Efficacy and Pharmacokinetics of SCYX-7158: A Novel and Potent Oxaborole-6-Carboxamide Selected as a Pre-Clinical Candidate for Once-Daily Oral Treatment for Stage 2 Human African Trypanosomiasis

Robert Jacobs1, Bakela Nare1, Stephen Wiring1, Cy Baccil6, Reto Brun2, Jacob Plattner1, Beth Beaudet1, Tana Bowling1, Daitao Chen1, Yvonne Freund1, Eric Gaukel1, Matthew Jenks1, Marcel Kaiser3, Luke Meier5, Andy Niel5, Matthew Orr1, Robin Parham1, Cindy Rewerts1, Jessica Sligar1, Nigel Taylor1, Robert Don5

1SCYNEXIS, Inc., Research Triangle Park, NC, United States, 2Pace University, New York, NY, United States, 3Swiss Tropical Institute, Basel, Switzerland, 4Anacor Pharmaceuticals, Inc., Palo Alto, CA, United States, 5Drugs for Neglected Disease initiative, Geneva, Switzerland.

Abstract

SCYX-7158, a 3,3-dimethyl-oxaborole-6-carboxamide, is distinguished from earlier trypanocidal oxaboroles by enhanced pharmacokinetic and CNS disposition properties allowing for a once per day (QD) dosing regimen at a markedly lower efficacious dose in a Stage 2 murine Human African Trypanosomiasis (HAT) model. The discovery of SCYX-7158 was achieved through application of integrated lead optimization strategies across medicinal chemistry, pharmacology and pharmacokinetic disciplines. SCYX-7158 is active in vitro against relevant strains of Trypanosoma brucei, including T. b. rhodesiense and T. b. gambiense, and is efficacious in both Stage 1 and Stage 2 murine HAT models. Pharmacokinetic and in vitro ADME properties of SCYX-7158 are consistent with the compound being orally available, metabolically stable, readily CNS permeable and with low risk for drug-drug interactions. In an ongoing murine Stage 2 study, SCYX-7158 is effective orally at doses as low as 12.5 mg/kg (QD x 7 days). In vivo pharmacokinetic characterization of SCYX-7158 demonstrates that the compound is highly bioavailable in rodents, has low intravenous plasma clearance, a 24 h elimination half-life and a volume of distribution that indicates good tissue distribution. Most importantly, SCYX-7158 readily distributes into brain and CSF and crosses the blood-brain barrier to achieve therapeutically-relevant concentrations in potential trypanosomiasis sanctuary sites. Based on these properties, which promise lower rates of resistance than with current standard of care, SCYX-7158 has been selected as a pre-clinical candidate for treatment of Stage 2 HAT.

In vitro activity against Trypanosoma brucei strains

<table>
<thead>
<tr>
<th>Strain</th>
<th>IC50 (µM)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. b. gambiense 410</td>
<td>0.09</td>
<td>Isolated from a patient in Tanzania in 1982, adapted to cell culture at Swiss Tropical Institute.</td>
</tr>
<tr>
<td>T. b. gambiense 1010R</td>
<td>0.44</td>
<td>Isolated from a patient in DRC in 2005, relapse 8 mo. after melarsoprol treatment.</td>
</tr>
<tr>
<td>T. b. gambiense 1058</td>
<td>0.23</td>
<td>Isolated from a patient in DRC in 1990.</td>
</tr>
</tbody>
</table>

In vivo efficacy in murine HAT models

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Treatment Duration (days)</th>
<th>Survival @ Day 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 Non-CNS Model (Acute)</td>
<td>1</td>
<td>25</td>
<td>i.p.</td>
<td>4</td>
<td>&gt;30</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>i.p.</td>
<td>4</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>p.o.</td>
<td>1</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>10</td>
<td>i.p.</td>
<td>4</td>
<td>&gt;30</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>25</td>
<td>p.o.</td>
<td>1</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>10</td>
<td>p.o.</td>
<td>1</td>
<td>8.3</td>
</tr>
</tbody>
</table>

In vitro PK of SCYX-7158 in rodents

<table>
<thead>
<tr>
<th>Assay</th>
<th>SCYX-7158 Exposure in Rodents</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCYX-7158 achieves drug concentrations in excess of the in vivo IC50 for 12 hours in rodents at a dose of 25 mg/kg in both plasma and brain. In rats, SCYX-7158 also achieves therapeutically relevant drug concentrations in the CSF for 8-10 hours. These data are consistent with observed levels of efficacy in the murine Stage 2 HAT model and form the basis for development of PK-PD relationships for alometric scaling to select doses for human trials.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary

- SCYX-7158 exhibits good in vitro activity against T. b. brucei, T. b. rhodesiense and T. b. gambiense.
- In vitro pharmacocchemical and ADME properties of SCYX-7158 are consistent with expectations for oral availability and CNS exposure.
- Pharmacokinetics of SCYX-7158 in rodents suggest sufficient exposure in plasma, brain and CSF.
- An ongoing Stage 2 (CNS) murine HAT model has demonstrated efficacy of SCYX-7158 at a dose of 25 mg/kg, p.o. q.d. for 7 days.
- SCYX-7158 has been selected for further development as a pre-clinical candidate for Stage 2 HAT.

Synthesis of SCYX-7158

SCYX-7158 is achieved in five steps from 2-bromo phenylboronic acid. Protection of the boronic acid as the n-butyl borocan facilitates generation of an aryllithium reagent, which is trapped by aldehyde. Acid-catalyzed hydrolysis and ring formation delivers the oxaborole ring. Nitration at C(6), followed by reduction of the nitro function and acylation of the resultant amine provides the final drug candidate in 42% overall yield. The current synthetic route requires no chromatographic purification and is anticipated to be operable on multi-kilogram scale.

In vitro ADMET profile of SCYX-7158

<table>
<thead>
<tr>
<th>Protein</th>
<th>Binding Fraction (%)</th>
<th>Mass Balance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasma</td>
<td>98.7</td>
<td>112</td>
</tr>
<tr>
<td>Mouse plasma</td>
<td>99.7</td>
<td>114</td>
</tr>
<tr>
<td>Mouse brain</td>
<td>94.6</td>
<td>114</td>
</tr>
<tr>
<td>Human liver</td>
<td>&gt;350</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Mouse liver</td>
<td>&gt;350</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Brain homogenate</td>
<td>77-80</td>
<td>NT</td>
</tr>
</tbody>
</table>

In vivo efficacy in murine HAT models

<table>
<thead>
<tr>
<th>Stage 1 CNS Model (Chronic)</th>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Treatment Duration (days)</th>
<th>Survival @ Day 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>4</td>
<td>i.p.</td>
<td>4</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

Vehicle = historical negative control

Mice were each infected intraperitoneally (i.p.) with 2.5 x 10⁶ T. b. brucei (EATRO 110) parasites isolated from infected rats. SCYX-7158 was dosed once daily starting 24 hours after parasite infection for the duration of the study. Mice that achieved parasitemia twice weekly by microscopic examination of smear prepared from tail vein blood, or died, were sacrificed. Mean survival time in days.

In vivo pharmacokinetic characterization of SCYX-7158 demonstrates that the compound is highly bioavailable in rodents, has low intravenous plasma clearance, a 24 h elimination half-life and a volume of distribution that indicates good tissue distribution. Most importantly, SCYX-7158 readily distributes into brain and CSF and crosses the blood-brain barrier to achieve therapeutically-relevant concentrations in potential trypanosomiasis sanctuary sites. Based on these properties, which promise lower rates of resistance than with current standard of care, SCYX-7158 has been selected as a pre-clinical candidate for treatment of Stage 2 HAT.

In vivo PK of SCYX-7158 in rodents

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