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 pathway 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 (t1/2 < 2hr), with limited evidence of metabolism but extensive biliary excretion.
- Over 400 patients have been treated with intravenous Infusion, following dosing groups tested in 12 patients:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Amount</th>
<th>Time</th>
<th>Tmax</th>
<th>Cmax</th>
<th>AUC0-∞</th>
<th>%F</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg/m2</td>
<td>1521 mg</td>
<td>24 hr</td>
<td>1.86</td>
<td>0.46</td>
<td>97.4</td>
<td>100</td>
</tr>
<tr>
<td>600 mg/m2</td>
<td>1321 mg</td>
<td>24 hr</td>
<td>1.58</td>
<td>0.36</td>
<td>96.4</td>
<td>100</td>
</tr>
</tbody>
</table>

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 (WinNonLin®).
- Composition of the soft gelatin capsule formulation is as follows:
  - PEG 400
  - Viscosity Modifier

Results

- Pharmacodynamically Relevant Levels Achieved with Oral Dosing

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