XS04 Dasatinib (XS004) Improves Variability and Bioavailability in Humans Using Amorphous Solid Dispersion Formulation of Dasatinib with Implications for Its Clinical Use

Introduction

- The crystalisation formulation of dasatinib (Sprycel®) has low, pH-dependent solubility and highly variable intestinal absorption and plasma pharmacokinetics (PK).
- Comedication of dasatinib crystal and proton pump inhibitors (PPIs) can further reduce bioavailability by 40% and should be avoided, according to the FDA.
- Amorphous solid dispersion (ASD) formulations enhance drug bioavailability and reduce plasma PK variability by improving solubility and subsequent intestinal absorption, which may increase patient compliance, safety, and drug efficacy.

Results

- XS044 (Xspray Pharma, Solna, Sweden) is a novel, immediate release ASD formulation of dasatinib (tablet) produced by HyNap®, a technology designed to improve the solubility of dasatinib across a range of pH4 conditions.
- XS004 (Sprycel®) was statistically equivalent (within 80%-125% range, 90% confidence interval (CI)) for all PK parameters when compared to the reference (Table 1, Figure 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>XS004</th>
<th>Reference</th>
<th>Ratio (XS004/Reference)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>240.6±86.0</td>
<td>265.7±125.6</td>
<td>100.9</td>
<td>90.8-112.0</td>
</tr>
<tr>
<td>AUCinf (h*ng/mL)</td>
<td>864.0±213.2</td>
<td>989.2±390.6</td>
<td>94.2</td>
<td>87.5-101.4</td>
</tr>
<tr>
<td>AUC0-24h (h*ng/mL)</td>
<td>877.3±215.6</td>
<td>1011.4±387.6</td>
<td>92.2</td>
<td>86.2-98.6</td>
</tr>
</tbody>
</table>

Objectives

- Compare plasma PK of dasatinib from XS004 versus the reference (crystalline dasatinib) in healthy human subjects.
- Characterize the safety and tolerability of XS004 in healthy subjects.
- Determine in vitro solubility of ASD dasatinib at GI-relevant pH values.

Methods

- Open-label, single-center, randomized, 2-treatment, 2-sequence, 4-period, full-replicate, crossover, single-dose, phase I, oral comparative bioavailability study in healthy, adult subjects (NCT05439408; Figure 1).
- Comparison of plasma PK parameters followed single doses of XS004 (100 mg ASD dasatinib) and the reference product (40 mg crystalline dasatinib, Sprycel®) in 107 healthy volunteers at fasting conditions.
- ASD dasatinib and crystalline dasatinib (weak base with pKa values at 31 and 6.8) solubility was measured in aqueous media at pH 1.2, 2.0, 3.0, 4.5, 5.0, 6.8, and 8.0 at 37°C and sampled at 1 and 2 hours.

Conclusions

- XS004 was equipotent with crystalline dasatinib at a 30% lower dose (100 mg vs 140 mg) at fasting conditions.
- XS004 administration resulted in a 4-fold lower intersubject and a 3-fold lower intrasubject variability of AUCinf compared to crystalline dasatinib.
- The improved biopharmaceutical properties of XS004 can lead to reduced risk of exposure outside therapeutic window (ie, low and high exposure outliers) with the potential to minimize the risk of adverse events and optimize the therapeutic efficacy of dasatinib in patients with CML.

In vitro solubility

- ASD dasatinib demonstrated higher apparent and long-lasting solubility in vitro than crystalline dasatinib, remaining in solution over at least 2 hours at pH 1.250 (Figure 3).
- AOS dasatinib attained at least 10-fold greater solubility across pH 5.0-8.0 than the reference, and approximately 200-fold greater at pH 6.8 after 2 hours (Figure 3).

References