Background

- **4SC-202** is a orally available small molecule inhibitor, specifically targeting the epigenetic relevant enzymes HDACi, HDAC, and LSD1.
- LSD1 and HDACi2 are essential components of CREB and NuRD complexes, acting synergistically.
- NuRD and CoREST complexes are involved in gene regulation of multiple pathways like WNT and Hedgehog signaling.
- The combined inhibition of LSD1 and HDAC is a unique feature of 4SC.
- LSD1 and HDAC1/2 are essential components of CoREST and NuRD complexes.
- 4SC-202's mode of action via modulation of the WNT and HH signaling pathways could be determined in patient blood samples.

TOPAS Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>CL/F (C1D1)</th>
<th>Vd/F (C1D1)</th>
<th>T½ (C1D1)</th>
<th>CL/F (C1D)</th>
<th>Vd/F (C1D)</th>
<th>T½ (C1D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg OD</td>
<td>15.4 L</td>
<td>1.4 L</td>
<td>15.5 h</td>
<td>14.0 L</td>
<td>1.5 L</td>
<td>14.7 h</td>
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<tr>
<td>200 mg OD</td>
<td>15.0 L</td>
<td>1.3 L</td>
<td>13.6 h</td>
<td>11.5 L</td>
<td>1.4 L</td>
<td>12.2 h</td>
</tr>
<tr>
<td>400 mg OD</td>
<td>16.0 L</td>
<td>1.4 L</td>
<td>12.0 h</td>
<td>12.5 L</td>
<td>1.5 L</td>
<td>13.0 h</td>
</tr>
</tbody>
</table>

Study open for patients with advanced hematologic malignancies and not eligible for other (standard) therapy.

TOPAS Safety

- Overall very good tolerability even in elderly and heavily pre-treated patients.
- No cumulative toxicity observed despite long treatment durations.
- Safety profile for 14 + 7 schedule is favorable over continuous dosing.
- Pharmacodynamic response to 4SC-202 was determined by lysine acetylation
- Repression of genes associated to the WNT and HH signaling pathway can be monitored in whole blood samples of treated patients.

TOPAS Time on Treatment

- 75% (10/24) went into Follow Up treatment
- 1 patient had long term treatment for 720 days, 1 patient (CR) still on treatment

TOPAS Case Studies

- Pat. 308, male, 69 years old (at inclusion)
  - In 04/2012, relapse in 11/2012
  - At study start (11/2012)
  - Event (PT) related with Grade 2 or higher
  - Recommended Phase II Dose is 200 mg BID in 14 + 7 design

TOPAS Biomarker

- Hematologic malignancies and showed favorable PK properties
- 4SC-202 showed signs of anti-tumor efficacy with 1 CR, 1 PR and long term stabilization of several patients
- 4SC-202’s mode of action via modulation of the WNT and HH signaling pathways could be determined in patient blood samples
- Anticipated Phase II development addresses indications with a causal relationship to aberrant WNT and HH signaling
- Recommended Phase II Dose is 200 mg BID in 14 + 7 design