SUPPLEMENTARY APPENDIX

Sotatercept, a novel transforming growth factor β ligand trap, improves anemia in β-thalassemia: a phase II, open-label, dose-finding study

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Supplemental Data

Methods

Exclusion criteria

Exclusion criteria included major cardiac problems, erythropoiesis-stimulating agent use ≤28 days prior to enrollment, history of grade ≥3 thromboembolic events, and initiation of, or change in, hydroxyurea treatment ≤1 year prior to enrollment.

Study design

Patients with transfusion-dependent β-thalassemia (TDT) and patients with non-transfusion-dependent β-thalassemia (NTDT) were assigned alternately to receive either 0.1 mg/kg or 0.3 mg/kg sotatercept (Figure S1), with the first TDT patient enrolled receiving 0.1 mg/kg and the first NTDT patient enrolled receiving 0.3 mg/kg. Sotatercept was provided as a lyophilized powder in labeled, rubber-stoppered glass vials, which was reconstituted with water for injection prior to administration. Each dose was administered by subcutaneous injection in the upper arm, abdomen, or thigh once every 21 days. Higher dose levels were opened to enrollment sequentially if ≤1 of 6 patients experienced a dose-limiting toxicity (DLT) ≥21 days after the last patient in that cohort received his or her first dose of sotatercept. A potential recommended dose (PRD), defined as the highest dose level at which ≤1 of 6 patients experienced a DLT, was to be determined based on the first 3 doses of sotatercept administered. Once the PRD was established, an additional 10 patients were planned to be enrolled at the PRD level (Figure S1). If the previous dose level studied exceeded the PRD, doses were reduced as required. The actual recommended dose was to be defined and assessed after review of the safety and efficacy data. A DLT was defined as any 1 or more of the following: grade ≥3 hypertension (according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], version 4.0 available at

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm), hemoglobin (Hb) >14 g/dL (within 7 days posttransfusion) sustained for 1 week, or any NCI-CTCAE version 4.0 grade ≥3 toxicity related to sotatercept.

Patients were scheduled to participate in the study for approximately 9 months, up to a maximum of 27 months. Patients were enrolled to receive up to 6 doses of sotatercept with the treatment period planned to last approximately 4 to 5 months, up to a maximum of 22 months, dependent on dose delays. Patients receiving 6 doses of sotatercept, who showed signs of efficacy with no dose delay or a <12-week delay between each dose, could continue treatment for ≤22 months (subject to investigator discretion). Upon completion of the main treatment phase, any patient who demonstrated clinical benefit, as assessed by the investigator, could continue receiving treatment under the “long-term treatment period”, up to a maximum of 3 years. The posttreatment follow-up period was 112 days from the last dose of sotatercept. Dose delays were defined as a dose not administered >4 days from the planned dosing day due to Hb >12.5 g/dL, and/or hematocrit >40%, and/or grade ≥2 hypertension. Patients who discontinued prior to receiving at least 6 doses of sotatercept continued into the posttreatment follow-up period. Patients who did not exhibit any sign of efficacy at the primary assigned dose level and who completed at least 3 doses could be dose-escalated to the highest open dose level. Patients who showed intermittent signs of efficacy at the primary assigned dose level (including reduction in transfusion burden or intermittent Hb increase ≥1 g/dL compared with mean pretreatment Hb values but with mean on-treatment increase <1 g/dL over the previous 3 doses) could be dose-escalated to the next higher open dose level. Patients who showed signs of efficacy at the primary assigned dose level but lost the response during the treatment period could be dose-escalated to the next higher open dose level. Intrapatient dose escalation was planned to be carried out once over the whole treatment period. However, after safety and efficacy data review, the steering committee could allow dose escalation following special

intrapatient dose-escalation requests such as, but not limited to, patients who had been dose-escalated once but lost the response to treatment.

During the study treatment period and the follow-up period, concomitant blood transfusions could be given if the patient's Hb fell below the mean Hb value calculated based on the patient's transfusion history record 168 days prior to study day 1. All transfusion decisions were at investigator discretion and per local practice. In order to see a rapid effect of sotatercept without potential confounding caused by red blood cell (RBC) transfusions, the first dose of sotatercept should have been administered 7-17 days after the last transfusion prior to patient enrollment (study day 1). For all subsequent doses, if the next planned RBC transfusion was to be administered on the same day as sotatercept, sotatercept administration should have occurred at least 24 hours after the RBC transfusion.

Statistical analyses

Demographics and baseline characteristics were analyzed by assigned dose level for the safety population; baseline values were the last values collected on or before the start of study therapy. Dose reductions/interruptions were summarized by cohort and assigned dose level, including patients experiencing ≥1 dose reduction/interruption and time to first dose reduction/interruption.

All efficacy analyses were presented by assigned dose level of sotatercept. Descriptive statistics such as mean, minimum, median, maximum, and sample size were used to describe transfusion burden at baseline and during treatment. Changes in transfusion burden from baseline to on-treatment Hb values prior to each RBC unit transfusion were summarized for

transfusions received prior to sotatercept treatment and during sotatercept treatment, if applicable.

Transfusion burden reduction from baseline to treatment was analyzed by dose level, based on the RBC transfusion-dependent population. Transfusion burden at baseline was defined as the total number of RBC units transfused within 168 days (24 weeks) prior to the first dose of study therapy. Transfusion burden during treatment was defined as the total number of RBC units transfused during the treatment divided by the treatment duration and multiplied by 168 days. The result was a 168-day transfusion burden average.

Hb levels were analyzed for both TDT and NTDT patients. Baseline Hb level was determined as the last Hb level measured prior to the first dose of sotatercept. Mean pretreatment Hb level was calculated from all Hb levels collected for a period of 168 days prior to study day 1. The proportion of patients with erythroid response, defined as transfusion-free with a Hb increase from baseline of ≥1.0 or ≥1.5 g/dL, was measured over a continuous 12-week rolling interval during the treatment period.

Safety analyses were performed on the safety population. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs were summarized by worst severity grade, system organ class, and preferred term. Treatment-emergent AEs leading to death or treatment discontinuation, those classified by the NCI CTCAE, version 4.0 as grade ≥3, those related to investigational product, and serious treatment-emergent AEs were summarized separately.

Clinical laboratory results were summarized descriptively by treatment group. Clinically significant hematologic and non-hematologic laboratory abnormalities were listed and summarized according to the NCI CTCAE, version 4.0, by treatment group.

Sample size and patient allocation

This was a dose-finding study; sample size depended on the dose levels evaluated. Up to a maximum of 65 patients were planned for enrollment into the study, including approximately 10 patients who were planned for enrollment into an extended cohort to evaluate the safety and efficacy end points at the PRD level.

A unique multi-digit patient identification number was manually assigned by site staff to each patient entering the treatment period. The two starting doses, 0.1 mg/kg and 0.3 mg/kg, were opened for enrollment in parallel, with TDT and NTDT patients assigned alternately to each dose level.

Study locations

Hôpital Henri Mondor, Creteil, France
Hôpital Necker-Enfants Malades, Paris, France
Laikon General Hospital, Athens, Greece
Universita degli Studi Cagliari, Cagliari, Italy
Ospedale Galliera, Genoa, Italy
Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico, Milan, Italy
University College London Cancer Institute, London, United Kingdom

IRB sites and approval dates

Name of IRB	Address	Date of Approval
CPP Ile-de-France II Ethics Committee	149, rue de Sevres 75743 Paris France Cedex 15 Carre Necker- Porte N2	Sep 27, 2017
London Central Research Ethics Committee	Health Research Authority Ground Floor, Skipton House 80 London Rd. London SE1 6LH United Kingdom	Aug 02, 2017
Regional Ethics Committee of Liguria	Largo Rosanna Benzi, 10 16132 Genoa Italy	Aug 10, 2017
Ethics Committee - Milano Area 2	Via Francesco Sforza, 28 20122 Milano Italy	Jul 05, 2017
Independent Ethics Committee of Azienda Ospedaliera Universitaria Di Cagliari	Via Ospedale, 54 09124 Cagliari Italy	Nov 27, 2017
National Ethics Committee	284 Mesogeion Ave. 15562 Cholargos Athens Greece	Aug 02, 2017
Scientific Council of LAIKO General Hospital of Athens	17 Ag. Thoma str. 11527 Athens Greece	Aug 10, 2017

Table S1. Incidence of treatment-emergent AEs of any grade; AEs occurring in ≥5% of sotatercept-treated patients reported overall.

AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Patients with ≥1 AE	8 (100)	9 (100)	8 (100)	12 (100)	9 (100)	46 (100)
Arthralgia	3 (38)	3 (33)	6 (75)	6 (50)	1 (11)	21 (46)
Asthenia/fatigue	4 (50)	1 (11)	5 (63)	6 (50)	3 (33)	20 (44)
Headache	0	4 (44)	4 (50)	9 (75)	1 (11)	23 (50)
Bone pain	3 (38)	3 (33)	4 (50)	3 (25)	4 (44)	18 (39)
Back pain	2 (25)	2 (22)	3 (38)	3 (25)	3 (33)	16 (35)
Cough	1 (13)	2 (22)	4 (50)	3 (25)	2 (22)	16 (35)
Pyrexia	1 (13)	5 (56)	1 (13)	3 (25)	4 (44)	15 (33)
Oropharyngeal pain	3 (38)	1 (11)	2 (25)	3 (25)	1 (11)	14 (30)
Pain in extremity	3 (38)	0	3 (38)	2 (17)	2 (22)	12 (26)
Hypertension	0	0	3 (38)	3 (25)	2 (22)	12 (26)
Dizziness	0	1 (11)	3 (38)	2 (17)	0	11 (24)

AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Nausea	0	1 (11)	3 (38)	3 (25)	1 (11)	10 (22)
Myalgia	0	2 (22)	3 (38)	2 (17)	1 (11)	10 (22)
Upper abdominal pain	2 (25)	3 (33)	1 (13)	3 (25)	0	9 (20)
Influenza-like illness	1 (13)	3 (33)	2 (25)	1 (8)	0	8 (17)
Rhinitis	1 (13)	1 (11)	4 (50)	1 (8)	0	8 (17)
Neck pain	0	0	2 (25)	4 (33)	0	8 (17)
Upper respiratory tract infection	0	2 (22)	3 (38)	1 (8)	1 (11)	7 (15)
Epistaxis	0	0	0	2 (17)	3 (33)	7 (15)
Diarrhea	0	1 (11)	0	2 (17)	0	6 (13)
Musculoskeletal pain	0	2 (22)	1 (13)	2 (17)	0	6 (13)
Toothache	0	1 (11)	1 (13)	1 (8)	1 (11)	6 (13)
Increased alanine aminotransferase	1 (13)	1 (11)	1 (13)	1 (8)	1 (11)	5 (11)
Nasopharyngitis	1 (13)	0	2 (25)	1 (8)	0	5 (11)
Sinusitis	0	1 (11)	2 (25)	0	1 (11)	5 (11)

AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Hypotension	2 (25)	0	2 (25)	0	0	5 (11)
Influenza	0	2 (22)	1 (13)	1 (8)	0	5 (11)
Amenorrhea	0	1 (11)	0	2 (17)	0	5 (11)
Lower abdominal pain	1 (13)	1 (11)	0	2 (17)	0	4 (9)
Oral herpes	1 (13)	2 (22)	0	0	0	4 (9)
Nasal congestion	0	2 (22)	0	1 (8)	0	4 (9)
Teething	0	2 (22)	1 (13)	0	0	4 (9)
Tinnitus	0	1 (11)	0	1 (8)	1 (11)	4 (9)
Musculoskeletal chest pain	0	0	0	2 (17)	0	4 (9)
Musculoskeletal stiffness	0	0	1 (13)	1 (8)	0	4 (9)
Pharyngitis	1 (13)	0	0	0	1 (11)	4 (9)
Vomiting	0	0	1 (13)	1 (8)	0	4 (9)
Dysuria	0	1 (11)	1 (13)	1 (8)	0	3 (7)
Dyspepsia	0	1 (11)	0	1 (8)	1 (11)	3 (7)

AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Increased aspartate aminotransferase	0	1 (11)	0	1 (8)	1 (11)	3 (7)
Tachycardia	0	2 (22)	0	0	1 (11)	3 (7)
Abdominal pain	0	0	1 (13)	1 (8)	0	3 (7)
Escherichia urinary tract infection	0	0	0	0	2 (22)	3 (7)
Sciatica	0	1 (11)	0	1 (8)	0	3 (7)
Somnolence	1 (13)	0	0	1 (8)	0	3 (7)
Local swelling	1 (13)	0	1 (13)	0	0	3 (7)
Skin ulcer	1 (13)	0	1 (13)	0	0	3 (7)
Fall	0	1 (11)	1 (13)	0	0	3 (7)
Posttraumatic pain	0	0	2 (25)	0	0	3 (7)
Nephrolithiasis	0	1 (11)	0	0	1 (11)	3 (7)
Extramedullary hemopoiesis	0	0	0	0	2 (22)	3 (7)
Seasonal allergy	0	0	0	0	1 (11)	3 (7)
Decreased appetite	0	0	1 (13)	1 (8)	0	3 (7)

AEs in each dose cohort are presented prior to intrapatient dose escalation. Total AEs are presented post-intrapatient dose escalation. AE: adverse event.

Table S2. Incidence of serious AEs among sotatercept-treated patients.

Serious AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Patients with ≥1 serious AE	2 (25)	1 (11)	1 (13)	1 (8)	1 (11)	6 (13)
Bacterial prostatitis	0	0	0	1 (8)	0	1 (2)
Pharyngotonsillitis	0	1 (11)	0	0	0	1 (2)
Subcutaneous abscess	0	1 (11)	0	0	0	1 (2)
Pyrexia	0	1 (11)	0	0	0	1 (2)
Lumbar vertebral fracture	0	0	1 (13)	0	0	1 (2)
Bone pain	1 (13)	0	0	0	0	1 (2)
Syncope	0	0	0	0	1 (11)	1 (2)
Superficial thrombophlebitis	1 (13)	0	0	0	0	1 (2)

AEs in each dose cohort are presented prior to intrapatient dose escalation. Total AEs are presented post-intrapatient dose escalation. AE: adverse event.

Table S3. Incidence of grade 3-4 treatment-emergent AEs among sotatercept-treated patients.

Grade 3-4 treatment-emergent AEs, n (%)	Sotatercept dose (data presented prior to intrapatient dose escalation)					Overall (data presented post-intrapatient dose escalation) (N=46)
	0.1 mg/kg (n=8)	0.3 mg/kg (n=9)	0.5 mg/kg (n=8)	0.75 mg/kg (n=12)	1.0 mg/kg (n=9)	
Patients with ≥1 grade 3-4 AE	1 (13)	1 (11)	1 (13)	4 (33)	2 (22)	9 (20)
Hypertension	0	0	0	2 (17)	0	2 (4)
Anemia	1 (13)	0	0	1 (8)	0	2 (4)
Bone pain	1 (13)	0	0	0	0	1 (2)
Alloimmunization	0	0	0	0	1 (11)	1 (2)
Asthenia/fatigue	0	0	0	1 (8)	0	1 (2)
Ventricular extrasystoles	0	0	1 (13)	0	0	1 (2)
Bacterial prostatitis	0	0	0	1 (8)	0	1 (2)
Hemolytic transfusion reaction	0	0	0	0	1 (11)	1 (2)
Increased fetal hemoglobin	0	0	0	0	1 (11)	1 (2)
Syncope	0	0	0	0	1 (11)	1 (2)
Amenorrhea	0	1 (11)	0	0	0	1 (2)

AEs in each dose cohort are presented prior to intrapatient dose escalation. Total AEs are presented post-intrapatient dose escalation. AE: adverse event.

Table S4. Incidence of treatment-emergent AEs in NTDT and TDT patients treated with sotatercept; treatment-emergent AEs occurring in ≥5% patients overall.

AEs, n (%)	TDT (n=16)	NTDT (n=30)	Overall (N=46)
Patients with ≥1 AE	16 (100)	30 (100)	46 (100)
Headache	7 (44)	16 (53)	23 (50)
Arthralgia	7 (44)	14 (47)	21 (46)
Asthenia/fatigue	9 (56)	11 (37)	20 (44)
Bone pain	10 (63)	8 (27)	18 (39)
Back pain	9 (56)	7 (23)	16 (34)
Cough	4 (25)	12 (40)	16 (35)
Pyrexia	5 (31)	10 (33)	15 (33)
Oropharyngeal pain	4 (25)	10 (33)	14 (30)
Pain in extremity	5 (31)	7 (23)	12 (26)
Hypertension	4 (25)	8 (27)	12 (26)
Dizziness	4 (25)	7 (23)	11 (24)
Nausea	4 (25)	6 (20)	10 (22)
Myalgia	4 (25)	6 (20)	10 (22)

AEs, n (%)	TDT (n=16)	NTDT (n=30)	Overall (N=46)
Upper abdominal pain	4 (25)	5 (17)	9 (20)
Influenza-like illness	3 (19)	5 (17)	8 (17)
Rhinitis	2 (13)	6 (20)	8 (17)
Neck pain	1 (6)	7 (23)	8 (17)
Upper respiratory tract infection	1 (6)	6 (20)	7 (15)
Epistaxis	3 (19)	4 (13)	7 (15)
Musculoskeletal pain	2 (13)	4 (13)	6 (13)
Diarrhea	1 (6)	5 (17)	6 (13)
Toothache	4 (25)	2 (7)	6 (13)
Influenza	2 (13)	3 (10)	5 (11)
Nasopharyngitis	2 (13)	3 (10)	5 (11)
Increased alanine aminotransferase	2 (13)	3 (10)	5 (11)
Hypotension	1 (6)	4 (13)	5 (11)
Sinusitis	3 (19)	2 (7)	5 (11)
Amenorrhea	1 (6)	4 (13)	5 (11)
Teething	2 (13)	2 (7)	4 (9)

AEs, n (%)	TDT (n=16)	NTDT (n=30)	Overall (N=46)
Nasal congestion	3 (19)	1 (3)	4 (9)
Lower abdominal pain	0	4 (13)	4 (9)
Tinnitus	1 (6)	3 (10)	4 (9)
Oral herpes	2 (13)	2 (7)	4 (9)
Vomiting	0	4 (13)	4 (9)
Pharyngitis	3 (19)	1 (3)	4 (9)
Musculoskeletal chest pain	1 (6)	3 (10)	4 (9)
Musculoskeletal stiffness	0	4 (13)	4 (9)
Tachycardia	1 (6)	2 (7)	3 (7)
Dysuria	1 (6)	2 (7)	3 (7)
Increased aspartate aminotransferase	1 (6)	2 (7)	3 (7)
Dyspepsia	2 (13)	1 (3)	3 (7)
Escherichia urinary tract infection	0	3 (10)	3 (7)
Local swelling	0	3 (10)	3 (7)
Sciatica	0	3 (10)	3 (7)

AEs, n (%)	TDT (n=16)	NTDT (n=30)	Overall (N=46)
Somnolence	2 (13)	1 (3)	3 (7)
Abdominal pain	0	3 (10)	3 (7)
Nephrolithiasis	1 (6)	2 (7)	3 (7)
Extramedullary hemopoiesis	2 (13)	1 (3)	3 (7)
Seasonal allergy	1 (6)	2 (7)	3 (7)
Decreased appetite	1 (6)	2 (7)	3 (7)
Fall	0	3 (10)	3 (7)
Posttraumatic pain	1 (6)	2 (7)	3 (7)
Skin ulcer	0	3 (10)	3 (7)

Data presented post-intrapatient dose escalation. AE: adverse event; NTDT: non-transfusion-dependent β-thalassemia; TDT: transfusion-dependent β-thalassemia.

Figure S1. Study design.

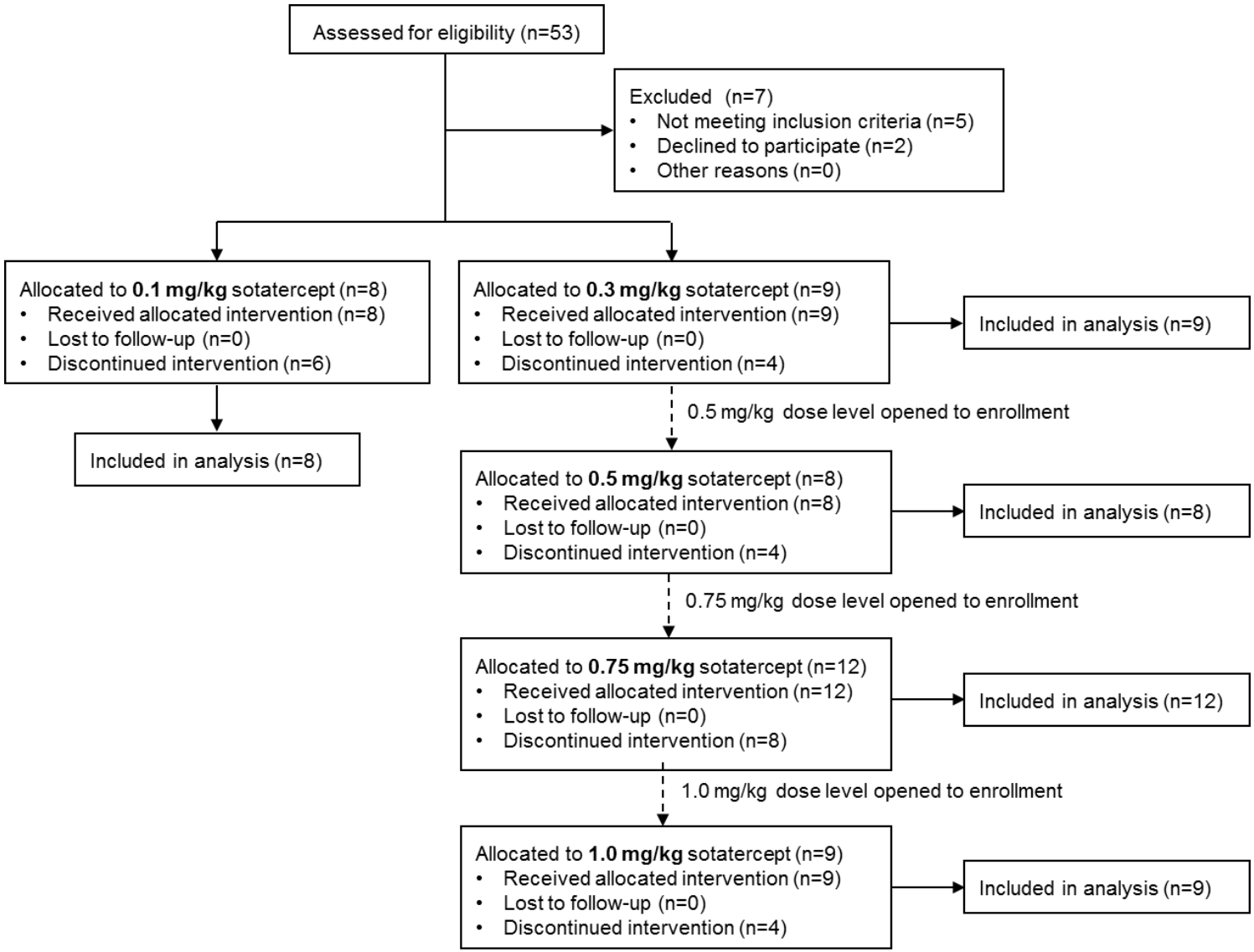

Figure S2. Mean (SD) change in levels of total bilirubin and indirect bilirubin from baseline during treatment with sotatercept. (A) Mean (SD) change in patients with non-transfusion-dependent β-thalassemia. (B) Mean (SD) change in patients with transfusion-dependent β-thalassemia. Data post-intrapatient dose escalation not included. SD: standard deviation.

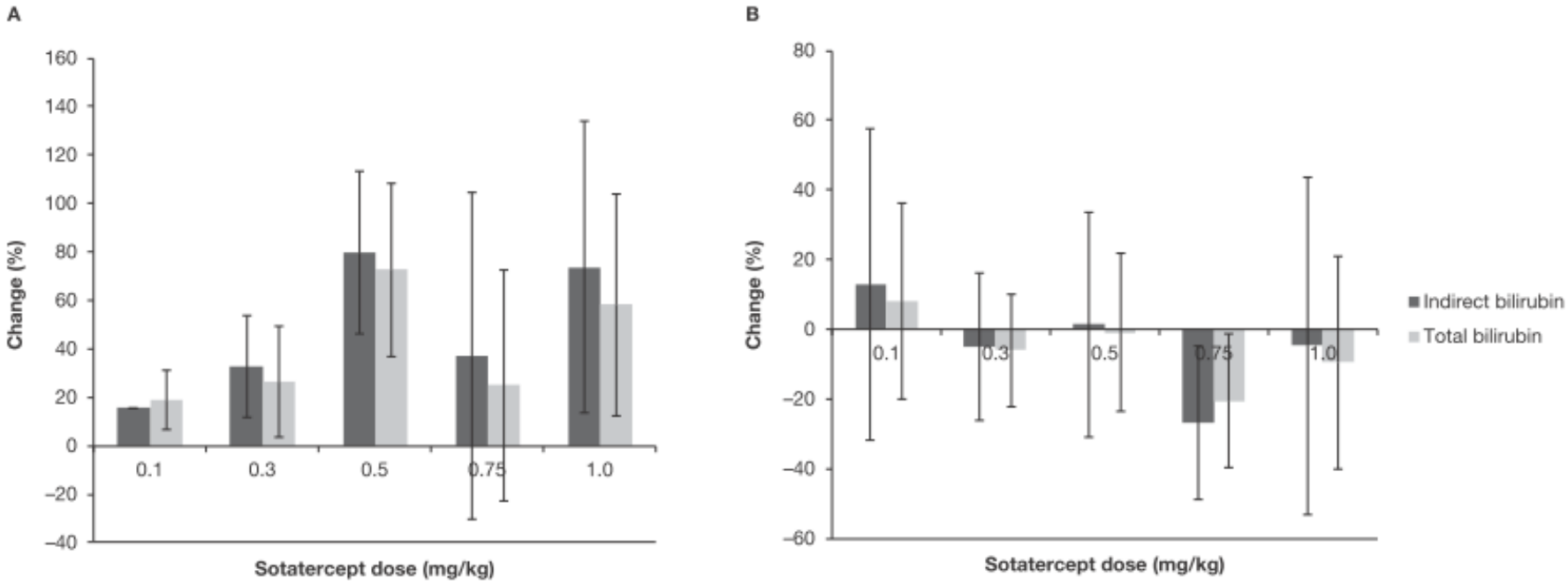

Figure S3. Change in extramedullary masses (EMM) in patients with non-transfusion-dependent β-thalassemia (NTDT). (A) EMM at baseline *(left*) and at 12 months posttreatment (*right*) in a patient enrolled to 0.3 mg/kg sotatercept. (B) EMM at baseline (*left*) and at 7 months posttreatment (*right*) in a patient enrolled to 1.0 mg/kg sotatercept. Hb: hemoglobin; MCV: mean corpuscular volume; RBC: red blood cell.

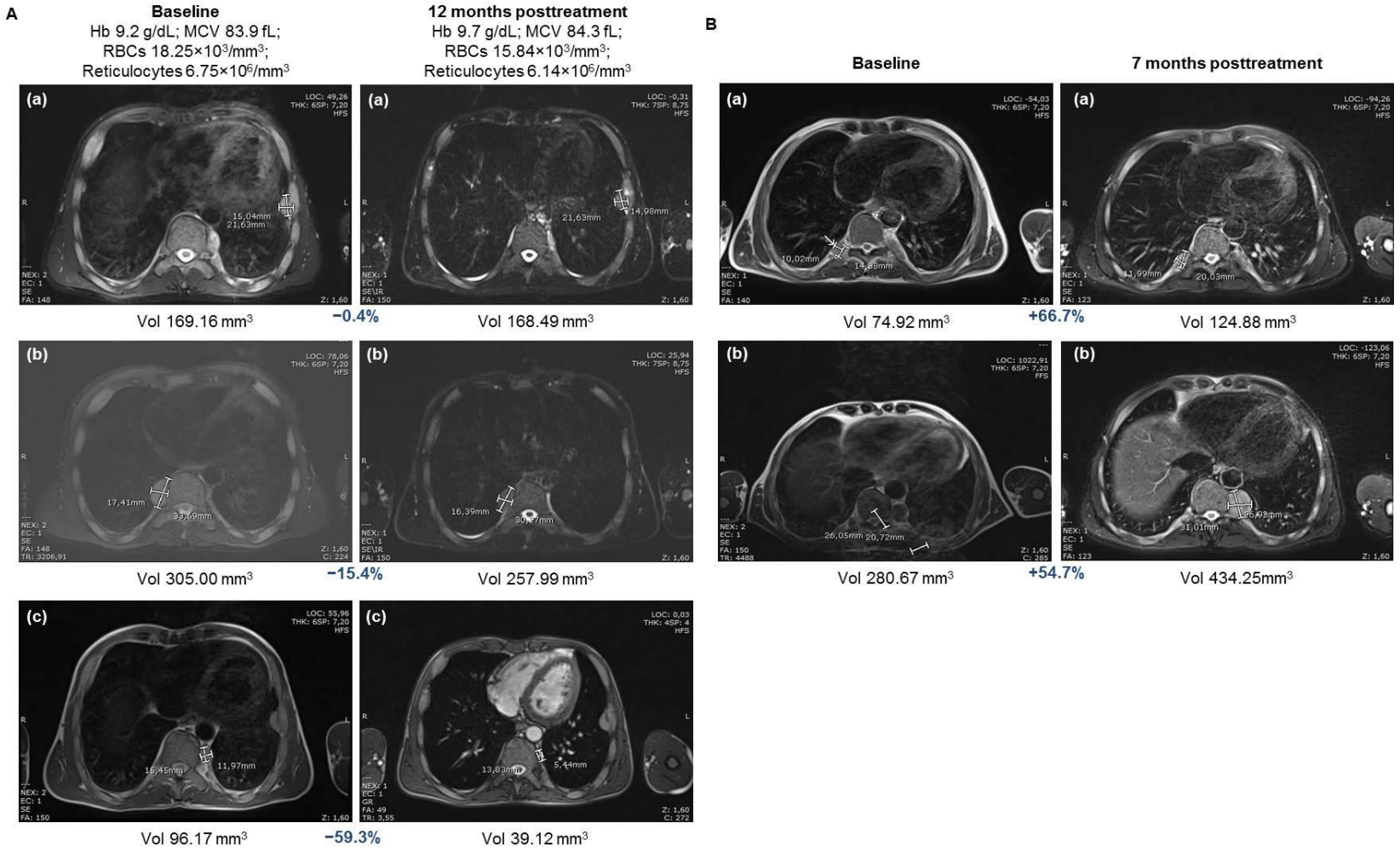

Figure S4. **Improvement in leg ulcers after 6 months treatment with sotatercept 0.5 mg/kg in a patient with non-transfusion-dependent β-thalassemia (NTDT).** The 51-year-old, female patient underwent a skin graft at 4.5 months posttreatment.

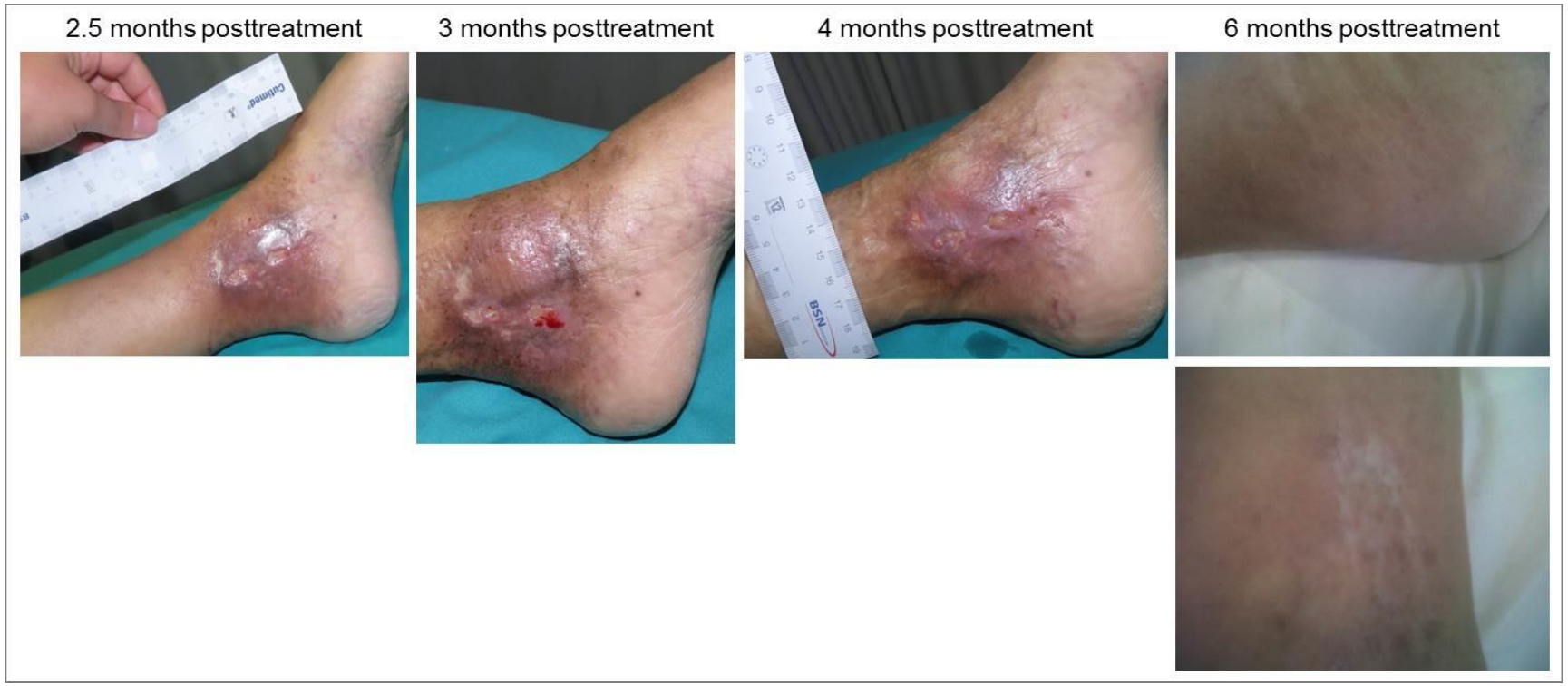

Figure S5. Change in red blood cell (RBC) morphology. (A) A 37-year-old, male patient with non-transfusion-dependent β-thalassemia (NTDT) treated with sotatercept 0.3 mg/kg (dose escalation to 0.5 mg/kg at 11 months). (B) A 54-year-old, male patient with NTDT treated with sotatercept 0.5 mg/kg. (C) A 65-year-old, female patient with NTDT treated with sotatercept 0.75 mg/kg. Hb: hemoglobin.

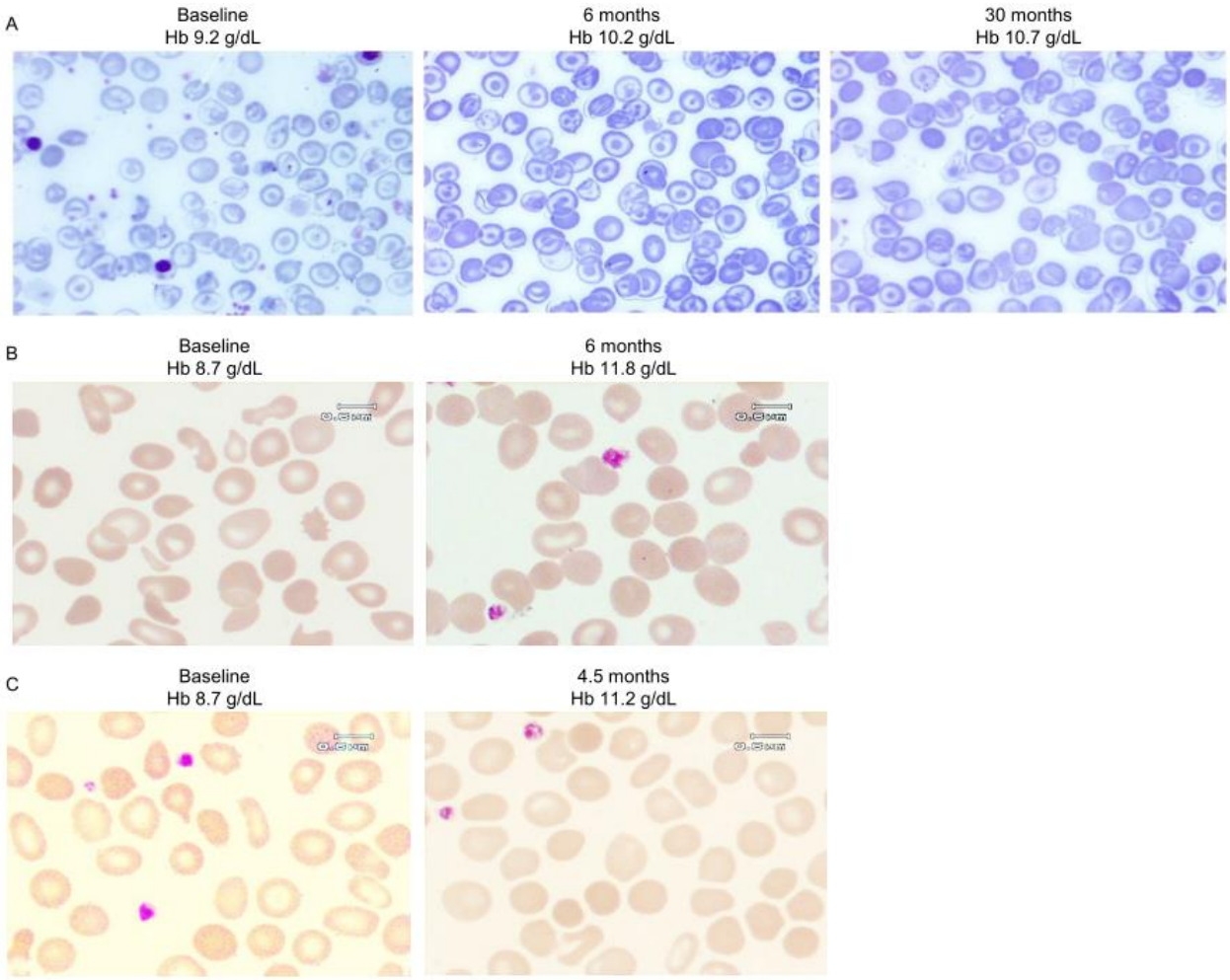

Figure S6. Mean absolute serum ferritin (SF) levels. (A) Patients with non-transfusion-dependent β-thalassemia (NTDT) receiving iron chelation therapy (ICT); (B) Patients with NTDT not receiving ICT; (C) Patients with transfusion-dependent β-thalassemia (TDT) receiving ICT. Data post-intrapatient dose escalation not included.