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

Shorena Archuadze, MD, PhD
R-Pharm, Moscow, Russia
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

Four cohorts of 8 HVs (n=32)
RPH-203: Placebo - 3:1

SC - preferred route of administration
IV – MTD achievement, dosing feasibility

* 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 $AUC_t$, $AUC_{inf}$, $C_{max}$, $T_{max}$, $\lambda_z$, $t\frac{1}{2}$, 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)
Exposure as measured by $C_{\text{max}}$ and AUC increased with dose, with the increase being apparently greater than dose proportional across the dose range. $T_{\text{max}}$ was 33 hours, $T_{1/2}$ was 161 hours (71 - 301 hours).
Single SC injection of RPH-203 resulted in dose-dependent decrease in uNTX and sCTX.
### RPH-203 safety

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>10 mg (N=6)</th>
<th>30 mg (N=6)</th>
<th>40 mg (N=6)</th>
<th>60 mg (N=6)</th>
<th>Placebo (N=8)</th>
<th>Total (N=32)</th>
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</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>2 (33%)</td>
<td></td>
<td></td>
<td>1 (17%)</td>
<td>1 (13%)</td>
<td>4 (13%)</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (17%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
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<td></td>
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<td>1 (17%)</td>
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<tr>
<td>Nervous system disorders</td>
<td>3 (50%)</td>
<td>3 (50%)</td>
<td>4 (67%)</td>
<td>5 (83%)</td>
<td>4 (50%)</td>
<td>19 (59%)</td>
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<tr>
<td>Vascular disorders</td>
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<td></td>
<td></td>
<td></td>
<td>1 (3%)</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>1 (17%)</td>
<td></td>
<td></td>
<td>1 (17%)</td>
<td>1 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (17%)</td>
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<td></td>
<td></td>
<td>1 (13%)</td>
<td>2 (25%)</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td>1 (17%)</td>
<td></td>
<td>1 (3%)</td>
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<tr>
<td>General disorders and administration site reactions</td>
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<td></td>
<td>2 (33%)</td>
<td>2 (25%)</td>
<td></td>
<td>5 (16%)</td>
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<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (17%)</td>
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<td></td>
<td></td>
<td></td>
<td>1 (3%)</td>
</tr>
<tr>
<td>ALL TEAEs</td>
<td>5 (83%)</td>
<td>3 (50%)</td>
<td>5 (83%)</td>
<td>6 (100%)</td>
<td>6 (75%)</td>
<td>25 (78%)</td>
</tr>
</tbody>
</table>
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!

Acknowledgements to all our partners!

Shorena Archuadze, MD, PhD
E-mail: archuadze@rpharm.ru
Tel: +7 495 9567937, Ext: 1524