Development of a Cathepsin S Inhibitor for Neuropathic Pain: Efficacy in a Preclinical Model of Taxol-Induced Neupathy and Phase 1 Clinical Profile

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Abstract

Cathepsin S is a cysteine protease known to be critical in the development of neuropathic pain. Following neuronal injury, membrane bound fractalkine (FKN) is expressed at the surface of injured neurons. Also following injury cathepsin S is released from resident immune cells, including microglia and macrophages, where it cleaves membrane bound FKN allowing the release of the pro-inflammatory chemokine soluble FKN. FKN-mediated recruitment and activation of microglia and other cells involved in immune defense triggers release of pro-inflammatory cytokines and other inflammatory mediators, which then propagate an exaggerated pain response. Cathepsin S lies at the intersection of neuronal-immune communication now recognized as critical in the development of chronic pain.

We have demonstrated efficacy of two selective cathepsin S inhibitors, VBY-036 and VBY-285, in rodent models of taxol-induced neuropathic pain. VBY-036 and VBY-285 are potent inhibitors with high selectivity for cathepsin S. Both compounds are efficacious at reversing established tactile allodynia which had been initiated 24 hours after the last dose of taxol. VBY-285 was also efficacious in reversing established tactile allodynia in a rat model after a single dose. Maximal efficacy, equal to that observed after gabapentin administration, was achieved with repeated once-a-day dosing. No tolerance to repeated dosing was observed and, unlike gabapentin, the taxol-induced neuropathic pain inhibition produces no sedative effects. Cessation of VBY-285 dosing was shown in a slow return of allodynia, with analgesic efficacy re-established when daily dosing was resumed. VBY-036 was also efficacious in reversing established tactile allodynia in a mouse model after taxol dosing. VBY-36 administration started prior to taxol administration resulted in a greater level of analgesic efficacy in a shorter time frame than administration following the establishment of allodynia. Virobay is progressing VBY-285 in human clinical studies in neuropathic pain. Results of these studies and a VBY-036 Phase 1 single ascending dose and multiple ascending dose studies in healthy volunteers will be presented where the safety and pharmacokinetics of VBY-036 oral administration were evaluated. VBY-036 was well tolerated with plasma pharmacokinetics exhibiting roughly dose-proportional exposures. Target engagement on cathepsin S was detected in PBMC using a pharmacodynamic biomarker, identifying plasma exposures required for maximal cathepsin S inhibition in development as a treatment for neuropathic pain, with a planned proof-of-concept Phase 2a study in chronic chemotherapy-induced peripheral neuropathy.

Introduction

Cathepsin S is a cysteine protease that regulates neural-immune interaction. In response to injuries, cathepsin S is released from resident immune cells, and is critical in the maintenance of neuropathic pain.

### Results

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>VBY-036 Ki (app) (nM)</th>
<th>VBY-285 Ki (app) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cathepsin S</td>
<td>113</td>
<td>230</td>
</tr>
<tr>
<td>Cathepsin L</td>
<td>180</td>
<td>22.2</td>
</tr>
<tr>
<td>Cathepsin B</td>
<td>250</td>
<td>2.8</td>
</tr>
<tr>
<td>Cathepsin F</td>
<td>300</td>
<td>3.4</td>
</tr>
<tr>
<td>Cathepsin K</td>
<td>150</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Neither compound has significant activity (IC50 > 100µM) against other cysteine/serine/aspartic proteases including trypsin, thrombin, chymotrypsin, cathepsin E, BACE, Factor Xa, Factor VIIa, ELA1, ELA2.

### Pharmacodynamic Biomarker

Biomarker detection with 7 days of dosing in a Phase 1 Study in Healthy Volunteers

Conclusions

- Cathepsin S inhibitors VBY-036 and VBY-285 are efficacious in reversing established tactile allodynia in rat and mouse models of neuropathic pain induced by administration of taxol.
- Cathepsin S inhibition is efficacious with no tolerance to repeated dosing and no sedation.
- VBY-036 is safe and well tolerated following repeated oral administration in a Phase 1 study in healthy volunteers.
- Use of a pharmacodynamic biomarker measured in PBMC samples in Phase 1 has established a dose in which cathepsin S inhibition is achieved.
- VBY-036 is in clinical development as a therapeutic for neuropathic pain with a Phase 2 study planned in CIPN.