Sotatercept in patients with osteolytic lesions of multiple myeloma

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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/C1, 0/C1, or 0/C1 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).
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).

Based on clinical data from two healthy volunteer studies (Chantry et al., 2007; Pearsall et al., 2008; Fajardo et al., 2010; Lotinun et al., 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 (Rucklé 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 (Rucklé 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 ≥1 × 10⁹/l, a platelet count ≥75 × 10⁹/l, creatinine levels ≤176·8 μmol/l, aspartate and alanine aminotransferase levels ≤× the upper limit of normal, and corrected calcium levels within normal limits (previous hypercalcæmia 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 (Rucklé 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
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/m² and oral prednisolone 40 mg/m² 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 isofrom 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 (t½), and terminal half-life after last dose (t½). 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 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 t½), or a non-compartmental model (t½, 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 anemic (<110 g/l haemoglobin) before the start of the study.

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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%
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
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 $t_{1/2}$

### Table V. Clinical responses.

| Response parameter, n (%) | Placebo (n = 6) | 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)        |
values estimated using the one-compartment model were close to the \( t_{1/2} \), \( z \) values estimated from a non-compartment
analysis. Mean \( t_{1/2} \), \( z \) 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 antmyeloma regi-
men, 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
\( \geq 0.5 \) mg/kg were associated with an excessive increase in hae-
moglobin in a healthy volunteer study (Sherman et al, 2013)
and were, therefore, not used in the current study. Grade 3
moglobin in a healthy volunteer study (Sherman
sotatercept at 0
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 treat-
ment-emergent AEs were mainly mild and drug unrelated.
Currently, the mechanisms underlying the effect of sotater-
cept on erythropoiesis are under investigation. It is possible
that sotatercept acts by blocking TGF-\( \beta \) superfamily mem-
ers, which negatively regulate late-stage erythropoiesis,
resulting in pro-erythroid effects (Shiozaki et al, 1992). Sota-
tercept increases haemoglobin by correcting defective eryth-
ocyte maturation without binding to erythropoietin
receptors (data not shown). This could offer a new treatment
possibility to patients with impaired or ineffective erythro-
poiesis, such as patients with beta-thalassaemia, myelodys-
plastic syndromes or chronic kidney disease.

Although no dose-related effects of sotatercept on serum
bone biomarkers were evident, improvements in bone forma-
tion 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 bio-
markers 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 con-
tribute to a limited interpretation of a sotatercept dose effect
on these pharmacodynamic and efficacy assessments, includ-
ing the presence of outliers, multiple dose interruptions and
failure to complete the planned dosing regimen, use of bis-
phosphonates in some patients and the use of melphalan and
thalidomide uniformly across treatment groups. Thalido-
mide-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 bisphospho-
nate 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.
The changes in the sotatercept serum concentrations after the first dose were linear to the administered dose. The Fp, 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 antitymeyeloma 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.

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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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