Cancer Stem Cells (CSCs)

- CSCs are tumor cells resistant to standard therapies and capable of seeding new tumors
- CSC survival may result in tumor recurrence and metastasis
- CSCs are tumor cells resistant to standard therapies

**Background**

- VS-6063 (defactinib)
- Preferentially targets CSCs through the inhibition of focal adhesion kinase (FAK)
- PK and toxicity profile previously characterized in Phase 1 studies in advanced solid tumors
- VS-5584
- Preferentially targets CSCs through dual inhibition of PI3K & mTOR kinases
- Phase 1 evaluation in advanced solid tumors is ongoing

**Methods**

- **Archival / optional biopsy**
- Escalating dose levels of VS-5584 will be studied in Part 1
- VS-6063 administered orally 400 mg BID
- VS-5584 administered orally on an intermittent (3x weekly) dosing

**Study Design**

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exploratory Efficacy Objectives</strong>&lt;br&gt;Assess pharmacokinetics of VS-5584 and VS-6063 when co-administered</td>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Assess pharmacokinetics of VS-5584 and VS-6063 when co-administered</td>
</tr>
<tr>
<td><strong>Primary Efficacy Objectives</strong>&lt;br&gt;Determine MTD of VS-5584 when given with fixed dose of VS-6063</td>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Assess safety and tolerability of the combination in relapsed mesothelioma</td>
</tr>
<tr>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Determine recommended Phase 2 dose (RP2D) and schedule of combination</td>
<td><strong>Primary Efficacy Objectives</strong>&lt;br&gt;Standard of care plus treatment after failure of standard of care</td>
</tr>
<tr>
<td><strong>Exploratory Efficacy Objectives</strong>&lt;br&gt;Response rate</td>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Duration of response</td>
</tr>
<tr>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Response rate</td>
<td><strong>Primary Efficacy Objectives</strong>&lt;br&gt;Biomarker correlation with response</td>
</tr>
<tr>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Response rate</td>
<td><strong>Secondary Efficacy Objectives</strong>&lt;br&gt;Pharmacodynamics</td>
</tr>
</tbody>
</table>

**Objectives**

- VS-5584 administered orally on an intermittent (3x weekly) dosing schedule
- VS-6063 administered orally 400 mg BID
- Escalating dose levels of VS-5584 will be studied in Part 1
- To up to an additional 20 evaluable patients will be enrolled in Part 2
- VS-5584 + VS-6063 combination for relapsed malignant mesothelioma
- VS-6063 + VS-5584 combination for relapsed malignant mesothelioma

**Eligibility Criteria**

- **Key Inclusion Criteria**
  - Histological proof of malignant mesothelioma (pleural or peritoneal)
  - Relapsed disease following at least one prior line of chemotherapy
  - Evaluable or measurable disease as assessed by RECIST v1.1
  - Archival tumor tissue or study-specific sample available for biomarker analysis
  - KPS ≥70%

- **Key Exclusion Criteria**
  - Previous extra pleural pneumonectomy (EPP)
  - History of upper GI bleed, ulceration or perforation
  - Uncontrolled or severe concurrent medical condition (including uncontrolled brain metastases)
  - Known history of stroke or cerebrovascular accident in prior 6 months
  - Major surgery within 28 days
  - Serious active infection

**Summary**

- Currently enrolling across 4 sites in the United Kingdom and United States
- VS-6063 (defactinib) is a potent, selective FAK kinase inhibitor
- VS-5584 is a potent, selective inhibitor of PI3K & mTORC1/2
- Both agents preferentially target CSCs and reduce bulk tumor growth in preclinical mesothelioma models
- Synergistic activity of VS-6063 & VS-5584 on CSCs & bulk tumor has been observed in preclinical models
- A Phase 1 combination study of VS-6063 & VS-5584 in patients with relapsed mesothelioma is ongoing