A Phase 1 Study to Assess Oral Bioavailability of a Novel Oral Soft Gelatin Capsule Formulation of Rigosertib (ON 01910.Na) Under Fasted and Fed Conditions in Patients with Myelodysplastic Syndromes

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Introduction

- Rigosertib (ON 01910.Na) is a novel small molecule being developed by Onconova Therapeutics, Inc. to treat cancer.
- The compound has a multi-targeted mechanism of action, including polo-like kinase and PI3 kinase pathways inhibition, resulting in a selective block of mitosis and death in cancer cells, even those carrying drug resistant mutations.
- Preclinical experiments show that Rigosertib is active against numerous cancer types alone or in combination with other chemotherapies.
- Pharmacokinetic studies show that the compound is rapidly eliminated from the plasma ($t_{1/2}$ < 2hr), with limited evidence of metabolism but extensive biliary excretion.
- Over 400 patients have been treated with intravenous Rigosertib in Phase I and Phase II clinical trials, and the compound has exhibited a good safety profile with a low incidence of toxicity.
- The lead indication is myelodysplastic syndromes (MDS), and ongoing studies show favorable results in MDS patients (bone marrow responses, improvemenst in cytopenias).
- The U.S. FDA has designated the compound as an Orphan Drug for treatment of MDS and has provided a Special Protocol Assessment (SPA), accepting a pivotal Phase III trial design for monotherapy in patients with MDS refractory to hypomethylating agents.

Rationale

- In vitro permeability studies with Caco-2 cells demonstrated that Rigosertib may have the potential for oral absorption as indicated by the high apparent permeability (~1.0x10^{-6} cm/s).
- The potential for oral absorption was confirmed with an in-situ perfused rat intestine model, which showed highest permeability and fraction absorbed in the jejunum compared with other intestinal segments.
- An oral formulation, mimicking the injectable formulation, was developed as a soft gelatin capsule for evaluation in MDS patients

Methods

- Phase I dose escalating (70 to 700 mg oral fasting rigosertib solution dosing bid for 2 out of 3 weeks) study in MDS patients refractory to ESA, lenalinomide or hypomethylating agents
- Single-dose, three-treatment, three-period sequential design for studying the effects of food on the bioavailability of an immediate-release soft gelatin capsule formulation
- Following dosing groups tested in 12 patients:
  - IV dose 800 mg/m^2 over 24 hours
  - Oral dose 560 mg (2 x 280 mg capsules) under fasting and fed conditions (recommended phase 2 dose, as reported previously[1]

Methods

- Plasma samples collected pre-dose, and over 32 hours (IV dose) or 8 hours (oral dose) after dose initiation
- Rigosertib plasma levels analyzed by a validated LC-MS/MS method
- Pharmacokinetic parameters estimated by noncompartmental analysis (WinNolin®)
- Composition of the soft gelatin capsule formulation is as follows:

Ingredient	Function
ON 01910.Na	Active Ingredient
PEG 400	Diluent
PEG 4000	Viscosity Modifier

- **LC-MS/MS bioanalysis**

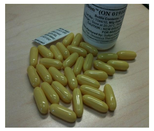
Instrument:	Sciex API 4000 LC-MS/MS system
Column:	BDS Hypersil C18, 100 x 3.0 mm, 3 µm
MPA:	10 mM Ammonium Acetate
MPB:	0.1% FA in acetonitrile
Flow rate:	0.3 mL/min (0.5 mL/min at 4 to 5.5 min)
Injection volume:	2-20 µL
Gradient:	Isocratic at 55% B for 5.5 min
Ionization mode:	Turbo IonSpray®, Positive Ion ESI
MRM Scan Mode:	ON 01910.Na 452.1 → 194.2
	ON 01500 394.0 → 136.0
	Temazepam (IS) 301.3 → 255.1

Oral Dosing with Capsules in MDS Patients

- Part III of Protocol: Absolute bioavailability under Fast / Fed Condition
- Cohort of 12 Patient at MTD; 560 mg administered as 2 x 280 mg Softgel
- Intravenous administration of drug – 800 mg/m^2 administered over 24 hours

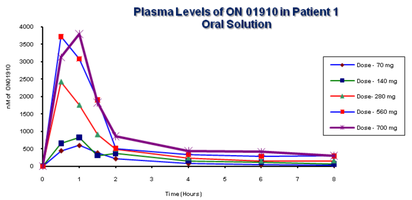
Day	1	2	3	4
ON 01910.Na IV	X			
ON 01910.Na PO Fasting			X	
ON 01910.Na PO Fed				X
PK Analysis	X[a]		X[b]	X[b]

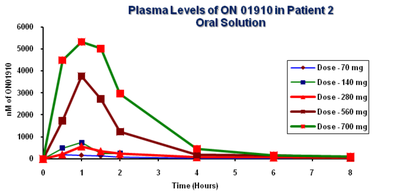
[a] Predose, 1 hr, 3 hr, 6 hr, 12 hr, 18 hr, 24 hr, and 15 min, 30 min, 1, 2, 4, and 8 hr post infusion
[b] Predose, 30 min, 1 hr, 1.5 hr, 2 hr, 4, 6, and 8 hours

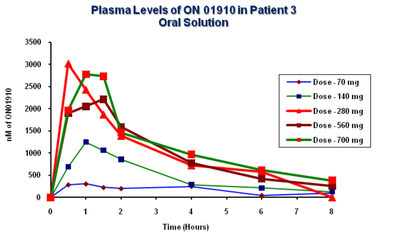


280 mg Soft Gelatin Capsule of Rigosertib

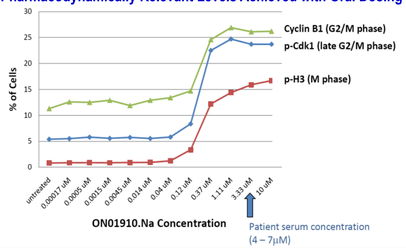
Results



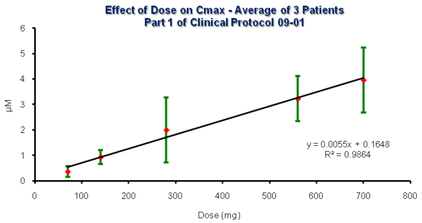




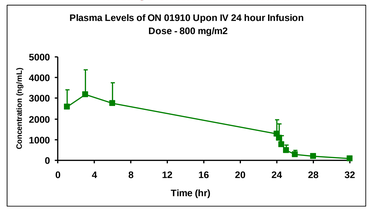
Pharmacodynamically Relevant Levels Achieved with Oral Dosing



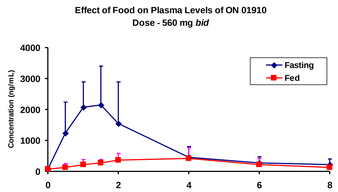
Results



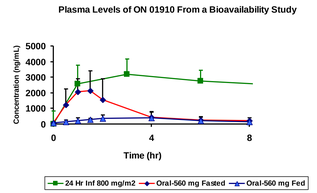
IV Dosing of ON 01910.Na in MDS Patients



Oral Dosing of ON 01910.Na in MDS Patients



Comparison of IV and Oral Dosing of ON 01910.Na in MDS Patients



Results

Absolute Bioavailability of Rigosertib

SUBJECT	C_{max} (µg/ml)			$AUC_{0-\infty}$ (µg-hr/ml)			F (% Bioavailability)	
#	Infusion	Oral Fast	Oral Fed	Infusion	Oral Fast	Oral Fed	Oral Fast	Oral Fed
27	2.74	3.46	0.26	58.28	7.93	2.05	37.30	9.66
29	1.99	0.99	0.51	29.57	2.70	1.80	24.77	16.54
30	2.26	1.61	0.87	37.96	10.44	3.68	83.72	29.54
31	4.16	2.34	0.88	68.47	6.94	4.14	26.51	15.79
32	2.88	2.43	0.58	45.71	5.36	2.10	36.03	14.09
33	3.99	4.39	0.50	67.35	11.08	3.64	41.37	13.60
34	2.50	1.73	0.38	43.25	3.83	1.69	24.06	10.62
35	1.86	1.98	0.30	36.52	4.60	1.65	36.18	12.99
38	5.69	4.80	1.22	97.11	15.30	6.08	30.16	11.98
39	3.44	1.34	0.46	49.68	4.99	2.23	25.70	11.47
40	2.99	1.58	0.18	45.48	2.64	0.80	18.15	5.47
Average	3.14	2.42	0.56	52.67	6.89	2.71	**34.90**	**13.80**

Average IV dose is 1521 mg administered over 24 hours
Oral dose is 560 mg; approximately **37%** of IV Dose
F (%Bioavailability) = 100*(AUC_{PO}*$Dose_{Iv}$)/ (AUC_{Iv}*$Dose_{po}$)

Summary of Bioavailability Study

Parameter	Dosing Group		
	800 mg/m^2 IV (24 hr Infusion)	560 mg Oral (Fasting)	560 mg Oral (Fed)
C_{max} (µg/ml)	3.14 ± 1.13	2.42 ± 1.26	0.56 ± 0.31
AUC (µg-hr/ml)	52.7 ± 19.2	6.89 ± 3.98	2.71 ± 1.51
T_{max} (hr)	2.91 ± 1.30	1.00 ± 0.45	2.82 ± 1.15
$T_{1/2}$ (hr)	3.25 ± 0.97	2.79 ± 1.23	2.61 ± 0.93
Bioavailability %	**N/A**	**34.9 ± 17.6**	**13.8 ± 6.04**

Conclusions

- **Good oral bioavailability of rigosertib under fasting condition**
- **Oral administration of rigosertib after a meal decreased Cmax and AUC by 77% and 61%, respectively, compared to fasting conditions**
- **The results of this study support the potential for oral delivery of rigosertib, which could become a preferred therapy over a 3-day continuous intravenous infusion**

Reference

1. R.S. Komrokji et al., Oral Formulation of Rigosertib (ON 01910.Na) in Patients with Myelodysplastic Syndrome (MDS) – Phase I Study Results. *Blood* 2011, 118:Abstract #3797