First-in-human study of RPH-203, a new potent RANKL blocker, for the treatment of bone metastasis

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Disclosure slide

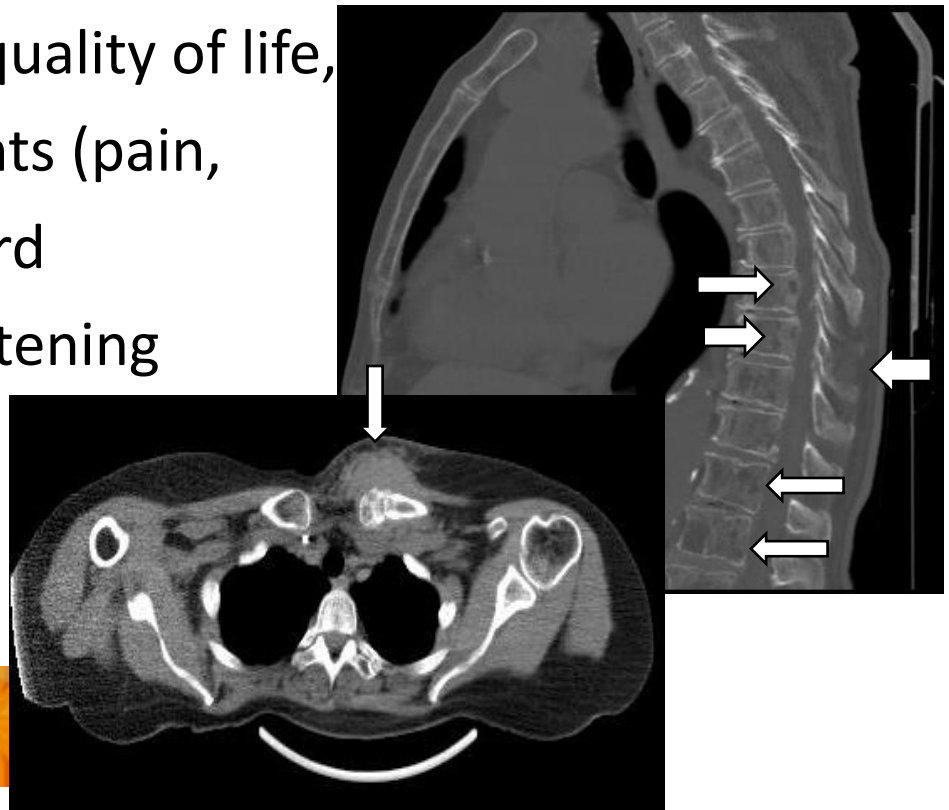
Shorena Archuadze, MD, PhD, has disclosed that she is an employee of R-Pharm pharmaceutical company

RPH-203, a new potent RANKL blocker, for the treatment of bone metastasis

- **RPH-203** represents innovative biotechnology drug being developed by R-Pharm – the leading and fully integrated Russian pharma company with global footprint
- **Structure** - 442 amino acid RANKL blocker created through fusion of N-terminal residues (D1-D4 domains) of human osteoprotegerin (OPG) with Fc-portion of human IgG1
- **MoA –** Similarly to natural OPG – RPH-203 blocks RANK/RANKL (receptor activator of nuclear factor-kB ligand) signalling pathway via binding to RANKL, inhibits osteoclast differentiation, proliferation, activation and thereby, markedly reduces bone resorption

Rationale for the development of human fusion protein RPH-203

- **Indication** - Bone metastasis (lytic, mixed)
- **Epidemiology** -15-75% of patients with advanced solid tumours (breast, lung, prostate, thyroid and renal cancers)
- **Unmet Medical Need** – Poor quality of life, high risk of skeletal-related events (pain, pathological fractures, spinal cord compression etc.) and life-threatening complications



Nonclinical and clinical studies of RPH-203

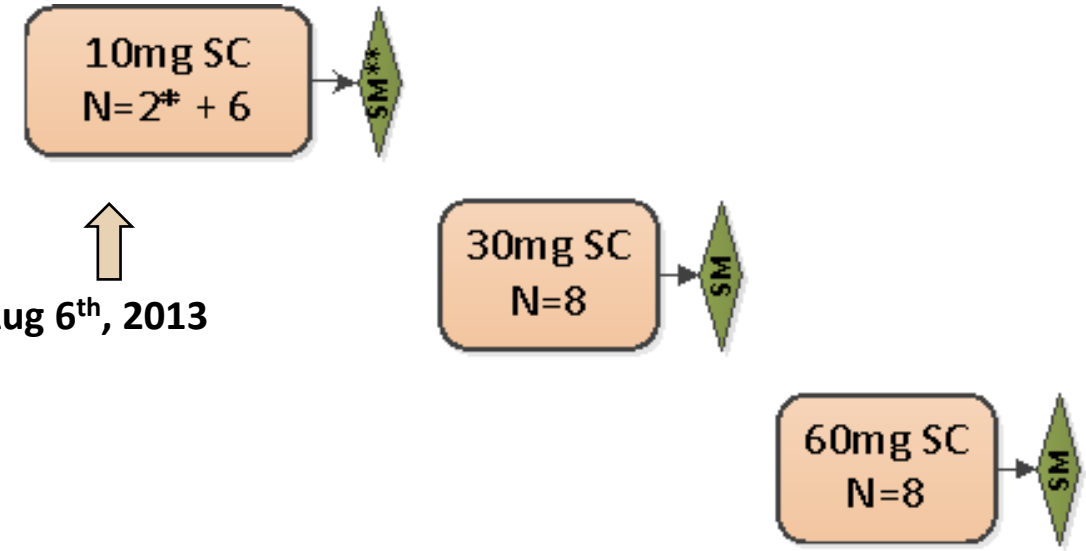
Key non-clinical studies

- Multiple comparative *in vitro* studies of specific bioactivity
- *In vivo* bioactivity against metastatic bone lysis in athymic nude-Foxn1nu mice
- *In vitro* hepatotoxicity (HepG2 cell line)
- *In vitro* tissue cross reactivity (human, monkey, mouse)
- *In vitro* immunotoxicity (FcγRIIIa/b – binding, cytokine release)
- *In vivo* allergenicity, skin sensitization (guinea pig), local tolerance (SPF mouse)
- Single dose PK and DRF/ MTD (SC and IV, Cynomolgus monkeys)
- Repeated Dose toxicity study (SC, 14 days, Cynomolgus monkeys)
- 32-week chronic toxicity study with 13-week Interim Analysis in Cynomolgus monkeys (Exploratory work is ongoing)

Clinical studies

- **First-in-human, Phase I randomized, double-blind, placebo-controlled study of safety, tolerability and PK/PD of RPH-203 following single SC dose in male healthy volunteers (HVs) (completed)**
- Multi-center open-label randomized study to compare PK/PD, efficacy and safety of RPH-203 and Xgeva® (denosumab, Amgen) in patients with breast cancer metastasis in bone (ongoing)

Clinical trial design



Aug 6th, 2013

Four cohorts of 8 HVs (n=32)

RPH-203 : Placebo - 3 : 1

SC - preferred route of administration

IV – MTD achievement, dosing feasibility

Oct 23th, 2013

* Sentinel group included 2 healthy volunteers to minimize risk of the first in humans dosing

** SM – Safety meetings are held by the end of week post dose of each dose group in order to make a decision whether the dose should be escalated of not

Clinical trial objectives and criteria for evaluation

Primary objective – Safety and tolerability:

- Safety monitoring included assessment of adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms and concomitant medications in all subjects, who received at least one dose of study drug. Reported AEs were coded to standard terms using a standard dictionary (MedDRA v. 16.0).

Secondary objectives – Pharmacokinetics (PK):

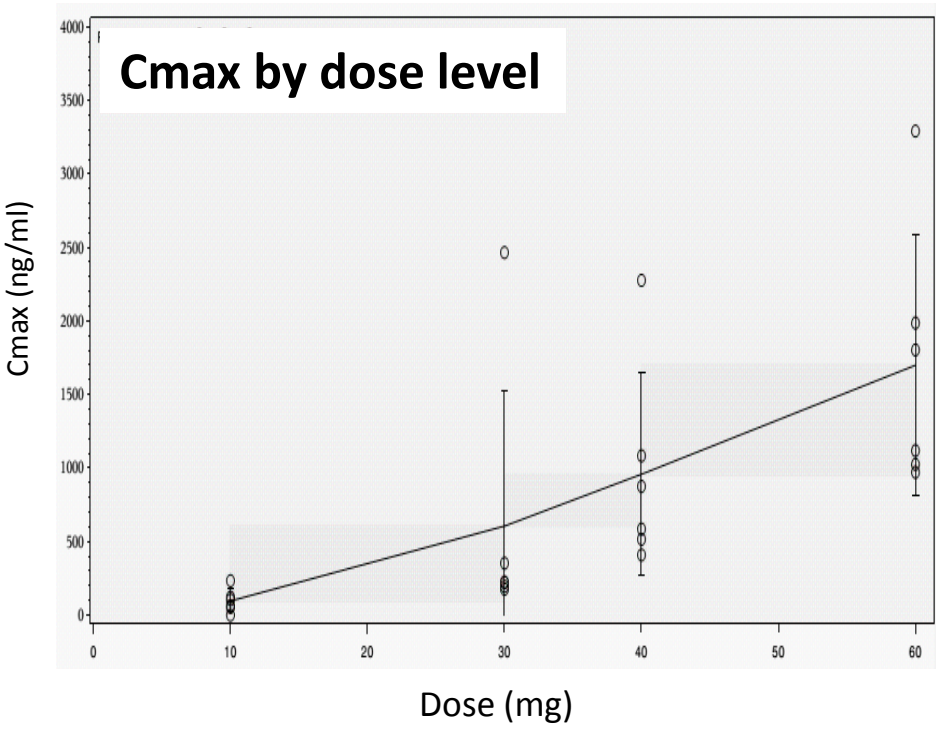
- PK samples were collected at Day 1 at pre-dose, then 0.5, 1, 2, 4, 8, 9, 10, 11, 12, 16 hours post-dose, Day 2 at 24 hours post-dose, Day 3 at 48 hours post-dose, Days 7, 12, 20, 27
- Non-compartmental methods were used to determine pharmacokinetic parameters, including AUC_t, AUC_{inf}, C_{max}, T_{max}, λ_z, t½, CL and V_d.

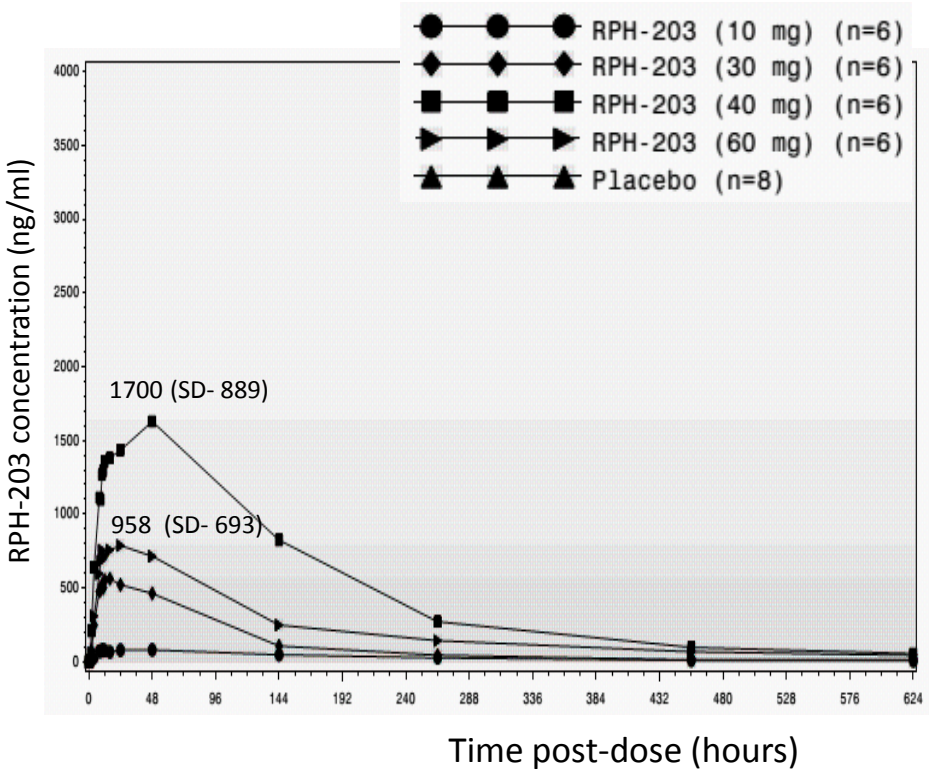
Pharmacodynamics (PD):

- Blood and urine samples were also collected for measurement of the following PD endpoints over the course of the study: Procollagen Type I N-terminal peptide (P1NP) -at Day 1 at pre-dose, Days 12, 20 and 27. Serum CTx and uNTX - at Day 1 at pre-dose, Day 2 at 24 hours post-dose, Day 3 at 48 hours post-dose, Days 7, 12, 20 and 27

Statistical methods: Descriptive statistics (mean, standard deviation (SD), coefficient of variation, median, min and max)

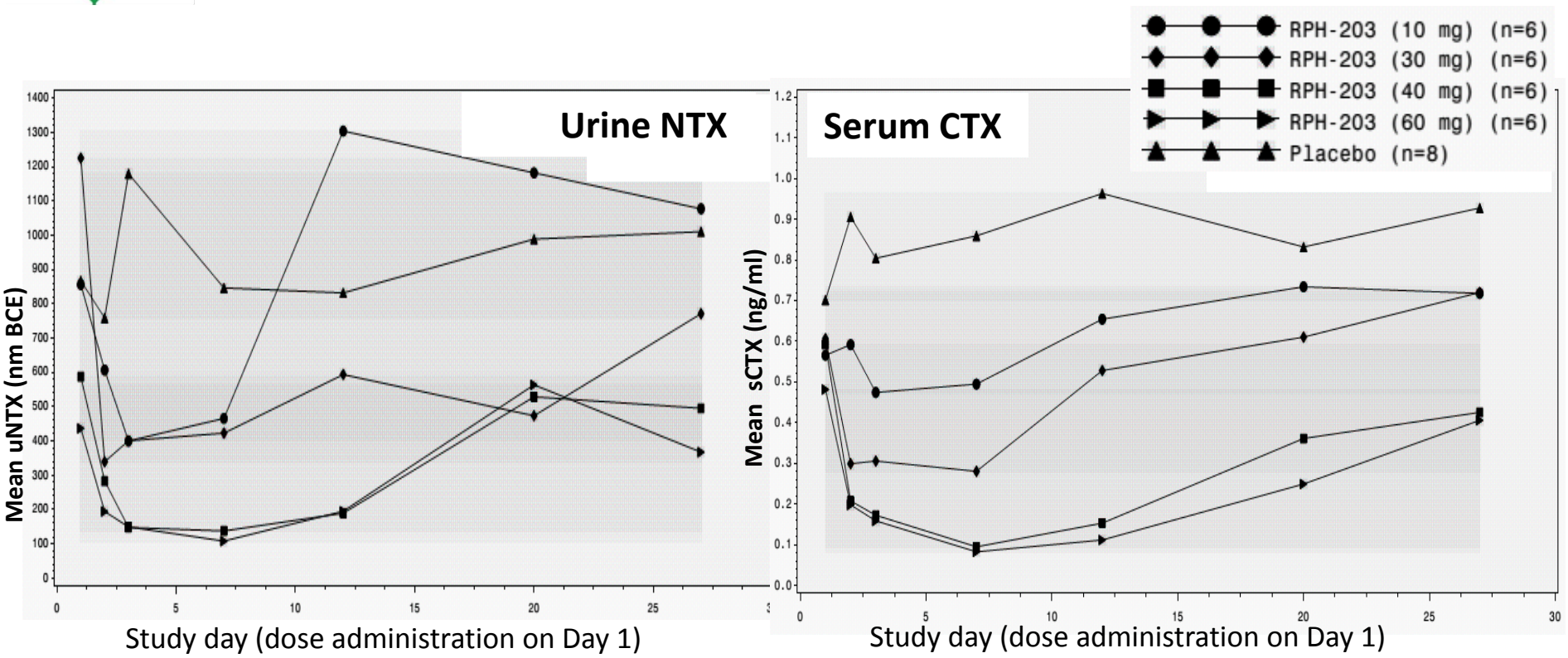
PK parameters of RPH-203 by dose level
Summary of serum concentration/time data





Exposure as measured by C_{max} and AUC increased with dose, with the increase being apparently greater than dose proportional across the dose range.
T_{max} was 33 hours, $T_{1/2}$ was 161 hours (71 - 301 hours).

PD parameters of RPH-203 by dose level
Mean levels of uNTX and sCTX (linear)



Single SC injection of RPH-203 resulted in dose-dependent decrease in uNTX and sCTX

RPH-203 safety

	Number (%) of Subjects with at least one TEAE [Number of TEAEs*]					
System Organ Class	**10 mg (N=6)**	**30 mg (N=6)**	**40 mg (N=6)**	**60 mg (N=6)**	**Placebo (N=8)**	**Total (N=32)**
Infections and infestations	2 (33%) [2]			1 (17%) [1]	1 (13%) [1]	4 (13%) [4]
Blood and lymphatic system disorders	1 (17%) [1]					1 (3%) [1]
Psychiatric disorders			1 (17%) [1]			1 (3%) [1]
Nervous system disorders	3 (50%) [4]	3 (50%) [4]	4 (67%) [5]	5 (83%) [6]	4 (50%) [4]	19 (59%) [23]
Vascular disorders	1 (17%) [1]					1 (3%) [1]
Gastrointestinal disorders	1 (17%) [1]		1 (17%) [1]	1 (17%) [1]	1 (13%) [2]	4 (13%) [7]
Skin and subcutaneous tissue disorders					2 (25%) [2]	2 (6%) [2]
Musculoskeletal and connective tissue disorders			1 (17%) [1]			1 (3%) [1]
General disorders and administration site reactions		1 (17%) [1]		2 (33%) [3]	2 (25%) [2]	5 (16%) [6]
Injury, poisoning and procedural complications	1 (17%) [1]					1 (3%) [1]
ALL TEAEs	5 (83%) [10]	3 (50%) [5]	5 (83%) [8]	6 (100%) [13]	6 (75%) [11]	25 (78%) [47]

Conclusions

- Single SC injection of RPH-203 was well tolerated up to 40mg with no apparent differences in safety profiles within 10 – 40mg dose range
- RPH-203 resulted in dose-dependent reduction in uNTX and sCTX. Duration and magnitude of decrease in bone resorption marker levels in 40mg and 60mg dose groups were comparable
- RPH-203 dose increase from 40mg to 60mg resulted in non-proportional elevation of mean Cmax and in the occurrence of dose-limiting toxicity in 2 of 6 healthy volunteers
- RPH-203 SC injection at 40mg is a recommended dose for further development with acceptable risk/benefit profile

Thank you for attention!

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