

# Comedication of Proton Pump Inhibitors and Dasatinib Is Common in CML but XS004, a Novel Amorphous Solid Dispersion Formulation of Dasatinib, Provides Improved Uptake and Low pH-Dependency, Minimizing Unwanted Drug-Drug Interactions

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## Introduction

- Increased gastric pH significantly reduces plasma concentrations of crystalline dasatinib (Sprycel®), which is known to be lipophilic, poorly soluble, and a weakly basic tyrosine kinase inhibitor (TKI) used in patients with chronic phase (CP) chronic myeloid leukemia (CML)<sup>1,2</sup>
- Comedication of crystalline dasatinib and proton pump inhibitors (PPIs) like omeprazole can decrease plasma exposure by >40% and should be avoided according to the FDA as the clinical efficacy may be reduced<sup>3</sup>
- Prior studies suggest that TKI and PPI comedication is relatively common among cancer patients, and is a clinically important concern<sup>4</sup>
- XS004 is a novel amorphous solid dispersion (ASD) formulation of dasatinib produced with HyNap™ technology, designed to provide higher intestinal absorption with less variability, regardless of gastric pH<sup>5</sup>

## Objectives

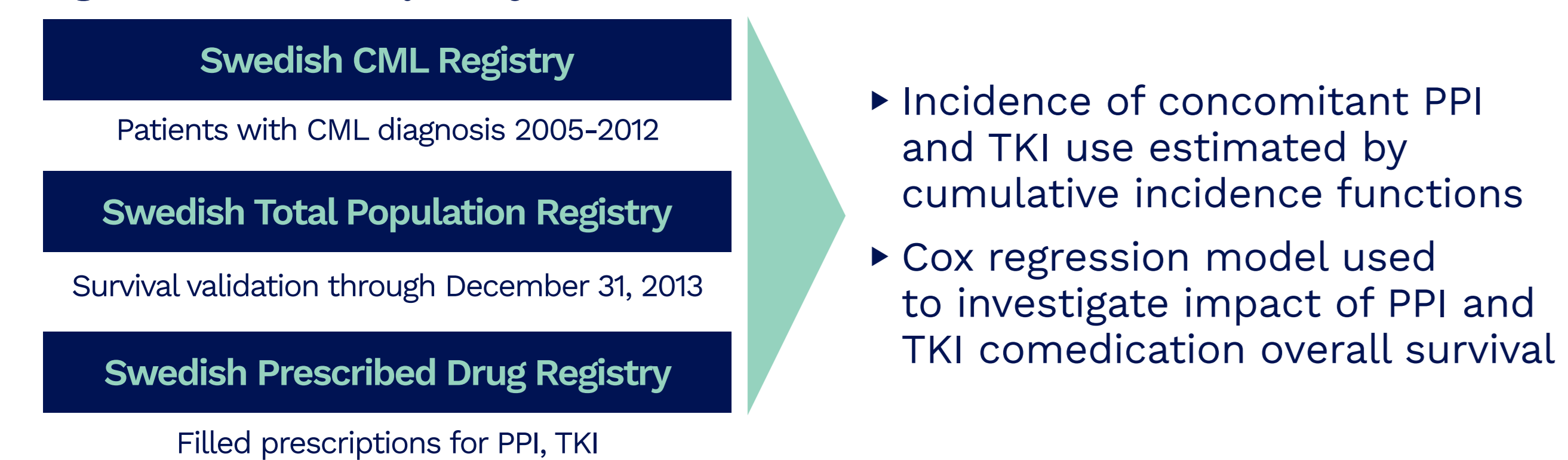
- To understand the prevalence and outcomes associated with PPI and dasatinib comedication in a real-world cohort study
- To confirm the pH-independent absorption of dasatinib with XS004 when comedicated with omeprazole in a clinical trial

## Methods

### Cohort Study: Swedish registries

- Real-world incidence and outcomes of dasatinib and PPI comedication among patients with CP CML (**Figure 1**)

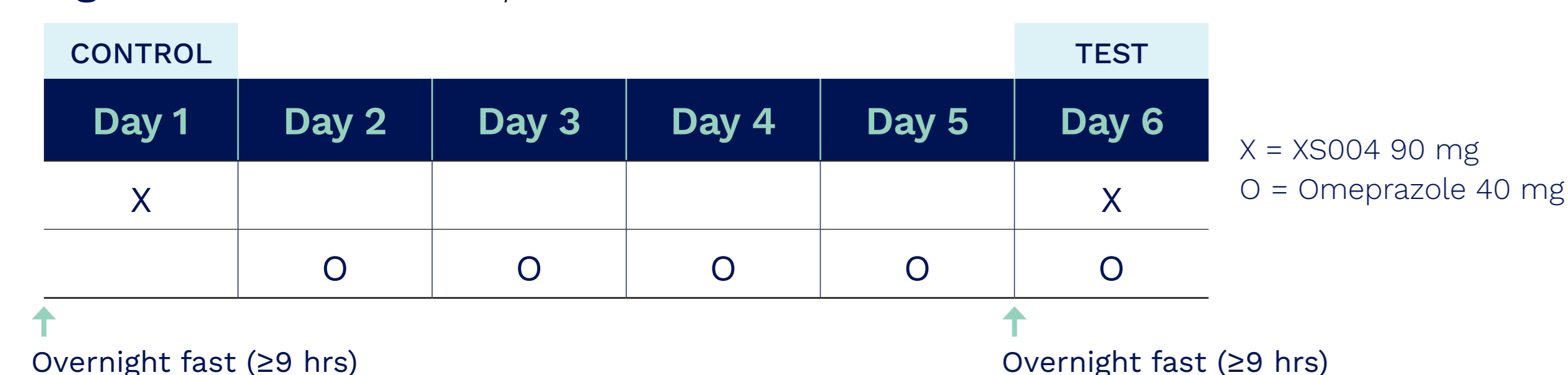
**Figure 1.** Cohort study design



### XS004 and omeprazole drug-drug interaction study

- Open-label, randomized, crossover trial (2 treatment periods) in 16 healthy volunteers (**Figure 2**)
- XS004 (90 mg ASD dasatinib, Xspray Pharma, AB, Solna, Sweden) administered alone (fasted) or with omeprazole (40 mg) (**Figure 2**)

**Figure 2.** XS004 and omeprazole administration schema



## Results

### Cohort Study

#### Baseline characteristics

- Of the 722 patients included in the Swedish CML registry, 676 (94%) filled a prescription for a TKI, with 320 (47%) of those patients having at least 1 PPI prescription filled between CML diagnosis and the end of follow-up (**Table 1**)
- TKI and PPI comedication occurred over 24% of the follow-up time

#### Dasatinib treatment incidence

- 193 patients had at least 1 filled prescription for dasatinib
  - Mean duration of dasatinib prescription fills was 1.8 years (range 0–6.7 years)
  - Mean follow-up of dasatinib-treated patients with a filled PPI prescription was 1.8 years

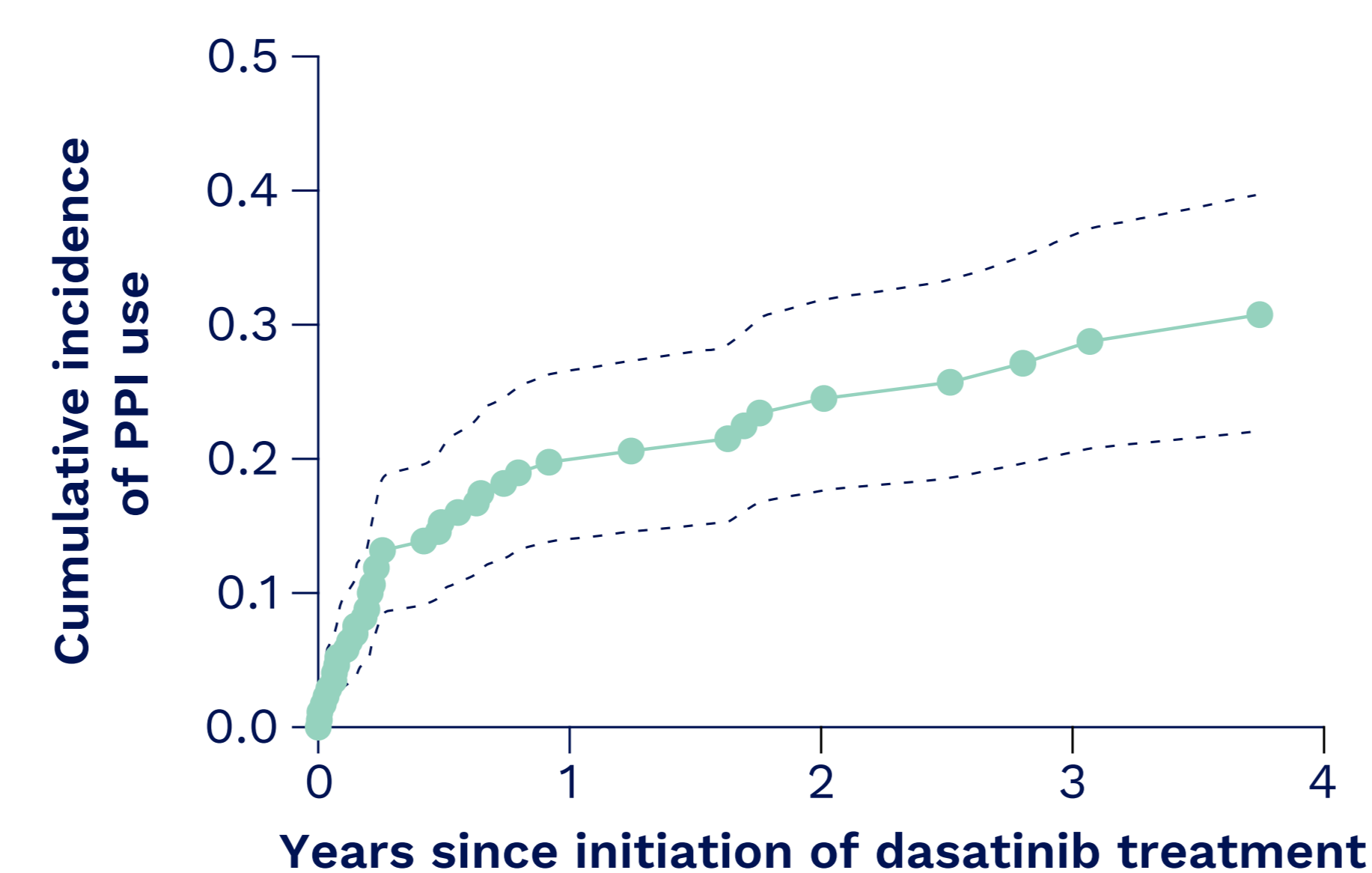
**Table 1.** PPI comedication in Swedish patients with CML

Population	Patients
Swedish CML Registry	722
≥ 1 PPI prescription	320 (44%)
TKI-treated CML patients	676
TKI + PPI comedication	320 (47%)
Dasatinib-treated	193 (29%)
Dasatinib + PPI comedication	40 (21%)

#### Cumulative incidence of PPI use

- Estimated cumulative incidence of PPI prescription fills 2 years after CML diagnosis was 30% in the total CML registry
- Estimated cumulative incidence of PPI prescription fills 2 years after initiating dasatinib treatment was 24% in the dasatinib-treated population (**Figure 3**)
- PPI-dasatinib comedication continuously increased over time (**Figure 3**)

**Figure 3.** Cumulative incidence of filled PPI prescriptions among dasatinib-treated CML patients with 95% confidence interval



#### Survival outcomes

- 5-year overall survival (OS) was significantly lower for patients with TKI-PPI comedication than for patients without PPI comedication (**Table 2**)
- The statistically significant difference was maintained after adjusting for age, sex, year of diagnosis, and Charlson comorbidity index (HR of 3.1, 95% CI, 2.0–4.7,  $P < 0.0001$ ) (**Table 2**)

**Table 2.** 5-year OS associated with TKI and PPI comedication

	TKI	TKI + PPI
5-year OS	94%	79%
Mortality HR	3.5 (95% CI 2.1–5.3)	$P < 0.0001$
Adjusted* Mortality HR	3.1 (95% CI 2.0–4.7)	$P < 0.0001$

\*Adjusted for age, sex, year of diagnosis, and Charlson comorbidity index. CI, confidence interval; HR, hazard ratio; OS, overall survival.

### XS004 and omeprazole drug-drug interaction study

- Omeprazole comedication with XS004 did not affect  $C_{max}$  and area under the plasma concentration curve ( $AUC_{0-24}$  and  $AUC_{0-inf}$ ) ( $P \geq 0.3$ ; **Table 3**)

**Table 3.** PK parameters following oral dosing of XS004 (90 mg ASD dasatinib) with and without omeprazole (40 mg)

Parameter (unit)	Geometric mean		Ratio test/control (%)	90% confidence interval	Intrasubject CV (%)	P (ANOVA)
	XS004 (control)	XS004+ Omeprazole (test)				
$C_{max}$ (ng/mL)	138.4	118.6	85.7	67.2–109	42.1	0.3
$AUC_{0-24}$ ( $h \cdot ng/mL$ )	426.3	455.1	106.8	90.3–126	28.5	0.5
$AUC_{0-inf}$ ( $h \cdot ng/mL$ )	433.6	466.3	107.5	91.0–127	28.4	0.5

ANOVA, analysis of variance; AUC, area under the plasma concentration vs time curve;  $C_{max}$ , Maximal plasma concentration; CV, coefficient of variation; Inf, Infinity.

## Conclusions

- Despite FDA warnings, comedication of PPI and Sprycel® (crystalline dasatinib) is common in a real-world setting
- Our finding of significantly inferior 5-yr OS for TKI-treated CML patients with vs without PPI comedication motivates additional studies to unravel explanatory key mechanisms (eg, compromised TKI absorption) linked to this particular comedication
- XS004 showed equivalent plasma exposures with and without omeprazole comedication
- XS004, with less pH dependency and enhanced intestinal absorption, may provide an improved option for safely administering an ASD formulation of dasatinib compatible with PPI comedication
- XS004 can potentially improve long-term efficacy and tolerability of dasatinib in CML

### References

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