Human Safety Testing of Subcutaneously-administered Ex-RAD® (ON 01210.Na), a Small Molecule Radioprotection Agent

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Abstract

Background: Threat of radiation exposure during natural or manmade disasters underpins the search for medical countermeasures to acute radiation injury. Ex-RAD® (recilisib sodium, ON 01210.Na) is being developed by Onconova Therapeutics, Inc. as a novel radiation countermeasure agent. When dosed either 24 h pre- or post-radiation, Ex-RAD® provided enhanced survival and rate of hematopoietic recovery in mice. FDA’s “Animal Rule” requires safety evaluation in healthy subjects, with efficacy testing only in animals. Here, we report results of two Phase I clinical studies of subcutaneously (SC)-administered Ex-RAD® in healthy adults.

Methods: First-in-man study was a randomized, placebo-controlled single ascending dose trial of 50, 100, 200 or 300 mg of Ex-RAD® (N=32 subjects). Inflammatory serum cytokines (IL-2, IL-6, IL-10, TNF-α, IFN-γ, MCP-1) were monitored. The second randomized, placebo-controlled trial (N=20) evaluated a fractionated 2-dose regimen (200 & 400 mg total doses) and compared absorption kinetics from SC injection sites (abdomen, thigh, buttock).

Results: In both studies, Ex-RAD® was well-tolerated, without clinically significant drug-related systemic toxicity. Main adverse events were mild, limited-injection site reactions, generally subsiding in a few hours. No clinically-significant trends were noted in plasma cytokines between the Ex-RAD® and placebo-treated groups.

Conclusions: Ex-RAD® administered SC to 40 healthy adults showed a good safety profile and rapid absorption, suggesting feasibility for emergency use for war fighters, first-responders, and potentially wider at-risk populations.

Background

Ex-RAD® (Recilisib sodium, ON 01210.Na)

- Novel small molecule drug being developed by Onconova Therapeutics, Inc. as a medical radiation countermeasure for prophylactic use;
- Increased survival, more rapid hematopoietic recovery and protection of GI tissues have been observed in mice following prophylactic dosing.1
- Oral or SC administration of Ex-RAD® is effective in mice.2

Methodology

- Studies were conducted at Covance Clinical Research Unit (Evanston, IL) following GCP regulations, with informed consent and IRB oversight;
- Randomized, double-blind, placebo-controlled trial design;
- Males or females, 18-50 years of age, with body mass index of 19-30 kg/m², inclusive; non-smoker, in good health, based upon results & medical history;
- Safety evaluation included adverse event (AE) & injection site assessments, 12-lead ECGs, vital signs, physical examinations and laboratory assessments;
- A validated LC/MS/MS assay was used for plasma drug determinations; non-compartmental analysis to determine pharmacokinetic (PK) parameters.

First-in-Man Clinical Trial (Study #1):

- Single ascending doses in 32 healthy adult volunteers, as 4 Cohorts (N=8);
- Subjects in each Cohort randomized to receive Ex-RAD® (N=4) or placebo (N=2);
- Subjects received 50 mg, 100 mg, 200 mg or 300 mg of Ex-RAD® as SC injections (or matching placebo injections), distributed over different locations: buttocks, thighs and lower abdomen;
- Cohort 4 subjects (receiving 300-mg or placebo) evaluated for selected plasma cytokines (IL-6, IL-10, TNF-α, IFN-γ, IL-2 and MCP-1) using a multiplex immunoassay; drug responses were compared to placebo & historical controls.

Fractionated SC Dosing Clinical Trial (Study #2):

- Fractionated doses, 4 hr apart, in 20 healthy adults; 2 Cohorts (N=10);
- Subjects in each Cohort (N=10) were randomized to two dosing sequences of Ex-RAD® (N=4) or placebo (N=6);
- Subjects received 200 mg or 400 mg total doses of Ex-RAD® (or matching placebo) as SC injections, in 2 sequences in buttocks, thighs and lower abdomen.

First-in-Man Clinical Trial

Study Objectives

- Primary objectives:
  - Determine local tolerability of single ascending doses of subcutaneously (SC)-administered Ex-RAD®;
  - Determine systemic safety of single ascending doses of SC-administered Ex-RAD®;
  - Determine maximum tolerated dose of SC-administered Ex-RAD®;
  - Determine PK behavior of single ascending doses of SC-administered Ex-RAD®.

Secondary objective:

- Evaluate the effect of Ex-RAD® on selected serum cytokines.

Study #1 Results

Pharmacokinetics:

- Ex-RAD® was readily absorbed (Tmax about 1.5 – 2 h), with rapid plasma clearance;
- Drug exposure increased with increasing dose; (Figure 1 & Table)

Safety:

- SC-administered Ex-RAD® was well-tolerated with no serious adverse events (AE) reported;
- Maximum tolerated dose for SC-administered Ex-RAD® was not determined;
- Mild injection site reaction was the major AE reported for both Ex-RAD® & placebo;
- Local irritation at the site of injection generally resolved within a few hours;
- Levels of plasma cytokines did not show significant drug- or time-dependence. (See Table)

Clinical Study #2

Study Objectives

- Primary objectives:
  - Determine the local tolerability of a 2-dose regimen of SC-administered Ex-RAD®;
  - Determine systemic safety of a 2-dose regimen of SC-administered Ex-RAD®;
  - Determine PK behavior of SC-administered Ex-RAD® under the conditions of the trial.

Secondary objective:

- Estimate effect of injection site on relative bioavailability of Ex-RAD®.

Pharmacokinetics:

- Ex-RAD® was readily absorbed, independent of the site of SC administration;
- Drug exposure increased in a less-than-dose-proportional manner from 200 to 400 mg doses;
- Sites of injection did not affect bioavailability, drug exposure or kinetics. (Figure 2 & Tables)

Conclusions

- SC dosing of Ex-RAD® was generally well tolerated and did not induce inflammatory plasma cytokines, with no reports of serious AEs;
- Mild injection site reaction was most commonly reported AE for both Ex-RAD® & placebo;
- All AEs were mild or moderate and resolved prior to the end of the study;
- No clinically-significant systemic toxicity, laboratory or safety-related findings.

References


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For more information about Onconova Therapeutics and Ex-RAD®, visit http://www.onconova.com