A phase 1, first-in-human, dose-escalation and -expansion study of RYZ401, a novel radiopharmaceutical therapy labeled with actinium-225, in patients with neuroendocrine tumors and other solid tumors expressing somatostatin receptors

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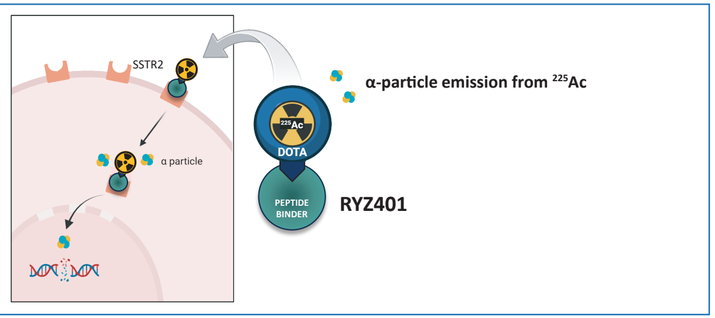
BACKGROUND

- Somatostatin receptor (SSTR)-targeted radiopharmaceutical therapy (RPT) has improved outcomes for patients with neuroendocrine tumors (NETs) in phase 3 studies versus targeted therapies.[1–3]
- Use of the α-emitter ^{225}Ac as the radioactive component in RPT has shown promising results in clinical studies: initial data from ACTION-1 suggest promising efficacy for RYZ101, a first-in-class, highly potent, α-emitting RPT, in patients with SSTR+ gastroenteropancreatic (GEP)-NETs progressing after 2–4 cycles of ^{177}Lu-somatostatin analogs.[4]
- A limitation of DOTATATE-based RPT is its kidney reuptake and prolonged retention, which can increase the risk for radiation-induced nephropathy. To mitigate this risk, a long amino acid co-infusion is required, which is associated with adverse reactions such as nausea and electrolyte abnormalities.
- RYZ401 (^{225}Ac-RYZ-SSA1; Figure 1) is a novel SSTR2-targeting RPT, engineered to improve renal clearance and tumor retention, eliminating the need for amino acid co-infusion.

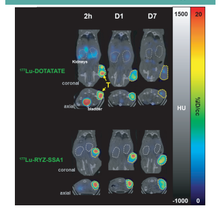
FIGURE 1. RYZ401 mechanism of action



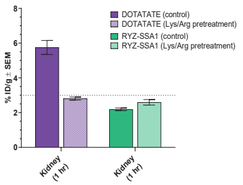
- Preclinical studies showed that RYZ401 delivered high radiation doses to tumors, with good renal clearance and low kidney-absorbed doses compared with DOTATATE, eliminating the need for the amino acid infusions commonly used to decrease renal reuptake.[5]
  - ^{177}Lu-RYZ-SSA1, which contains the same peptide and chelator as RYZ401, was used for biodistribution imaging and kidney uptake studies. Compared with DOTATATE, RYZ-SSA1 had improved tumor retention and renal clearance in mouse xenograft models (Figure 2A).
  - Non-tumor-bearing mice were pretreated with saline (control) or lysine/arginine amino acids. At 1 hour post-injection, DOTATATE kidney uptake was 50% lower with lysine/arginine pretreatment, whereas ^{177}Lu-RYZ-SSA1 kidney uptake was low regardless of amino acids (Figure 2B).
  - A single injection of RYZ401 (^{225}Ac-RYZ-SSA1) resulted in significant tumor growth inhibition (TGI) with durable regression and prolonged survival, with TGI values of >100% at day 32 for both the 1 µCi- and 3 µCi-treated groups (Figure 2C).

FIGURE 2. Biodistribution and efficacy in mouse models[5]

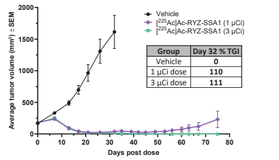
A. *In vivo* SPECT biodistribution of ^{177}Lu-RYZ-SSA1 in H524 xenograft



B. ^{177}Lu-RYZ-SSA1 biodistribution in athymic nude mice



C. *In vivo* efficacy of RYZ401 (^{225}Ac-RYZ-SSA1) in H524 xenograft



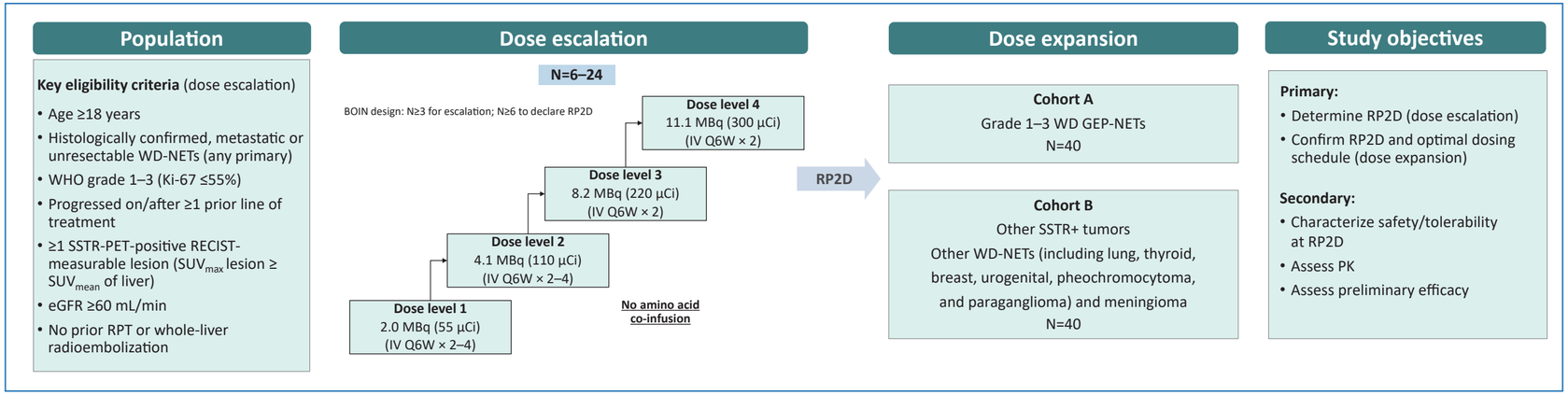
Group	Day 32 % TGI
Vehicle	0
1 µCi dose	110
3 µCi dose	111

% ID/g, percentage of injected dose per gram of tissue; Arg, arginine; Lys, lysine; SEM, standard error of the mean; SPECT, single photon emission computed tomography; TGI, tumor growth inhibition.

METHODS

- **Study design**: RYZ401-101 is a global, multicenter, phase 1, first-in-human, dose-escalation/-expansion study designed to determine the recommended phase 2 dose (RP2D) and optimal treatment regimen, safety and tolerability, and preliminary efficacy of RYZ401 in patients with NETs and other selected solid tumors expressing SSTRs (Clinicaltrials.gov identifier: NCT07165132) (Figure 3).
- **Treatment**: During dose escalation, 6–24 patients will receive escalating doses of RYZ401 based on a modified Bayesian optimal interval (BOIN) design.[6] No amino acid co-infusion is planned. In the dose-expansion phase, ~80 patients will receive RYZ401 at the RP2D: 40 patients with well-differentiated GEP-NETs (cohort A) and 40 with other SSTR+ tumors including non-GEP-NETs (cohort B).
- **Dosimetry**: RYZ401 dosimetry will be evaluated in a sub-study of approximately 16 patients.

FIGURE 3. Study design



BOIN, Bayesian optimal interval; eGFR, estimated glomerular filtration rate; GEP, gastroenteropancreatic; IV, intravenous; NET, neuroendocrine tumor; PET, positron emission tomography; PK, pharmacokinetics; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria for Solid Tumors; RP2D, recommended phase 2 dose; RPT, radiopharmaceutical therapy; SSTR, somatostatin receptor; SUV, standard uptake value; WD, well-differentiated; WHO, World Health Organization.

Primary objectives	Primary endpoints
Dose escalation	
• Determine the RP2D of RYZ401	• Incidence of DLTs during the first 4 weeks of RYZ401 treatment
Dose expansion	
• Confirm the RP2D of RYZ401 and optimal treatment regimen	• Incidence and severity of AEs by NCI-CTCAE v5.0, including SAEs, laboratory and ECG changes, frequency of dose delays/reductions and other safety findings from first dose of study drug until the last subject completes the second treatment cycle

AE, adverse event; ECG, electrocardiogram; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RP2D, recommended phase 2 dose; SAE, serious adverse event.

CURRENT STATUS

- The study will be open in the USA and Canada.

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For information about this clinical trial please scan the QR code

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