Sotatercept in patients with osteolytic lesions of multiple myeloma

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Received 18 December 2013; accepted for publication 5 February 2014

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Presented in part as an abstract in an oral session at the 51st Annual Meeting of the American Society of Hematology (ASH); New Orleans, LA, USA; December 5–8, 2009.

Summary

This phase IIa study evaluated the safety and tolerability of sotatercept, and its effects on bone metabolism and haematopoiesis in newly diagnosed and relapsed multiple myeloma (MM) patients. Patients were randomized (4:1) to receive four 28-d cycles of sotatercept (0·1, 0·3, or 0·5 mg/kg) or placebo. Patients also received six cycles of combination oral melphalan, prednisolone, and thalidomide (MPT). Thirty patients were enrolled; six received placebo and 24 received sotatercept. Overall, 25% of patients received all four sotatercept doses; 71% of sotatercept-treated patients had ≥1 dose interruption mainly due to increases in haemoglobin levels. Grade ≥3 adverse events (AEs) were reported in 17% of patients receiving placebo and 58% receiving sotatercept. Grade 4 AEs in sotatercept-treated patients were neutropenia, granulocytopenia, and atrial fibrillation (one patient each). In patients without bisphosphonate use, anabolic improvements in bone mineral density and in bone formation relative to placebo occurred, whereas bone resorption was minimally affected. Increases in haemoglobin levels, *versus* baseline, and the duration of the increases, were higher in the sotatercept-treated patients, with a trend suggesting a dose-related effect. Multiple doses of sotatercept plus MPT appear to be safe and generally well-tolerated in MM patients.

Keywords: anaemia, bone disease, haematopoiesis, multiple myeloma, sotatercept.

Multiple myeloma (MM) is the third most common haematological malignancy worldwide, with an estimated 114 251 new cases diagnosed and 80 015 deaths in 2012 (http://globocan.iarc.fr/). Although new treatments based on immunomodulatory drugs and proteasome inhibitors have prolonged life-expectancy, the prognosis is still typically a sequence of ongoing relapses. MM is characterized by the development of bone disease associated with impaired bone remodelling. Skeletal abnormalities and bone pain are among the most common clinical symptoms, and significantly impact patient quality of life (QoL) (Kyle, 1975; Rodan, 1997; Minter *et al*, 2011). Standard treatment for patients with bone disease includes adjunctive therapy with bisphosphonates (Rosen *et al*, 2003a; Hussein, 2007; Kyle *et al*, 2007; Terpos *et al*, 2009). However, bisphosphonates are associated with common, minor, transient side-effects and, occasionally, with more serious longer-term sequelae (Terpos *et al*, 2009). Current guidelines suggest discontinuing bisphosphonates after 2 years' use in patients with stable or responsive disease, and then reinstituting treatment with the occurrence of new-onset skeletal-related events (SREs) (Kyle *et al*, 2007; Terpos *et al*, 2009). A clear need thus exists for the development of new adjuvant therapy to prevent bone loss in patients as a significant number of patients also experience SREs despite bisphosphonate therapy (Berenson *et al*, 1998; Saad *et al*, 2002; Rosen *et al*, 2003b). In the recent UK Medical Research Council (MRC) Myeloma IX trial, 27–35% of patients receiving bisphosphonates experienced SREs during therapy (Morgan *et al*, 2011).

First published online 21 March 2014
doi: 10.1111/bjh.12835

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Activin regulates bone remodelling and is involved in osteoclast development and differentiation (Sugatani *et al*, 2003). Recently, activin A levels have been shown to be elevated in the serum of myeloma patients (Vallet *et al*, 2010; Terpos *et al*, 2012). Sotatercept [formerly known as ACE-011; Acceleron Pharma Inc. (Cambridge, MA, USA) and Celgene Corporation (Summit, NJ, USA)], a recombinant activin receptor type IIA (ActRIIA) ligand trap comprising the extracellular domain of the high-affinity human ActRIIA and human immunoglobulin G (IgG) Fc domain (ActRIIA–IgG), binds activin A/B and other transforming growth factor (TGF)-β superfamily members with high affinity (Lotinun *et al*, 2010). Sotatercept has potential therapeutic benefit by enhancing the deposition of new bone tissue and preventing the continued loss of bone in myeloma patients with osteolytic lesions (Raje & Vallet, 2010).

This is supported by preclinical studies of RAP-011 (a murine analogue of sotatercept) in MM that demonstrated dual anabolic and anti-resorptive effects (Chantry *et al*, 2007; Pearsall *et al*, 2008; Fajardo *et al*, 2010; Lotinun *et al*, 2010). In phase I studies in healthy postmenopausal women, single-dose sotatercept increased bone formation and decreased bone resorption (Ruckle *et al*, 2009; Sherman *et al*, 2013). Additionally, sotatercept elicited increases in haemoglobin, haematocrit, and red blood cell (RBC) counts after administration of a single dose.

Approximately two-thirds of patients with MM suffer from anaemia resulting from the disease process or from disease therapy (Ludwig *et al*, 2002; Kyle *et al*, 2003), and are treated with either RBC transfusions or erythropoiesis-stimulating agents (ESAs). However, both treatment modalities have their risks: RBC transfusions are associated with allo-immunization, allergic reactions, or infection transmission (Groopman & Itri, 1999); and ESAs are associated with an increase in thromboembolic events, promotion of tumour growth, and decreased overall survival (Henke *et al*, 2003; Leyland-Jones *et al*, 2005). Sotatercept has been shown to affect haematopoiesis by increasing serum haemoglobin in healthy volunteers (Ruckle *et al*, 2009; Sherman *et al*, 2013).

Based on these findings, we conducted this multicentre, dose-ranging phase II trial to evaluate the safety, tolerability, pharmacodynamics, and efficacy of sotatercept related to bone response in MM patients with osteolytic lesions.

Methods

This phase IIa, multicentre, randomized, placebo-controlled multiple-dose trial assessed the safety and tolerability of sotatercept at multiple dose-levels, and determined the effect of the drug on bone remodelling in MM patients with osteolytic lesions (ClinicalTrials.gov identifier: NCT00747123). The study was conducted in nine medical centres in the Russian Federation in full compliance with the ethical principles of the Declaration of Helsinki and its amendments, or with the laws and regulations of the locality in which the research was conducted. All subjects were fully informed of the investigational nature of the study, and written informed consent was obtained in their native language according to federal and local institutional guidelines. Sotatercept was supplied by Acceleron Pharma Inc.

Eligibility

Patients were aged ≥18 years with Durie-Salmon stage II or III, treated or untreated MM with evidence of ≥1 bone lesion, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–2. Patients had to have a life expectancy of >6 months, and adequate organ function, with haemoglobin levels ≥80 g/l, an absolute neutrophil count $\geq 1 \times 10^9$/l, a platelet count $\geq 75 \times 10^9$/l, creatinine levels ≤176·8 μmol/l, aspartate and alanine aminotransferase levels ≤3 × the upper limit of normal, and corrected calcium levels within normal limits (previous hypercalcaemia treatment was allowed). Patients receiving bisphosphonates at study entry were required to have been on a stable dose for ≥2 months (those not receiving bisphosphonates should not have received them for >2 months before study start).

Exclusion criteria included: history of non-myeloma malignancies; planned haematopoietic stem cell transplantation during the study; grade ≥3 polyneuropathy; antimyeloma therapy <21 d before study start; underlying condition that could cause abnormal bone metabolism (non-myeloma related); receiving bone-active drugs <4 months before study start; SREs <2 weeks before study start; history of hepatitis B or C virus, human immunodeficiency virus, or active infection requiring treatment <2 weeks before study start; moles or lesions currently undiagnosed but suspect for malignancy; plasma cell leukaemia; received ESAs <21 d before study start; scheduled to receive local radiation to bone during the course of the study; history of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational agent; major surgery <3 months before study start or minor surgery <2 weeks before study start; and history of cardiac, endocrinological, hepatic, immunological, metabolic, urological, pulmonary, or other major disease that could put the patient at risk or interfere with the study.

Treatment

Patients received either sotatercept or placebo, in combination with melphalan, prednisolone, and thalidomide (MPT). Three cohorts of 10 patients each were evaluated. Within each cohort, patients were randomized to receive either sotatercept or placebo (sterile normal saline) in a 4:1 ratio. Based on clinical data from two healthy volunteer studies (Ruckle *et al*, 2009; Sherman *et al*, 2013) dose levels of sotatercept in the three cohorts of 0·1, 0·3, and 0·5 mg/kg were administered via subcutaneous injection every 28 d for

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a total of four doses, with safety follow-up visits 1 week after each dose. Due to evolving ESA treatment guidelines during the conduct of this study, the cut-off point for the upper haemoglobin level was modified from 130 g/l to 110 g/l. Therefore, dose-modification rules included the following: (i) if a haemoglobin level <110 g/l increased by <20 g/l or increased by ≥20 g/l within 28 d of the last dosing day, dosing could be continued or should be reduced, respectively; (ii) if a haemoglobin level of ≥110 g/l increased by <20 g/l or increased by ≥20 g/l within 28 d of the last dosing day, the dose should be interrupted and held, or interrupted, held and then reduced, respectively; and (iii) if a patient experienced hypertension of grade ≥2, dosing should be interrupted and held. After completion of the treatment period, patients had three additional monthly follow-up assessments. Antimyeloma therapy (MPT regimen) comprised six 28-d cycles of oral melphalan 4 mg/m^2 and oral prednisolone 40 mg/m^2 on days 1–7, plus oral thalidomide 100 mg/d continuously during the four sotatercept treatment cycles.

Outcome parameters

The primary objectives of the study were to evaluate the safety and tolerability of multiple doses of sotatercept in MM patients, and to determine its effect on biochemical markers of bone formation and resorption. Secondary objectives were to assess the incidence of SREs, evaluate bone pain by visual analogue scale (VAS), determine the pharmacokinetic profile of sotatercept and perform an exploratory analysis of the effects of sotatercept, on haematopoiesis. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Variables for bone remodelling were assessed prior to dosing, at each treatment visit, and on a monthly basis thereafter: "bone-specific" alkaline phosphatase (bALP) and serum intact procollagen type I N-terminal propeptide (PINP), two of the most accurate biomarkers for bone formation (Abildgaard *et al*, 2004; Terpos *et al*, 2010a,b, 2013; Zhang *et al*, 2012); and serum C-terminal cross-linking telopeptide of type I collagen and tartrate-resistant acid phosphatase isoform 5b, two sensitive markers for bone resorption and osteoclast function, as biomarkers (Abildgaard *et al*, 2004; Terpos *et al*, 2010a,b; Tai *et al*, 2012). SREs were monitored throughout the study period, and were defined as pathological fracture, radiation therapy to bone, bone surgery, or spinal cord compression. Patient-reported bone pain was assessed by a 10 cm VAS at screening, at each treatment and follow-up visit, and at study termination.

Pharmacokinetic parameters included absorption rate constant (Ka), total clearance (CL/F), volume of distribution (*V*/*F*), elimination rate constant (K10), elimination half-life ($t_{½}$), and terminal half-life after last dose ($t_{½}$, *z*). Blood samples were collected before dosing on each treatment day, 1 week after each dose at safety visits, at follow-up visits, and at the final visit. Data were corrected for baseline values; baseline-corrected values below zero were set to zero.

Total body bone mineral density (BMD), lumbar spine BMD, and hip BMD were measured by dual-energy X-ray absorptiometry at screening (baseline), on day 85, at the final visit on day 169, and if clinically indicated. Skeletal surveys (including X-rays of the skull, entire spine, pelvis, ribs, humeri, and femora) were also undertaken at these time points. M-protein was quantified by serum protein electrophoresis and/or urine protein electrophoresis (including immunoelectrophoresis for serum-free light chains) on the day of screening, on each treatment day during therapy and at the final visit. M-protein and bone response assessments were based on criteria developed by the European Group for Blood and Marrow Transplantation (EMBT), and Autologous Blood and Marrow Transplant Registry (ABMTR)/International Bone Marrow Transplant Registry (IBMTR) as exploratory analysis (Bladé *et al*, 1998).

Statistical analysis

No formal sample size calculations were performed and no formal hypothesis testing was planned. The study was not designed for inferential analysis. Any patterns should be considered as numerical rather than as stochastically demonstrated patterns. The data were analysed using Dunnett's comparisons of the sotatercept-treated dose groups to the placebo control group. Non-parametric inferential analyses were not done for the *P*-values. Summary tables are presented by visit and treatment group, as appropriate. Descriptive statistics were used to summarize continuous variables and frequency distributions were used to summarize categorical variables.

All pharmacokinetic analyses were performed using standard techniques as implemented in WinNonlin® Professional, version 5.0.1 (Pharsight Corporation, Mountain View, CA, USA). Estimates of pharmacokinetic parameters were obtained using either a one-compartment model with first-order absorption and elimination (Ka, CL/F, *V*/*F*, K10, and $t_{½}$), or a non-compartmental model ($t_{½}$, *z*).

Results

Patient characteristics

All 30 patients received ≥1 dose of study medication: six received placebo and eight patients each received sotatercept 0·1, 0·3, or 0·5 mg/kg. Overall, 26 patients (87%) completed the study. Baseline patient characteristics are shown in Table I. Overall, patients were heavily pretreated, having received up to seven prior chemotherapy regimens. Only two patients had not received any prior antimyeloma therapy. Thirteen (43%) patients were anaemic (<110 g/l haemoglobin) before the start of the study.

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Table I. Baseline patient characteristics.

Parameter	Placebo (n = 6)	Sotatercept dose group 0·1 mg/kg (n = 8)	0·3 mg/kg (n = 8)	0·5 mg/kg (n = 8)
Female, n (%)	4 (66·7)	2 (25·0)	5 (62·5)	4 (50·0)
Median age, years (range)	63 (50–71)	61 (43–79)	64·5 (51–72)	57·5 (41–78)
Median time since MM diagnosis, years (range)	0·8 (0·2–2·2)	3·8 (0·2–12·9)	3·8 (0·6–18·0)	1 (0–3·7)
Durie-Salmon stage at screening, n (%)				
II	0	2 (25·0)	2 (25·0)	1 (12·5)
III	6 (100)	6 (75·0)	6 (75·0)	7 (87·5)
ECOG PS score, n (%)				
0	2 (33·3)	2 (25·0)	3 (37·5)	1 (12·5)
1	3 (50·0)	4 (50·0)	5 (62·5)	6 (75·0)
2	1 (16·7)	2 (25·0)	0	1 (12·5)
Median haemoglobin, g/l (range)	116 (93–141)	119 (93–132)	113 (89–136)	114 (96–134)
Bisphosphonates,* n (%)	3 (50·0)	4 (50·0)	2 (25·0)	4 (50·0)
Prior radiotherapy, n (%)	2 (33·3)	1 (12·5)	0	1 (12·5)
Prior chemotherapy, n (%)	6 (100)	8 (100)	8 (100)	6 (75·0)
Prior melphalan, n (%)	6 (100)	6 (75·0)	6 (75·0)	4 (50·0)
Prior thalidomide, n (%)	0	1 (12·5)	0	0

ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma.
*Bisphosphonates used concomitantly during the study.

Safety and tolerability

Overall, 6 of 24 (25%) sotatercept-treated patients received all four cycles of sotatercept; 3, 1 and 2 patients in the 0·1, 0·3 and 0·5 mg/kg dose groups, respectively. Also, 17 (71%) patients experienced ≥1 dose interruption, mainly due to protocol-defined limit of haemoglobin levels of >110 g/l (10 of 24 patients). Grade ≥2 hypertension led to dose interruption in one patient. No dose reductions occurred and one patient discontinued treatment due to an AE of atrial fibrillation (on day 47) prior to his second sotatercept dose, one patient discontinued treatment after withdrawing consent during the treatment period, and two patients discontinued during the follow-up period due to unacceptable toxicity/sudden death (one patient; see below) and upon investigator's request (one patient). Twenty-two (92%) patients receiving sotatercept and 4 (68%) patients receiving placebo had ≥1 treatment-emergent AE. Grade 3–4 AEs, regardless of attribution, were reported in 58% of patients receiving sotatercept and in 17% of patients receiving placebo (Table II); no dose-related effect was apparent. One patient had a grade 5 AE (sudden death 18 d after receiving a second dose of sotatercept); a post-mortem evaluation was not obtained. The investigator assessed the sudden death as possibly related to sotatercept and probably related to the current antimyeloma therapy, MPT.

Three patients experienced study-treatment-related AEs. The first, a patient in the 0·1 mg/kg dose group, had 2 AEs [increased blood pressure (grade 3) and sudden death (grade 5)]. The second patient (0·5 mg/kg dose group) had multiple episodes of grade 2 hypertension. The grade 2–3 AEs experienced by both patients were probably related to sotatercept and to MPT. The third patient experienced increased blood pressure (grade 2) which was not related to study drug, but possibly related to MPT; this patient's fourth sotatercept dose was interrupted due to haemoglobin levels of >130 g/l. Episodes of hypertension, when they occurred, resolved either on the same day after administration of antihypertensives or following interruption of sotatercept treatment, and only occurred in patients with haemoglobin levels ≥110 g/l. Increases in haemoglobin levels were observed in all sotatercept dose groups (Table III). There was a trend of higher haemoglobin levels in patients who received sotatercept compared with placebo, as well as a trend suggesting a dose-related effect.

Effect on biomarkers for bone formation

Elevated bALP levels from baseline were observed in the sotatercept 0·1 mg/kg dose group up to day 113 (data not shown). Mean changes from baseline in serum levels of bALP were increased in the 0·1 and 0·5 mg/kg dose groups relative to the placebo group at days 57 and 85. Although mean bALP levels were generally elevated with sotatercept during the dosing period (up to day 85), a dose-related effect was not observed during the study period. The results were similar for serum PINP (data not shown).

An exploratory analysis of maximum mean change in percentage from baseline in bALP levels in patients, stratified by bisphosphonate use at baseline, suggested a dose-related effect in patients not receiving bisphosphonates (Table IV). Patients receiving the full four cycles of sotatercept treatment were more likely to respond to treatment, exhibiting a ≥30%

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Table II. Grade 3–5 adverse events.

		Sotatercept dose group		
n (%)	Placebo (*n* = 6)	0·1 mg/kg (*n* = 8)	0·3 mg/kg (*n* = 8)	0·5 mg/kg (*n* = 8)
Patients with ≥1 adverse event	1 (16·7)	5 (62·5)	3 (37·5)	6 (75·0)
Neutropenia	1 (16·7)	2 (25·0)	2 (25·0)	3 (37·5)
Anaemia	0	1 (12·5)	1 (12·5)	1 (12·5)
Granulocytopenia	0	1 (12·5)	1 (12·5)	1 (12·5)
Leucopenia	0	1 (12·5)	0	1 (12·5)
Thrombocytopenia	0	0	0	1 (12·5)
Increased blood pressure*	0	1 (12·5)	0	0
Respiratory tract infection	0	1 (12·5)	0	0
Decreased platelet count	0	0	1 (12·5)	0
Atrial fibrillation	0	0	0	1 (12·5)
Back pain	0	0	0	1 (12·5)
Pathological fracture	0	0	0	1 (12·5)
Death**	0	1	0	0

*Increased blood pressure: possibly related to MPT and possibly related to sotatercept.

**Death: probably related to MPT and possibly related to sotatercept.

Table III. Increases from baseline in haemoglobin levels.

		Sotatercept dose group		
Haemoglobin increase	Placebo (*n* = 6)	0·1 mg/kg (*n* = 8)	0·3 mg/kg (*n* = 8)	0·5 mg/kg (*n* = 8)
≥10 g/l on day 29 (after first dose)	2 (33·3)	1 (12·5)	1 (12·5)	5 (62·5)
≥15 g/l on day 29 (after first dose)	0	0	1 (12·5)	3 (37·5)
≥20 g/l on day 29 (after first dose)	0	0	0	2 (25·0)
≥10 g/l at any time and sustained for ≥28 d	4 (66·7)	5 (62·5)	3 (37·5)	7 (87·5)
≥15 g/l at any time and sustained for ≥28 d	2 (33·3)	3 (37·5)	3 (37·5)	5 (62·5)
≥20 g/l at any time and sustained for ≥28 d	0	2 (25·0)	3 (37·5)	2 (25·0)

Table IV. Maximum percent change from baseline in bALP by use of bisphosphonates.

		Sotatercept dose group		
Parameter	Placebo (*n* = 6)	0·1 mg/kg (*n* = 8)	0·3 mg/kg (*n* = 8)	0·5 mg/kg (*n* = 8)
No bisphosphonates				
n	3	4	6	4
bALP, max. mean change from baseline (%)	39·2	22·7	36·9	104·4
Bisphosphonates				
n	3	4	2	4
bALP, max. mean change from baseline (%)	25·6	348·5	11·3	6·6

bALP, bone-specific alkaline phosphatase.

increase from baseline in serum bALP levels at ≥1 time points: 83·3% (five of six), 37·5% (three of eight) and 30·0% (3 of 10) of patients receiving all four doses, three doses, and 1–2 doses, respectively. Serum bALP levels increased from baseline by ≥30% in 45·8% of patients (11 of 24) receiving sotatercept and in 50·0% of patients (three of six) in the placebo group. Serum bALP levels were lower in patients receiving biphosphonates; serum bALP levels increased from baseline by ≥30% in 30·0% (3 of 10) and 33·3% (one of three) of patients receiving biphosphonates in the sotatercept and placebo group, respectively. For patients not taking biphosphonates, an increase of serum bALP from baseline by ≥30% was seen in 57·1% (8 of 14) of patients in the sotatercept group and 66·7% (two of three) of patients in the placebo group.

BMD and skeletal X-rays

Hip BMD increased in patients receiving 0·1 and 0·3 mg/kg sotatercept from day 85 to day 169/early termination, whereas it decreased in the placebo arm and in the 0·5 mg/kg dose group at both time points. Mean percentage change

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from baseline in lumbar spine BMD increased in the 0·1 and 0·3 mg/kg sotatercept groups and the placebo group on day 85 and day 169, but decreased in the 0·5 mg/kg sotatercept dose group on day 85 (data not shown). A dose-related increase from baseline in BMD variables and serum bone biomarkers was not observed with sotatercept, although improvements in BMD were observed in some dose groups.

An exploratory analysis of maximum mean percentage change from baseline in BMD stratified by bisphosphonate use at baseline showed no statistically significant differences between sotatercept dose groups and the placebo group (data not shown).

Body bone mineral density levels were more likely to increase after all four cycles of sotatercept treatment. An increase of ≥5% in either spinal or femoral BMD was observed at ≥1 time points during study in 33% of patients (8 of 24) receiving sotatercept, and an increase of ≥5% in BMD over time in 67% of patients (four of six), 25% (two of eight) and 20% (2 of 10) of patients receiving the full four cycles, three cycles, and 1–2 sotatercept cycles, respectively. Similar increases were observed in only one of six placebo-treated patients. Skeletal survey X-rays revealed that ≥1 bone lesion had decreased or disappeared in 33% of placebo-treated patients (two of six), and in 29% (two of seven), 25% (two of eight) and 71% (five of seven) of patients receiving sotatercept 0·1, 0·3 and 0·5 mg/kg, respectively.

SREs and bone pain

Skeletal-related events were observed in five sotatercept-treated patients: two patients had compression fractures, two had pathological fractures and one had a rib fracture. Although SREs were not reported for patients receiving placebo, there were too few patients with SREs to make meaningful comparisons across treatment groups. At least one lesion decreased in size or disappeared in two of six subjects in the placebo group, two of seven subjects in the 0·1 mg/kg sotatercept dose group, two of eight subjects in the 0·3 mg/kg sotatercept dose group, and five of seven subjects in the 0·5 mg/kg sotatercept dose group. Although a dose-related effect was not observed, the data suggest an increase in bone lesion response at the highest sotatercept dose (0·5 mg/kg). Patients treated with sotatercept reported an overall improvement in bone pain (mean decrease in VAS score of 5·8–12·7) at all post-baseline time points and at all dose levels. Patients receiving placebo reported a lower overall improvement in bone pain (mean decrease in VAS score of −0·7 to 7·2).

MM response

Exploratory clinical responses, measured as M-protein and bone responses, based on EBMT and ABMTR/IBMTR criteria (Bladé *et al*, 1998), revealed that two patients from the sotatercept 0·5 mg/kg patient cohort achieved a complete M-protein response. Overall, M-protein responses, either complete or partial, were achieved in half of the patients treated with sotatercept and half of the patients treated with placebo (Table V). Partial bone response was documented in 38% of patients receiving sotatercept and in 33% of placebo-treated patients (Table V).

Pharmacokinetics

All 24 patients assigned to sotatercept received ≥1 dose and provided evaluable pharmacokinetic data, although one patient in the 0·5 mg/kg dose group was excluded (sotatercept serum concentration not available). Sotatercept concentrations (±standard deviation) on days 8 and 29 after the first dose appeared to increase in a roughly dose-proportional manner: day 8, 703 (±351) ng/ml, 1612 (±604) ng/ml and 2628 (±967) ng/ml; and day 29, 374 (±184) ng/ml, 834 (±690) ng/ml and 1670 (±1193) ng/ml for patients in the 0·1, 0·3 and 0·5 mg/kg sotatercept dose groups, respectively. Estimation of mean pharmacokinetic parameters using the one-compartmental model appeared to be similar among the sotatercept dose groups (Table VI). In addition, the mean $t_{½}$

Table V. Clinical responses.

Response parameter, *n* (%)	Placebo (*n* = 6)	Sotatercept dose group 0·1 mg/kg (*n* = 8)	0·3 mg/kg (*n* = 8)	0·5 mg/kg (*n* = 8)
M-protein response				
Complete	0	0	0	2 (25·0)
Partial	3 (50·0)	4 (50·0)	4 (50·0)	2 (25·0)
Stable	2 (33·3)	3 (37·5)	3 (37·5)	3 (37·5)
Progression	1 (16·7)	1 (12·5)	1 (12·5)	1 (12·5)
Bone response				
Complete	0	0	0	0
Partial	2 (33·3)	1 (12·5)	3 (37·5)	5 (62·5)
Stable	4 (66·7)	6 (75·0)	4 (50·0)	1 (12·5)
Progression	0	0	1 (12·5)	0
Progression (bone)	0	0	0	1 (12·5)
Follow-up missing	0	1 (12·5)	0	1 (12·5)

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Table VI. Pharmacokinetic parameters of sotatercept (one-compartment analysis).

Parameter	Sotatercept dose group 0·1 mg/kg (n = 8)	0·3 mg/kg (n = 8)	0·5 mg/kg (n = 7)
Ka (/d)	0·429 (±0·354)	0·674 (±0·559)	0·799 (±0·463)
CL/F (ml/d/kg)	3·92 (±2·34)	5·75 (±3·60)	5·77 (±4·40)
V/F (ml/kg)	93·6 (±34·1)	139·7 (±55·9)	123·3 (±19·0)
K10 (/d)	0·045 (±0·027)	0·041 (±0·025)	0·044 (±0·028)
$t_{½}$ (d)	20·0 (±10·5)	25·2 (±19·9)	21·7 (±12·8)
$t_{½}$, z (d)*	21·9 (±7·6)†	25·5 (±16·1)	22·8 (±12·7)

CL/F, total clearance; K10, elimination rate constant; Ka, absorption rate constant; $t_{½}$, elimination half-life; $t_{½}$, z, terminal half-life after last dose; V/F, volume of distribution.
All values are mean (±standard deviation).
*Non-compartment analysis.
†n = 7.

values estimated using the one-compartment model were close to the $t_{½}$, z values estimated from a non-compartment analysis. Mean $t_{½}$, z values were similar among the three dose levels ranging from 22 to 26 d, and were gender-independent (data not shown). Sotatercept-specific antibodies were not detected in any of the 24 patients who received sotatercept at any sampling point during the study.

Discussion

This study was primarily designed to assess the safety and pharmacodynamic activity of sotatercept in combination with MPT in patients with osteolytic lesions associated with MM. MPT was used because it is a very effective antimyeloma regimen, with a neutral or negative effect on bone formation. Treatment with four cycles of sotatercept at all tested doses appeared to be safe and all reported AEs were consistent with the known AE profiles in this patient population. Dose levels >0·5 mg/kg were associated with an excessive increase in haemoglobin in a healthy volunteer study (Sherman *et al*, 2013) and were, therefore, not used in the current study. Grade 3–4 AEs occurred in 58% of patients receiving sotatercept; three patients experienced AEs possibly related to either sotatercept and/or MPT. Cytopenias that were commonly observed in the study could be secondary to the use of melphalan and to the fact that the patients were heavily pretreated; these side-effects are, therefore, possibly not related to sotatercept use. Overall, AEs were transient and manageable with sotatercept dose modification or interruption; only two patients discontinued treatment during the study due to AEs.

Increased haemoglobin levels were observed in all sotatercept dose groups, with a trend towards a dose-response relationship. This effect has also been observed in healthy postmenopausal women who received up to four doses of sotatercept at 0·1, 0·3, 1 mg/kg or placebo once a month (Sherman *et al*, 2013). Mean haemoglobin levels increased from baseline with 0·3 or 1 mg/kg sotatercept compared with placebo on days 8, 15 and 29. Sotatercept 1 mg/kg every 4 weeks for two cycles was the maximum administered dose, and increased haemoglobin was the main dose-limiting toxicity (Sherman *et al*, 2013). Non-haematological treatment-emergent AEs were mainly mild and drug unrelated. Currently, the mechanisms underlying the effect of sotatercept on erythropoiesis are under investigation. It is possible that sotatercept acts by blocking TGF-β superfamily members, which negatively regulate late-stage erythropoiesis, resulting in pro-erythroid effects (Shiozaki *et al*, 1992). Sotatercept increases haemoglobin by correcting defective erythrocyte maturation without binding to erythropoietin receptors (data not shown). This could offer a new treatment possibility to patients with impaired or ineffective erythropoiesis, such as patients with beta-thalassaemia, myelodysplastic syndromes or chronic kidney disease.

Although no dose-related effects of sotatercept on serum bone biomarkers were evident, improvements in bone formation biomarkers relative to placebo were observed in some dose groups. There was a suggestion of a dose-dependent increasing effect of sotatercept on bALP, mainly in patients who did not receive bisphosphonates. Bone resorption biomarkers showed small mean changes from baseline in all treatment groups, with no consistent trend to change over time. Improvements in BMD were also observed in patients who did not receive bisphosphonates and in selected patients who did receive bisphosphonates.

Although the safety and haematological objectives of this study were supported by the data, certain conclusions about pharmacodynamics and efficacy endpoints, although plausible, were not demonstrable due to potentially high false-negative rates associated with smaller sample sizes (6–8 patients per treatment group). Several other factors may contribute to a limited interpretation of a sotatercept dose effect on these pharmacodynamic and efficacy assessments, including the presence of outliers, multiple dose interruptions and failure to complete the planned dosing regimen, use of bisphosphonates in some patients and the use of melphalan and thalidomide uniformly across treatment groups. Thalidomide-based therapies are known to either reduce or have no effect on bone formation (Tosi *et al*, 2006; Terpos *et al*, 2008). Prior and concurrent use of melphalan (a known toxic agent to osteoblasts) varied due to dose-adjustments for myelosuppression, and may also have contributed to the variation in observed biomarker levels during the study. Exploratory analyses of maximum mean percentage change from baseline in bALP and BMD suggest that bisphosphonate use at baseline may have been a confounding factor, and a dose–response effect for sotatercept was suggested from data on bone formation markers and BMD in patients who did not receive bisphosphonates. Reduced reporting of bone pain in all sotatercept dose groups relative to placebo suggests potential treatment-related improvements in QoL.

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The changes in the sotatercept serum concentrations after the first dose were linear to the administered dose. The $t_{½}, z$ was similar across dose groups and gender independent – consistent with the linear pharmacokinetics of sotatercept that were observed previously (Ruckle *et al*, 2009). All women participating in the current trial were postmenopausal, and the pharmacokinetics described in these women with MM were similar to that previously observed in healthy postmenopausal women (Ruckle *et al*, 2009). MPT treatment did not affect sotatercept elimination in this study.

Bisphosphonate-associated AEs include impaired renal function, acute-phase reactions, and osteonecrosis of the jaw (Chang *et al*, 2003; Rosen *et al*, 2003a,b; Dimopoulos *et al*, 2006; Terpos *et al*, 2009). Sotatercept treatment increased biomarkers of bone formation and lumbar BMD, and appeared to produce clinical responses in heavily pretreated MM patients with osteolytic bone lesions. By decoupling pathological bone remodelling, sotatercept may be able to direct the bone remodelling balance more in favour of bone formation, and may potentially have a role in counteracting the osteolytic bone lesions associated with myeloma. In myeloma patients, osteoblasts are exhausted and thus circulating bALP is reduced or not altered in the majority of patients compared to gender- and age-matched controls (Terpos *et al*, 2010a). The levels of bALP cannot predict and did not associate with the presence of SREs in myeloma patients (Terpos *et al*, 2010c). Thus it seems that the elevation of bALP observed in our study may be due to the use of sotatercept. Further research is needed to support these findings. However, encouraging data were recently published for the combination of bortezomib, dexamethasone, and zoledronic acid, the first antimyeloma regimen to report increases in BMD in MM patients (Terpos *et al*, 2010c).

In conclusion, sotatercept had an anabolic effect in patients who had not received bisphosphonates within 2 months prior to study initiation, even in the presence of MPT which includes agents with inhibitory effects on osteoblasts. In addition, sotatercept increased haemoglobin levels in patients with MM, suggesting a role in erythropoiesis. Therefore, sotatercept could be used as an erythropoietic agent in the future.

Acknowledgements

This study was funded by Acceleron Pharma and Celgene Corporation. Site and patient monitoring was conducted by PSI Co, Ltd (St Petersburg, Russia), a clinical research organization. Medical writing services were provided by Ronald van Olffen, PhD, of Excerpta Medica BV, funded by Celgene Corporation. The authors are fully responsible for all content and editorial decisions for this manuscript.

Authorship and disclosure

KMA, GNS and NKK reviewed and provided critical feedback on the manuscript; MLS and RK were responsible for study design, scientific rationale, medical monitoring and interpretation of data; AL was involved in data cleaning, analysis and interpretation; RB was the clinical study manager; SS generated and analysed the data; ET was responsible for interpreting the data and writing and reviewing the manuscript.

Conflict of interest

KMA, GNS, NKK, and ET have nothing to disclose. MLS and RB are or were employees of and/or own stock in Acceleron Pharma Inc. AL, RK, and SS are employees of and/or own stock in Celgene Corporation.

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