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

Hans Lennernäs[1], Charlotta Liljebris[2], Magnus Brisander[2], Gérald Jesson[2], Per Andersson[2], Gunnar Larfors[3], Leif Stenke[4]

[1]Uppsala University, Department of Pharmaceutical Biosciences, Translational Drug Discovery and Development, Uppsala, Sweden; [2]Xspray Pharma, Solna, Sweden; [3]Uppsala University, Department of Medical Sciences, Unit of Hematology, Uppsala, Sweden; [4]Karolinska University Hospital and Karolinska Institutet, Department of Hematology, Theme Cancer and Department of Medicine, Solna, Sweden

Introduction

- The crystalline formulation of dasatinib (Sprycel®) has low, pH-dependent solubility and highly variable intestinal absorption and plasma pharmacokinetics (PK)[1]
- Comedication of crystalline dasatinib and proton pump inhibitors (PPIs) can further reduce bioavailability—by 40%—and should be avoided, according to the FDA[2]
- 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[3]
- XS004 (Xspray Pharma, Solna, Sweden) is a novel, immediate release ASD formulation of dasatinib (tablet) produced with HyNap™, a technology designed to improve the solubility of dasatinib across a range of pH conditions[4]

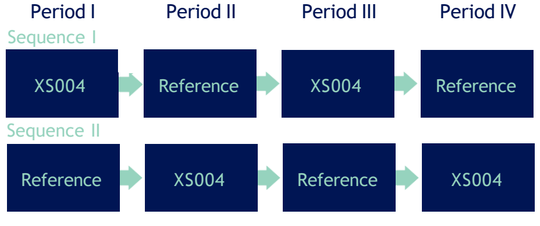
Objectives

- 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 1, 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 (140 mg crystalline dasatinib, Sprycel® Bristol-Myers Squibb Company, NJ, USA) in 107 healthy volunteers at fasting conditions
- ASD dasatinib and crystalline dasatinib (weak base with pKa values at 3.1 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

Figure 1. *Subject treatment sequences. Between-period washout of 7 days*



Results

Plasma exposure and pharmacokinetic parameters

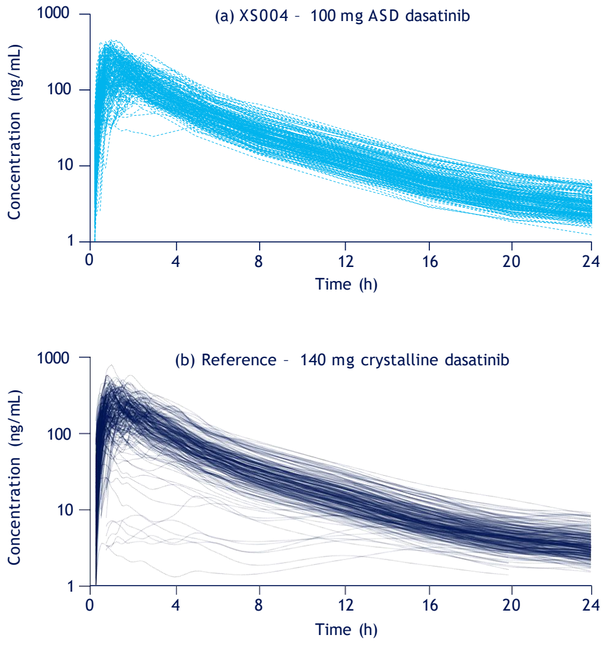
- Dasatinib plasma exposure from XS004 was statistically equivalent (within 80%-125% range, 90% confidence interval [CI]) for all PK parameters when compared to the reference (Table 1; Figure 2)

Table 1. *Plasma PK parameters (Mean ±SD) of XS004 vs reference*

	XS004	Reference	Ratio (%)	90% CI
C_{max} (ng/mL)	240.6±86.0	265.7±125.6	100.9	90.8-112.0
AUC_{0-24h} (h*ng/mL)	864.0±213.2	989.2±390.6	94.2	87.5-101.4
AUC_{0-inf} (h*ng/mL)	877.3±215.6	1011.4±387.6	92.2	86.2-98.6

T_{max} was 1.3 hr (0.3-3.0) for XS004 and 1.3 hr (0.5-24.0) for the reference.
$T_{1/2}$ was 6.1±1.2 hr for XS004 and 6.5±2.5 hr for the reference.
AUC, Area Under the plasma concentration versus time Curve;
C_{max}, Maximum measured plasma Concentration; CI, Confidence interval; Inf, Infinity.

Figure 2. *Individual plasma concentration-time profiles of dasatinib following single-dose oral administration of (a) XS004 and (b) reference in the fasted state*



Intra- and intersubject pharmacokinetics variability

- XS004 demonstrated 3-, 2.5-, and 2-fold less intrasubject variability (coefficient of variation [CV%]) than the reference for AUC_{0-24}, AUC_{0-inf}, and C_{max}, respectively (Table 2)
- Intersubject variability was also 4.3 to 4.8-fold lower across all PK parameters with XS004 than the reference (Table 2)
- Only 1.4% of plasma profiles dosed with XS004 vs 12% reference-dosed resulted in ≥40% reduced bioavailability of dasatinib (<60% of geometric mean AUC) (Figure 2)

Table 2. *Intra- and intersubject PK-variability (CV%)* of XS004 vs reference*

	Mean Intrasubject CV%		Mean Intersubject CV%	
	XS004	Reference	XS004	Reference
C_{max} (ng/mL)	28.8	60.1	12.3	58.3
AUC_{0-24h} (h*ng/mL)	14.2	41.5	8.7	38.9
AUC_{0-inf} (h*ng/mL)	13.9	34.6	8.6	36.5

*Ln-transformed PK parameters.
AUC, Area Under the plasma concentration versus time Curve;
C_{max}, Maximum measured plasma Concentration;
CV%, Coefficient of variation.

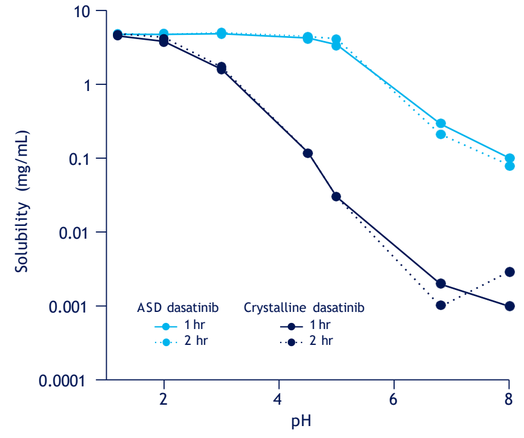
Safety and adverse events

- Incidence of treatment-emergent adverse events (TEAEs) for XS004 and crystalline dasatinib were 88.1% and 90.0%, respectively
- TEAEs were mild (53.3%) or moderate (46.7%); no serious TEAEs were reported

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 across pH 1.2-5.0 (Figure 3)
- ASD 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)
- The human GI tract has a variable pH. The improved solubility of ASD dasatinib at higher pH can contribute to the significantly lower variability of XS004 vs crystalline dasatinib

Figure 3. *Mean in vitro solubility of ASD dasatinib and crystalline dasatinib at 37˚C up to 2 hours in aqueous media throughout the pH range 1.2-8.0*



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 AUC_{0-24} 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

References
1. Tsume Y, Takeuchi S, Matsui K, et al. *Eur J Pharm Sci*. 2015;76:203-212.
2. Sprycel® (dasatinib) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2021.
3. Augustijns P, Brewster ME. *J Pharm Sci*. 2012;101(1):7-9.
4. Jesson G, Brisander M, Andersson P, et al. *Pharm Res*. 2014;31(3):694-705.

xspray