	0	9 (15)
Dyspnea	0	1 (17)	4 (19)	2 (10)	0	7 (12)
Grade 3–4 TEAEs[b]	1 (14)	1 (17)	9 (43)	5 (25)	2 (40)	18 (31)

[a]Pooled incidence of fatigue and asthenia. [b]Treatment-related AEs were reported in 3 patients: 1 patient with grade 3 pain in extremity, 1 patient with grade 3 hypertension, and 1 patient with grade 4 acute myeloid leukemia.
TEAE, treatment-emergent adverse event.

Results: Patient Discontinuations

- 4 patients discontinued due to suspected treatment-related adverse events, 1 each with:
  - Grade 2 hemolytic anemia in the sotatercept 0.3 mg/kg group
  - Grade 2 hypertension in the sotatercept 0.5 mg/kg group
  - Grade 2 muscular weakness in the sotatercept 1.0 mg/kg group
  - Grade 2 increased blood pressure with grade 2 diarrhea in the sotatercept 2.0 mg/kg group

Conclusions

- Sotatercept was well tolerated in lower-risk MDS patients
- Sotatercept showed clinical activity in this cohort of heavily pre-treated, anemic, lower-risk MDS patients who were refractory to prior ESAs
- HI-E was achieved in 40% of HTB patients treated with sotatercept 1.0 mg/kg, and sustained mean Hb level increases ≥ 1.5 g/dL with RBC-TI ≥ 8 weeks were observed in a majority of LTB patients

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