Safety and Efficacy Experience of Voreloxin (formerly SNS-595) in Relapsed/Refractory Acute Leukemia

Patients ≥ 60 years old: Results of a Phase 1b Study

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Abstract

Efficacy and safety experience of voreloxin (formerly SNS-595) was evaluated in adult patients with relapsed/refractory acute leukemia who had failed prior therapy. Patients were ≥60 y (n=26) or <60 y (n=42). Study Design Phase 1b single agent dose escalation with 2 dose schedules: Weekly IV administration of voreloxin injection (Days 1, 8, and 15) for 3 dose-escalation and twice weekly IV administration of voreloxin injection (Days 1, 4, 8, and 11) for 4 dose-escalation. Safety and Efficacy Experience System Organ Class Preferred Term ≤ 60 y (%) ≥ 60 y (%) Total (%) Population 21 42 63

Patients who reported any NCI CTCAE v3 G3 or G4 AE by < 60 y and ≥ 60 y

Safety: G3 or Higher AE By < 60 y and ≥ 60 y

Blood and lymphatic system disorders

• Febrile neutropenia 34 (39) 20 (48) 54 (37)
• Neutropenia 37 (32) 21 (48) 58 (37)
• Thrombocytopenia 15 (15) 10 (23) 25 (19)
• Thrombocytopenia with bleeding 4 (4) 2 (4) 6 (5)

Gastrointestinal disorders

• Diarrhea 34 (39) 20 (48) 54 (37)
• Diarrhea with dehydration 5 (5) 2 (4) 7 (5)

Infections and infestations

• Bacteraemia 6 (7) 4 (9) 10 (7)
• Fungal pneumonia 8 (9) 8 (19) 16 (12)
• Pneumonia 9 (10) 9 (21) 18 (13)

Neurological disorders

• Seizures 1 (1) 1 (2) 2 (1)

Pharmacokinetics were not affected by age; no age-related change was observed in voreloxin Cl, Vss, MRT or T1/2. Preliminary results of voreloxin in combination with cytarabine in relapsed/refractory AML in patients ≥60 y. Preliminary results of the combination study are reported here as well.

Aims

- Complete the safety and pharmacokinetics for patients treated with voreloxin as front line treatment for AML, particularly ≥60 y. Complete remissions were observed in both age groups. Pharmacokinetics were not influenced by age. Given this safety profile, a single agent study of voreloxin as front line treatment for AML patients ≥60 y is underway as a combination study with cytarabine for relapsed/refractory AML in patients ≥60 y. Preliminary results of the combination study are reported here as well.

Conclusions

- Complete remissions were observed in both age groups. Pharmacokinetics were not influenced by age. Given this safety profile, a single agent study of voreloxin as front line treatment for AML patients ≥60 y is underway as a combination study with cytarabine for relapsed/refractory AML in patients ≥60 y. Preliminary results of the combination study are reported here as well.

Study Design

• Phase 1b single agent dose escalation with 2 dose schedules: Weekly IV administration of voreloxin injection (Days 1, 8, and 15) for 3 dose-escalation and twice weekly IV administration of voreloxin injection (Days 1, 4, 8, and 11) for 4 dose-escalation

• Primary endpoints were safety, pharmacokinetics and MTD determination

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• Clinical response assessment per NCI criteria

• Analysis of safety and efficacy completed for patients younger than 60 and age 60 and older.

Demographics

< 60 y N = 26 ≥ 60 y N = 42

- Median Age (Range) 43.5 (21-59) 69 (60-80)
- % Female 36% 37%
- ECOG PS (<3) 90% 95%
- Relapse/Refract/Both 11% (43/60) 20% (85/425)
- AML 74% 88%

Conclusions and Future Directions

- Voreloxin behaves similarly in patients < 60 y and ≥ 60 y:
  - Overall incidence and type of adverse events was similar
  - Complete Remissions (CR/CRp) were observed in both populations with 4 of 6 CR/CRp ≥ 60 y
  - Pharmacokinetics were not affected by age; no age-related change was observed in voreloxin Cl, Vss, MRT or T1/2

- Preliminary results of voreloxin in combination with cytarabine show:
  - Complete remissions have been observed in relapsed/refractory patients
  - Historical single agent cytarabine response in this population 14-29% [SWOG Arch. Int. Med. 1974]
  - No dose limiting toxicities to date, dose escalation continues (at 70 mg/m2)
  - Voreloxin pharmacokinetics are unaffected by cytarabine thus far

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- Prior phase 1b dose escalation study of voreloxin given within 10 minute IV infusion on days 1 and 4 in combination with 400 mg/m2/day CIV x 5 days cytarabine

- Patients with relapsed and/or refractory AML

- Primary objectives are safety and pharmacokinetics of voreloxin

- Secondary objectives are preliminary assessment of anti-leukemic responses and pharmacodynamic markers

- Patients can be 18 y and older and have failed up to 3 prior regimens

- Median age for all patients enrolled thus far is 60-64 y (range 44-75 y)

Voreloxin and Cytarabine Combination Study Design

- Multi-center phase 1b dose escalation study of voreloxin given within 10 minute IV infusion on days 1 and 4 in combination with 400 mg/m2/day CIV x 5 days cytarabine

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Combination Study Preliminary Results

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Voreloxin mg/m2</th>
<th>Ts / Enrolled</th>
<th>DLTs</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>6/4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>3/4</td>
<td>0</td>
<td>1 CR (sent for BMT)</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>6/4</td>
<td>0</td>
<td>2 CRs (sent for BMT)</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>6/4</td>
<td>TBD</td>
<td>2 BM cleared, in recovery 1 BM cleared, relapsed 1 too early for evaluation 1 PD, 1 off-study unrelated AE</td>
</tr>
</tbody>
</table>

Clinical Responses By ≤ 60 y and ≥ 60 y

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose and Schedule (mg/m2)</th>
<th>Relapsed/Refractory (No. Prior Refract)</th>
<th>Cytogenetics</th>
<th>Cycle Received</th>
<th>Response Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>72/52</td>
<td>Refractory (1)</td>
<td>Unavailable 1</td>
<td>4 followed by BM</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>72px</td>
<td>Refractory (1)</td>
<td>Unavailable</td>
<td>2</td>
<td>6+</td>
</tr>
<tr>
<td>66</td>
<td>50px</td>
<td>Remission (1)</td>
<td>Intermediate</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>74</td>
<td>60px</td>
<td>Remission (1)</td>
<td>Unavailable 1</td>
<td>1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>71</td>
<td>90/72px</td>
<td>Remission (1)</td>
<td>Intermediate</td>
<td>1*</td>
<td>7*</td>
</tr>
<tr>
<td>74</td>
<td>420px</td>
<td>Remission (1)</td>
<td>Intermediate</td>
<td>3</td>
<td>7/5</td>
</tr>
</tbody>
</table>

Notes:

*Patient treated at 90 mg/m2 then dose reduced to 72 mg/m2. First voreloxin remission was 7 months, patient relapsed and is now receiving second voreloxin induction.

**First voreloxin remission was 7 months, patient relapsed and was reinduced with voreloxin, achieved complete remission with duration of ~5 months, relapsed and is now receiving 3rd voreloxin induction.