Safety, Tolerability and Pharmacokinetic Behavior of Escalating Single Oral Doses of Ex-RAD® (ON 01210.Na) in Healthy Volunteers

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ABSTRACT

Background: Ex-RAD® (ON 01210.Na), a novel benzyl styrylsulfone, is being developed by Onconova Therapeutics as a new radioprotectant displaying both prophylactic and mitigation effects by enhancing cell survival and DNA repair mechanisms. *Ex-RAD* has completed four Phase I clinical trials (3 SC and 1 oral) in healthy volunteers under two Investigational New Drug (IND) exemptions. Upon subcutaneous (SC) administration, the drug was rapidly absorbed, reaching maximal blood levels in about 2 hours and was very well-tolerated. Here, we report results of the first clinical trial of orally-administered *Ex-RAD* in healthy adults and compare drug exposure achieved in humans to that observed in animals during radiation injury efficacy studies.

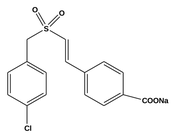
Methods: In an open-label, single ascending dose study, three cohorts (3 subjects/cohort) received 200 mg, 400 mg or 800 mg of oral *Ex-RAD* solution under fasting conditions. Blood samples were taken pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hrs post-dose for pharmacokinetic (PK) analysis using a validated LC-MS/MS method. Non-compartmental PK analysis was performed using WinNolin (Pharsight Corp.).

Results: The drug was very well tolerated. Maximum plasma drug concentration was reached within 0.5-1.5 h of dosing. With increasing dose, mean C_{max} and $AUC_{0-\infty}$ values increased more than dose-proportionately, with corresponding decreases in the clearance of *Ex-RAD*. For the 200-, 400- and 800-mg cohorts, mean elimination half-lives were 4.08 h, 4.11 h and 4.85 h, while the overall drug exposure values were 11.9 µg-hr/mL, 28.3 µg-hr/mL and 88.6 µg-hr/mL, respectively. Furthermore, drug exposure achieved for the 200-mg oral dose was ~135% of that observed with a 200-mg SC injection in an earlier clinical study. Drug exposure levels in small animal efficacy studies ranged from 74.8 to 202 µg-hr/mL.

Conclusions: *Ex-RAD* displayed excellent oral bioavailability and was well tolerated. Exposure levels of *Ex-RAD* predicted by allometric scaling to be efficacious in humans can be readily achieved upon oral administration. Oral delivery of *Ex-RAD* is feasible and would provide a convenient route of administration for first-responders, civilian mass casualties or at-risk populations in imminent danger of exposure to harmful ionizing radiation.

BACKGROUND

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



- A medical countermeasure being developed by Onconova Therapeutics, Inc. that protects cells from harmful effects of ionizing radiation (IR).
- Four Phase I clinical trials (3 subcutaneous and 1 Oral) completed in healthy adult volunteers.
- Demonstrated good local tolerance following SC administration.
- Oral administration in mice showed comparable bioavailability relative to subcutaneous administration.[1]
- Has a novel mode of action, involving the enhancement of cellular DNA repair pathways and key elements of the DNA damage cascade.[2,3,]
- Demonstrates both prophylactic (prior to exposure to IR) as well as mitigation effects (shortly after IR exposure) in mice.[4]
- Both injection and oral administration are available for convenient use and rapid distribution.

OBJECTIVES

- To determine the systemic exposure, PK behavior and systemic safety of a single ascending dose of orally-administered ON 01210.Na

STUDY DESIGN

- Study was conducted at the Covance Clinical Research Unit (Evansville, IN) under IRB supervision.
- Open-label, non-controlled, escalating single dose of ON 01210.Na, administered orally to healthy adult male and female volunteers.
- Three ascending doses of stabilized ON 01210.Na solution were sequentially evaluated:
  - Cohort 1 (3 subjects): 200 mg
  - Cohort 2 (3 subjects): 400 mg
  - Cohort 3 (3 subjects): 800 mg

STUDY DESIGN

- Subjects were admitted on Day-1 and fasted overnight for at least 10 hours before oral dosing.
- Water was permitted during the fasting period; no food was allowed for at least 1 hour after dosing on Day 1.
- A 1-hour safety observation period was observed after dosing (prior to dosing the next subject).
- Subjects were discharged after evaluation on Day 2.
- An End-of-Study (EOS) visit occurred at Day 7 (±2 days).
- There was a 30-day post-dosing safety reporting period, during which all reported Adverse Effects (AEs) were recorded.
- Blood PK samples were taken at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hrs post-dose on Day 1 and urine PK samples were collected pre-dose and pooled from 0 to 24 hrs post-dose.
- The plasma concentrations were determined by a validated LC-MS/MS assay.
- Pharmacokinetic calculations were performed using the non-compartmental model in WinNolin (Pharsight Corporation, Version 5.2) and AUC was calculated by the linear trapezoidal rule.
- An analysis of variance (ANOVA) was performed on PK data.

RESULTS

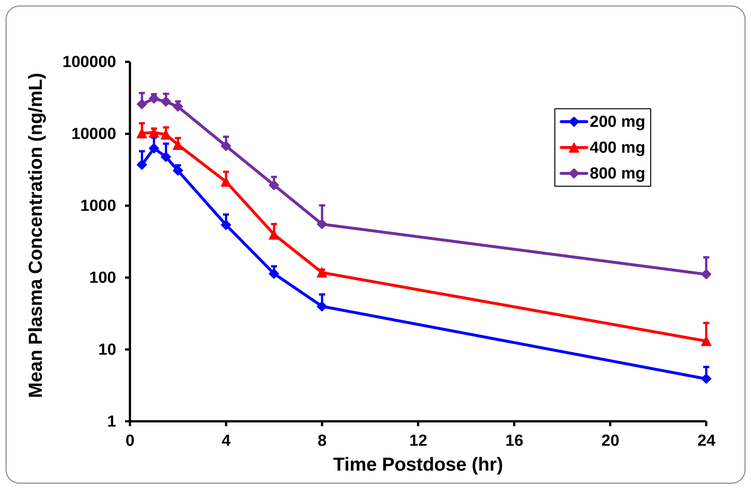


Figure 1: Arithmetic mean concentration-time profiles for ON 01210 (Semi-logarithmic scale) at different doses.

Table 1: Mean (SD) Plasma PK Parameter Data for ON 01210

PK Parameter	Units	ON 01210.Na 200 mg	N	400 mg	N	800 mg	N
AUC_{0-t}	(ng·hr/mL)	12909(2819)	3	30267 (2457)	3	95661 (15672)	3
$AUC_{0-\infty}$	(ng·hr/mL)	12932 (2810)	3	30357 (2452)	3	96542 (15833)	3
C_{max}	(ng/mL)	6270 (2597)	3	11700 (2022)	3	34567 (5750)	3
t_{max}[a]		1.00		0.500		1.00	
	(hr)	(1.00, 1.00)	3	(0.500, 1.00)	3	(0.500, 1.50)	3
λ_{z}	(1/hr)	0.172 (0.0254)	3	0.179 (0.0491)	3	0.157 (0.0620)	3
$t_{1/2}$	(hr)	4.08 (0.570)	3	4.11 (1.29)	3	4.85 (1.62)	3
CL/F	(L/hr)	16.0 (3.84)	3	13.2 (1.07)	3	8.43 (1.36)	3
V_z/F	(L)	94.2 (26.1)	3	78.3 (24.5)	3	59.6 (25.5)	3

AUC_{0-t} = area under the concentration-time curve from hour 0 to the last measurable concentration
$AUC_{0-\infty}$ = area under the concentration-time curve from hour 0 to infinity
C_{max} = Maximum observed plasma concentration
T_{max} = Time to reach maximum plasma concentration
λ_z = Apparent terminal phase rate constant
$t_{1/2}$= Apparent mean half-life
CL/F= Apparent extravascular clearance
V_z/F= Apparent volume of distribution after extravascular administration
[a] Median (min, max) presented for t_{max}.

Table 2: ANOVA Analysis of Dose-Normalized (DN) PK Parameters

Parameters (Units)	ON 01210.Na	N[a]	Geometric LS mean[b]	Ratio of Geometric LS mean (90% CI)[c] vs 400 mg	vs 200 mg
DN-AUC_{0-t} (ng·hr/mL)/(mg)	800 mg	3	119	1.57(1.20 , 2.06)	1.87(1.43 , 2.45)
	400 mg	3	75.5		1.19(0.91 , 1.56)
	200 mg	3	63.4		
DN-$AUC_{0-\infty}$ (ng·hr/mL)/(mg)	800 mg	3	120	1.58(1.20 , 2.07)	1.88(1.44 , 2.47)
	400 mg	3	75.7		1.19(0.91 , 1.56)
	200 mg	3	63.5		
DN-C_{max} (ng/mL)/(mg)	800 mg	3	42.8	1.48(0.91 , 2.38)	1.46(0.90 , 2.35)
	400 mg	3	29.0		0.988(0.61 , 1.59)
	200 mg	3	29.4		

[a] N was the number of subjects with evaluable PK data for the treatment.
[b] Least squares mean from ANOVA.
[c] Ratio of parameter mean for ln transformed parameter. If the 90% confidence interval (CI) of the geometric mean ratio contained the value of 1, then the increases in that PK parameter is dose proportional.

RESULTS

Table 3. Summary of Treatment Emergent Adverse Effects

	200 mg ON 01210.Na (N=3)	400 mg ON 01210.Na (N=3)	800 mg ON 01210.Na (N=3)	Overall (N=9)
Subjects with adverse events	0 (0.0%)	1 (33.3%)	1 (33.3%)	2 (22.2%)
Number of adverse events	---	1	3	4
Subjects with serious adverse events	---	---	---	---
Subjects discontinued due to adverse events	---	---	---	---
Severity (all adverse events)				
Mild	---	1 (33.3%) [1]	1 (33.3%) [3]	2 (22.2%) [4]
Moderate	---	---	---	---
Severe	---	---	---	---
Total	---	1 (33.3%) [1]	1 (33.3%) [3]	2 (22.2%) [4]
Relationship to study drug				
Not Related	---	---	---	---
Unlikely Related	---	---	---	---
Possibly Related	---	---	1 (33.3%) [1]	1 (11.1%) [1]
Probably Related	---	---	1 (33.3%) [2]	1 (11.1%) [2]
Definitely Related	---	1 (33.3%) [1]	---	1 (11.1%) [1]

( ) = Percentage of subjects with adverse effects; [ ] = Number of adverse events; N = Number of study subjects
Overall, 4 Treatment-Emergent Adverse Events (TEAEs) were reported:
1 TEAE was reported by 1 subject following 400 mg dose of ON 01210.Na (dysgeusia);
3 TEAEs were reported by 1 subject following 800 mg dose of ON 01210.Na (headache, dizziness, nausea);
All 4 TEAEs were considered treatment-related and were mild in severity.

SUMMARY OF RESULTS

- ***Ex-RAD* was rapidly absorbed following a single oral administration at dose 200, 400 and 800 mg.**
- ***Ex-RAD* levels peaked in 30-90 minutes and declined rapidly, with mean $t_{1/2}$ ranging from 4.08 to 4.85 hrs and were generally dose independent.**
- **The mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of *Ex-RAD* increased with increase in dose. Increases in C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were dose proportional between the 200 mg and the 400 mg dose levels. The increases in drug exposure from 200 to 800 mg and from 400 to 800 mg were greater than dose proportional for AUC_{0-t} and $AUC_{0-\infty}$, but were dose proportional for C_{max}.**
- ***Ex-RAD* mean CL/F and Vz/F generally decreased with increase in dose level.**

CONCLUSIONS

- ***Ex-RAD* displayed excellent oral bioavailability comparable to SC administration and was well tolerated.**
- **Clinical safety assessments including AEs, laboratory evaluations, vital signs and ECGs were unremarkable.**
- **Oral delivery of *Ex-RAD* is a feasible and convenient route of administration.**

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