Despite warnings, co-medication with proton pump inhibitors and dasatinib is common in chronic myeloid leukemia, but XS004, a novel oral dasatinib formulation, provides reduced pH-dependence, minimizing undesirable drug–drug interactions

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Abstract

Background: Dasatinib and other tyrosine kinase inhibitors (TKI) have revolutionized the treatment of chronic myeloid leukemia (CML). However, as a lipophilic weak base, crystalline monohydrate, dasatinib (Sprycel®) is poorly soluble, rendering a pH-dependent absorption and a highly variable bioavailability. Thus, co-medication with proton pump inhibitors (PPI) profoundly impairs dasatinib uptake and is clearly recommended against.

XS004 is a novel oral immediate release and amorphous solid dispersion (ASD) formulation of dasatinib and is bioequivalent to the original crystalline dasatinib at 30% lower dosages. XS004 is designed to mitigate gastric pH dependency, thus optimizing absorption and bioavailability.

Methods: We investigated the prevalence of dasatinib and PPI co-medication among chronic-phase CML patients in a real-world setting and assessed the plasma pharmacokinetics (PK) of XS004 with and without PPI co-medication (omeprazole) in healthy volunteers.

Results: Using the Swedish CML and Prescribed Drug Registers, we identified 676 TKI-treated CML patients; 320 (47%) had been prescribed PPI at some point after CML diagnosis. Among dasatinib-treated patients, the 2-year cumulative PPI co-medication was 24%. Interestingly, the 5-year overall survival was significantly lower for TKI-treated CML patients with versus without PPI co-medication (79% vs. 94%; hazard ratio 3.5; 95% confidence interval, 2.1–5.3; p < .0001).

When assessing PK of XS004, neither Cmax nor area under the plasma concentration curve levels in plasma were significantly altered by the PPI co-medication.

Conclusion: In conclusion, despite warnings, PPI co-medication is common among dasatinib-treated CML patients in a real-world setting. The new XS004 ASD formulation of dasatinib provided, in contrast to original crystalline dasatinib, superior pH-dependent absorption and bioavailability.

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independence with stable bioavailability, thereby minimizing drug–drug interactions. This may improve the long-term efficacy and tolerability of dasatinib in CML.

KEYWORDS
CML, dasatinib, drug–drug interactions, pharmacokinetics, PPI, XS004

Novelty Statements

What is the new aspect of the work?
- This work describes a high prevalence of co-medication with tyrosine kinase inhibitors (TKI), such as dasatinib, and proton pump inhibitors (PPI) in a large real-life cohort of chronic myeloid leukemia (CML) patients.
- We uncover a significantly inferior overall survival of TKI-treated CML patients with versus without PPI co-medication.
- We present drug–drug interaction pharmacology results of a novel formulated dasatinib tablet, XS004, demonstrating that it can be co-medicated with a PPI without any major interaction.

What is the central finding of your work?
- Even though recommended against, co-medication with PPIs and tyrosine kinase inhibitors is common in CML patients, increases over time and is associated with inferior survival.
- Furthermore, by manufacturing dasatinib with a novel amorphous solid dispersion technique, the medicine can be co-medicated with PPIs without any significant impairment of bioavailability or pharmacology.

What is (or could be) the specific clinical relevance of your work?
- Clinicians should consider the risk of co-medication of TKIs with PPIs and should emphasize the risk of such co-medication when informing patients as PPIs are not only prescribed but also commonly used “over the counter.”
- The use of XS004 could provide a solution for patients who are in need of dasatinib and PPI co-medication.

INTRODUCTION

The use of tyrosine kinase inhibitors (TKIs) has revolutionized the treatment of chronic myeloid leukemia (CML). These oral medications are highly efficient to prevent phosphorylation of the Bcr-Abl target protein and subsequent signaling events and have resulted in a remarkable improvement of patients’ prognosis. Thus, particularly in Western countries, the relative CML survival, that is, the overall survival after CML diagnosis as compared to the survival as observed in a similar population not diagnosed with CML has soared. As an example, in Sweden the relative 5-year survival of CML patients diagnosed 1995 versus those diagnosed 2008 increased from approximately 42% to 85% and 5-year survival of CML patients reaches almost 100% today. The tolerability of TKIs is also superior to that of previous CML treatments.

However, one challenge in the clinical use of several TKIs is their dependence on low gastric pH for a proper intestinal absorption and bioavailability. A pH-dependent absorption is particularly evident for dasatinib and nilotinib, two of the most widely used TKIs in CML. They, as imatinib, are lipophilic and poorly soluble, weak bases formulated in a crystalline form for oral use. Dasatinib is recognized as a Class II drug in the Biopharmaceutical Classification System, exhibiting a high intestinal permeability and strong pH-dependent solubility. Hence, the pH level of the gastrointestinal tract, in particular the ventricle of the stomach, impacts the solubility and dissolution and ultimately the intestinal absorption and bioavailability of dasatinib. Consequently, the coadministration of gastric acid reducing agents may decrease the bioavailability of crystalline formulated dasatinib and lead to reduced efficacy. Hence, concomitant treatment with dasatinib and H2-antagonists or proton pump inhibitors (PPI) should be avoided according to the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) as the clinical efficacy may be reduced.

PPIs (omeprazole, lansoprazole, rabeprazole and esomeprazole), which are commonly used in cancer patients to treat upper tract GI diseases, decrease dasatinib exposure. For instance, the concomitant use of dasatinib and omeprazole or rabeprazole reduces the bioavailability of dasatinib in the ranges of 40%–80%, respectively.
use of PPIs typically increases gastric pH by two to three units. When pH rises by two units, dasatinib solubility is reduced by more than 99%. Obtaining optimal dasatinib plasma exposure-time profiles is clinically important in CML as high plasma concentrations increases the risk of adverse effects, while the anti-leukemic effect appears suboptimal when below the defined threshold concentrations over time. Several practical solutions have been suggested to avoid drug-drug interactions between dasatinib and gastric acid regulators. These include dose separation, co-administration of dasatinib with betaine-hydrochloride, and co-administration of dasatinib with acidic soft drinks. These strategies, however, remain poorly studied and are heavily dependent on patient compliance. Optimizing the formulation with the goal to increase bioavailability and reduce intra- and inter-patient variability of dasatinib by decreasing the pH-dependent in vivo absorption process is a more viable strategy. Amorphous solid dispersion (ASD) formulation is one approach to enhance the bioavailability of active pharmaceutical ingredients (API). Spray drying and hot-melt extrusion are examples of techniques used for creating amorphous APIs. The techniques are each associated with challenges, but with a successful approach, the variability in plasma pharmacokinetics (PK) is reduced, as the solubility and the intestinal absorption improve, and most importantly patient compliance, safety, and efficacy can be increased.

XS004 (Xspray, Solna, Sweden) is a novel immediate release and ASD formulation of dasatinib produced with the HyNap™ technology. XS004 is designed to provide an increased solubility of dasatinib in acidic to neutral pH conditions, mitigating gastric pH dependency, leading to reduced variability, increased absorption, and bioavailability of dasatinib. Furthermore, by applying the specific technology when producing the ASD formulation, XS004 is bioequivalent to the original, crystalline-formulated dasatinib (Sprycel®) at 30% lower dosages.

Here, we report of two studies with the objectives to: (1) assess the real-world prevalence of and long-term outcome linked to PPI co-administration to dasatinib (Sprycel®) in a large population-based CML cohort (Cohort Study) and (2) evaluate the clinical PK of XS004, alone and during the influence of co-medication with the PPI, omeprazole (clinical drug–drug interaction trial).

2 | MATERIALS AND METHODS

2.1 | Cohort study

Patients were retrieved from the Swedish CML Register and included all patients’ resident in Sweden and diagnosed with CML (ICD10 = C92.1) between January 2005 and December 2012. The CML Register was initiated in 2002 and includes approximately 97% of all Swedish CML patients as evaluated by mandatory pathology reports recorded in the Swedish Cancer Register. Information retrieved from the CML Register included baseline parameters such as age, sex, date of diagnosis, prognostic indices, performance status, treatment modalities, and a selection of clinical characteristics. To each patient, five population comparator subjects were randomly chosen from the Swedish Total Population Register. The comparator subjects were of the same sex, born in the same year and alive, and resident in the same region as the respective CML patient, as assessed in the beginning of the year during which the patient was diagnosed. Comparator subjects who already had a CML diagnosis or died between 1 January and the date of diagnosis were excluded from analysis. Both patients and comparator subjects were followed for death or permanent emigration, as documented in the Swedish Total Population Register until December 31, 2013.

Charlson Comorbidity Index was calculated from diagnoses in the Swedish Patient Register for 10 years preceding CML diagnosis. The Swedish Patient Register includes diagnoses from all Swedish in-patient care and specialized out-patient visits. The choice of diagnoses was based on the Royal College of Surgeons modified Charlson score, which has been recommended for registry-based research.

Data on medications were retrieved from the Swedish Prescribed Drug Register, initiated in 2005. The register documents all drug prescriptions as well as all filled prescriptions at pharmacies in Sweden, but does not include prescription free medicines (i.e., over the counter use [OTC]), medicines within clinical trials, medicines administered during in-patient care, or chemotherapy ordered from specialized chemotherapy preparation units.

When estimating the concomitant use of TKI and PPI, only patients with prescribed TKI were used, and not those taking TKI as part of a clinical trial (19% of patients had at some point been treated within a study protocol). TKI prescriptions were considered to better represent clinical practice, whereas TKI within studies were associated with uncertainties regarding duration of treatment and may also have been subject to specific restrictions regarding co-medication. Only PPIs associated with a prescription could be accounted for as OTC use is not registered in the Swedish Prescribed Drug Register.

The proportion of time during CML disease when patients used PPI was estimated by comparing dispenses in defined daily doses (DDD) to the follow-up time in days. DDD can be retrieved from https://www.whocc.no/atc_ddd_index/ and is included in the Swedish Prescribed Drug Register. For omeprazole, a DDD is 20 mg, for pantoprazole 40 mg, lansoprazole 30 mg, and for esomeprazole 30 mg. Only dispenses after the date of CML diagnosis were counted and dispenses less than 3 months before end of follow-up were limited to one DDD per remaining follow-up day in the analysis.

2.2 | Clinical drug–drug interaction trial

2.2.1 | Study population

Sixteen healthy volunteers were included in the experimental clinical trial of this study. The subjects were between 21 and 52 years of age (median 39.5) and 13 were male and three females. The median height was 171 cm (range 160–200), median body weight was 80.8 kg (range 60.9–113.5), and median body mass index was 26.8 kg/m².
The trial was conducted as an open-label, non-randomized, two-treatment, single-period, single-dose, drug–drug interaction study to evaluate the effects of omeprazole on the plasma PK of XS004 (dasatinib). The study drugs were XS004 (containing 90 mg dasatinib, Xspray, Solna, Sweden) and omeprazole delayed release capsules, United States Pharmacopeia (USP) (omeprazole, 40 mg, Dr Reddy’s Laboratories, Bachupally, India).

XS004 is an oral tablet formulation of dasatinib developed to increase solubility of the active substance in slightly acid to neutral luminal pH conditions (approximately pH 4.5–7.0). The pharmaceutical formulation is based on an ASD of dasatinib embedded in a matrix-forming polymer, created using the HyNap™ technology. The ASD-­formulated dasatinib in XS004 provides increased bioavailability and reduced intra- and inter-individual variability and the drug is equipotent to the original, crystalline-­formulated dasatinib (Sprycel™) 30% lower dosages.

The 90 mg dose strength represents the highest dose strength of XS004. As the in vitro solubility of XS004 is at least twofold higher and long-lasting during 2 h in the pH range 1.2–5.0 compared to crystalline dasatinib, it is expected that XS004 is completely dissolved in the gastrointestinal tract. All dose strengths of XS004 have the same composition and have been shown to be dose proportional. XS004 was administered alone (control) on Day 1 and together with omeprazole on Day 6 (test). Omeprazole was given orally once daily (40 mg) on Days 2–6. Each subject was in fasted state and served as his own control at Days 1 and 6. XS004 was administered in the morning at Days 1 and 6 with a glass of water (approximately 240 mL at room temperature water), and each subject had been fasting for at least 9 h before and 4 h after intake of study drug. Omeprazole was administered with approximately 150 mL of room temperature water before the meal in the evenings on Days 2–6. No food was allowed 2 h prior and 1 h after the administration of omeprazole.

Blood samples (6 mL) were collected by direct venipuncture in Vacutainer® tubes (BD Vacutainer Systems, NJ, USA, containing K₂EDTA) at predose (0.00 h), within 30 min prior to XS004 administration on Days 1 and 6 and postdose at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, and 24.00 h. The samples were kept on ice bath and then centrifuged (3000 RPM at 4°C ± 3°C for 10 min) to separate the plasma. Plasma samples were transferred to an Ultralow (−86 to −50°C) freezer within 90 min after the blood sample was collected.

The plasma samples of subjects were analyzed using a validated Liquid Chromatography - tandem mass spectrometry (LC-MS/MS) method for dasatinib at AXIS Clinicals (1711 Center Avenue West Dilworth, MN 56529-1342, USA). The linear dynamic range of the method in human plasma containing K₂EDTA was from 0.5000 to 200.0 ng/mL. Samples were chromatographically separated on a Phenomenex Kinetex Biphenyl analytical column (50 × 3.0 mm) by a gradient method using ammonium formate in water with formic acid and methanol. The API 4500 mass spectrometric instrument is operated in positive ion mode using a turbo ion-spray source and Multiple Reaction Monitoring (MRM) detection. Total run time for a 10 µL injection is 4.00 min per sample.

The analyses were based on assessment of plasma PK parameters of dasatinib and were calculated on Day 1 (dasatinib treatment) and Day 6 (dasatinib and omeprazole treatment) for each subject using plasma drug concentration–time data by non-compartmental methods. They included Cₘₐₓ (maximum plasma concentration), AUC₀–ₚ₈₉₉ (area under plasma concentration–time curve during the first 24 h), AUC₀–inf (area under plasma concentration–time curve from time zero to infinity), Tₘₐₓ (time of the maximum plasma concentration), Kᵣₐₜ (apparent first-order terminal elimination rate), and terminal half-life. The AUC versus time curve from time 0 to infinite time was calculated as the sum of the AUC₀–ₚ₈₉₉ + Cₘₐₓ/Kᵣₐₜ. The terminal half-life (t₁/₂) was calculated as 0.693/Kᵣₐₜ. Phoenix WinNonlin 8.3 software was used for the calculation of pharmacokinetic parameters (Certara USA Inc., Princeton, NJ, USA).

The comparison of plasma PK parameters of dasatinib on Day 1 (dasatinib alone) and Day 6 (dasatinib + omeprazole) was carried out using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA). Analysis of variance (ANOVA) was carried out by employing PROC GLM for the untransformed and Ln-transformed values of Cₘₐₓ, AUC₀–ₚ₈₉₉, and AUC₀–inf for dasatinib PK data on Day 1 and on Day 6. The ANOVA model included treatment received, the period in which it was given along with the sequence in which each treatment was being received, and the subject effect (nested within the sequence). Sequence effect was tested by using the subject nested within sequence mean square from the ANOVA as the error term. An F-test was performed to determine the statistical significance of the period, sequence, and treatment effects involved in the model at a significance level of 5% (alpha = .05). Ratio analysis was calculated for Ln-transformed pharmacokinetic parameters of dasatinib Cₘₐₓ, AUC₀–ₚ₈₉₉, and AUC₀–inf data on Day 1 and on Day 6. The 90% confidence interval for the ratio of XS004 on Day 6 versus Day 1 averages (geometric least squares mean) was calculated using the LSM for Ln-transformed Cₘₐₓ, AUC₀–ₚ₈₉₉ and AUC₀–inf of data. Intra-subject variability was calculated for Ln-transformed
pharmacokinetic parameters of $C_{\text{max}}$, AUC$_{0-24}$, and AUC$_{0-\text{inf}}$ of dasatinib PK data on Day 1 and on Day 6. A Day 6/Day 1 ratio for the PK parameters that was between 80% and 125% indicated that there was no clinically significant DDI. Differences between ln-transformed pharmacokinetic parameters were assessed with ANOVA using PROC GLM in SAS. Geometric least square means were estimated by exponentiation of the least square means from ANOVA.

2.4 | CML Registry data analysis

The proportion of patients treated with PPI over time was analyzed with cumulative incidence functions with death as a competing event, using Gray's test to assess equivalence between patients and comparators. Relative survival between groups in the cohort study was analyzed by Cox regression, and 5-year survival was estimated by the actuarial approach using PROC LIFETEST in SAS. In analyses of survival, time before first PPI dispense in PPI users was classified as unexposed time, to avoid immortal time bias.

All $p$-values were two-sided and a value below 0.05 was considered statistically significant. All statistical analyses were performed with SAS 9.4 software (SAS Institute Inc.).

2.5 | Ethical considerations

The cohort study was approved by the Uppsala regional research ethics committee, Uppsala, Sweden (2013/069). Record linkages were performed at Statistics Sweden and the National Board of Health and Welfare. All data were de-identified before delivery to the researchers.

The experimental study was approved by the IntegReview Institutional Review Board, Austin, Texas (November 2020) and registered at clinicaltrials.gov (reference number: NCT05433896). For the experimental study, all participants provided written informed consent.

3 | RESULTS

3.1 | Cohort study

3.1.1 | PPI use during CML disease

Between 2005 and 2012, 722 patients were included into the Swedish CML Registry, of those 676 (93.6%) received TKI treatment. Median age at the diagnosis of CML (ICD10: C92.1) was 60 years (range 17–93) and the majority were male (413/722; 57%).

Among all 722 patients, 320 (44%) had at least one filled PPI prescription between CML diagnosis and end of follow-up. PPI included ATC codes A02BC (proton pump inhibitors) and A02BD (combinations for eradication of Helicobacter pylori). No patient had a prescription of M01AE52 (naproxen and esomeprazole). The number of dispenses ranged between 1 and 218, with a median of 4. Among patients with at least one filled PPI prescription, the median use in DDD/follow-up day was 0.24, while 25% of patients had a filled prescription of 0.66 DDD/follow-up day or more. Ten percent of PPI users had filled prescriptions of 30 DDD or less during follow-up.

Among the 3587 comparators, 24% (869 individuals) had at least one filled PPI prescription between the date of CML diagnosis of their matched case and end of follow-up. This proportion was significantly lower than in CML patients (44% vs. 24%; $p < .0001$).

3.1.2 | Characteristics of PPI users

Table 1 outlines the baseline characteristics of PPI users among CML patients and matched comparators from the general population. There was a higher proportion of PPI users among older patients, and among patients with high comorbidity index. Due to shorter follow-up, there was a smaller proportion of PPI users among those diagnosed in later years, but the difference between patients and comparators remained.

3.1.3 | Cumulative incidence of PPI use amongst CML patients and during concomitant dasatinib use

Dasatinib was prescribed to 193 patients, and the time between first and last dasatinib prescription ranged between 0 and 6.7 years, with a mean of 1.8 years. Among the 193 patients with recorded dasatinib use, 40 (21%) were prescribed PPI at any time point during follow-up. In these 40 patients, PPIs were taken together with dasatinib during 36% of the dasatinib treatment time (range 1% [in one patient] and 100% [in four patients]).

At 2 years after CML diagnosis, the estimated cumulative incidence of PPI was 30% (Figure 1A), and 2 years following the first dasatinib dispense the cumulative incidence of PPI dispense was 24% (Figure 1B). The highest increase of PPI use occurred in the first 2 years (Figure 1AB). However, the use of PPIs after CML diagnosis was associated with a trend of substantial increase also in the time beyond 2 years after the diagnosis of CML (Figure 1A). The cumulative incidence of filled PPI prescriptions in CML patients in the time between the first- and last-recorded dasatinib dispense is demonstrated in Figure 1B.

3.1.4 | Survival among PPI using CML patients

Median follow-up among CML patients was 4.1 years. The estimated 5-year survival among CML patients using PPIs was 79% compared to 94% among non-PPI users (88% for the population as a whole). The hazard ratio (HR) of death among PPI users compared to non-users was 3.5 (95% confidence interval [CI], 2.1–5.3, $p < .0001$) and maintained significant after adjusting for age, sex, year of diagnosis, use of anti-coagulants, and comorbidity index (HR 3.1, 95% CI, 2.0–4.7, $p < .0001$; Table 2).
3.2 | Clinical drug–drug interaction trial

3.2.1 | Gastrointestinal absorption and bioavailability of XS004 with and without concomitant PPI

The median time ($T_{\text{max}}$) to maximum plasma dasatinib concentration was 1.0 and 1.5 h without and with omeprazole pretreatment, respectively. As demonstrated in Table 3, maximum plasma concentration ($C_{\text{max}}$) and total systemic drug exposure (by means of AUC [AUC$_{\text{0-24}}$ and AUC$_{\text{0-inf}}$]) were similar in the 16 healthy volunteers when administering XS004 with and without omeprazole pretreatment, with ratios of 85.7% ($C_{\text{max}}$), 106.8% (AUC$_{\text{0-24}}$) and 107.5% (AUC$_{\text{0-inf}}$). Mean $C_{\text{max}}$ was estimated slightly lower, whereas AUC$_{\text{0-24}}$ and AUC$_{\text{0-inf}}$ were estimated slightly higher with PPI co-medication, but neither of them differed significantly from baseline (Table 3). As the ratios for all three parameters were between 80% and 125%, it was concluded that there was no clinically significant DDI between omeprazole and XS004. The extrapolated area in the plasma concentration–time profile did not exceed 4% for any subject.

3.2.2 | Safety and tolerability

No serious adverse events were recorded among the 16 healthy volunteers during this trial. One subject discontinued the study due to adverse events after first dose (hematuria, pain from the renal tract, and pruritus). Reported adverse events were similar after XS004 alone and following omeprazole. The most commonly noted adverse event was headache, reported by seven subjects (44%) following intake of XS004 alone and by eight subjects (50%) following omeprazole and XS004.

4 | DISCUSSION

This report strengthens the case that PPI co-medication to TKI in general, and also to dasatinib in particular, is common among CML.
patients in a real-world setting, and additionally suggests a poorer prognosis of patients on crystalline formulated dasatinib and PPI co-medication. Furthermore, the report concludes that the gastrointestinal absorption of XS004, a new oral amorphous solid dispersion tablet formulation of dasatinib, is significantly less pH dependent than that of existing crystalline formulations of dasatinib. Consequently, XS004 could provide a solution for CML patients in need of concomitant treatment with TKIs and PPIs, minimizing the risk of decreased and insufficient dasatinib plasma concentrations due to drug–drug interactions.

We observed that the use of PPIs in CML patients is common over all age groups and both genders. Among CML patients treated with dasatinib more than 20% filled a PPI prescription during a short follow-up time. The analyses of the number of PPI prescriptions suggest that a minority of the PPI-treated patients are occasional users only. As few as 10% of users had a single prescription covering a month or less, while the median user was estimated to have used PPI 36% of the time while being treated with an TKI. This finding underlines the clinical significance and points towards a risk that PPI use may have an impact on the efficacy and adverse events frequency for oral TKI medications.

PPI use following prescription of TKI in the United States has recently been evaluated using SEER (Surveillance, Epidemiology, and End Results) data from the NIH. In that study, 23% of all CML patients were treated with PPI during the first 3 months following a first prescription of a TKI. In our study, the corresponding frequency would be 15%, suggesting that co-medication may be even more common in the United States compared to Sweden. Furthermore, we estimated that the proportion continues to rise over the years, with 1 in 4 CML patients after 2 years and as much as 40% of the CML patients will have used PPI 4 years after their diagnosis. In a French study on 3633 CML patients published in 2021, 62% had been prescribed PPI in the year before CML diagnosis (the second most prevalent medication after acetaminophen), and 22% were prescribed PPI in the first month following TKI initiation. The use of PPIs in the general population differs between countries, with reports of up to 10% (USA, Denmark, Australia, and Island), around 20% (Switzerland) until almost 30% (France). There is, however, a common trend in the majority of studies of an increasing use of PPIs. Studies on cancer patients in the United States in general reveal numbers, amounting to 20–33% of patients treated with any acid-reduction agent and that PPIs are the most commonly used drugs.

Apart from prescriptions, PPIs are also sold over-the-counter (OTC) in most countries, including the United States and Sweden. Such use was not included in this report and hence the co-medication of PPIs and TKIs is underestimated in our analysis as in most studies. Swedish prescription-free sales statistics are not available since 2019 and generally, data are scarce describing OTC use of PPIs. However, OTC use of PPIs has been reported as high as 32% in patients with gastroesophageal reflux disease. Whether this can be extrapolated to cancer is uncertain as such patients are managed in special care and not primary care and practices differ. Nevertheless, there are clear indications that OTC use of PPIs is substantial. Hence, with longer follow-up time and given the fact that unprescribed but difficult to quantify OTC usage of PPI is common, the proportion of patients with co-medication is likely to be considerably larger.

An important outstanding question is whether PPI co-medication leads to more treatment failures with clinical impact among dasatinib users as the plasma exposure reduces more than 40%–60% with crystalline-based products. Co-medication of PPIs and TKIs with pH-dependent absorption has previously been shown to be associated with reduced survival among lung cancer patients treated with erlotinib, gefitinib or dacomitinib. More recent studies with dacomitinib or gefitinib have failed to replicate an association between concomitant PPI use and overall survival. However, in the latter study, overall survival was decreased among “extensive users” of PPIs, defined as having at least one PPI prescription before and one prescription after cancer diagnosis.

We demonstrate a lower survival in CML patients during concomitant PPI and TKI/dasatinib use, this finding was maintained when adjusting for age, gender, and co-morbidity index. However, the retrospective design cannot rule out the alternative explanation that PPI use could be a marker of underlying diseases with impact on survival chance. PPI co-medication could also affect TKI discontinuation, progression to accelerated phase/blast crisis or to stem cell transplantation and should be subject for future studies. In our present data, we...
Hence, (95% CI 2.0–4.7) $p < .0001$

Several studies, investigating different doses and dosing schemes to mitigate exposure response and toxicity, indicate a possible improvement in benefit-risk profile, this remains though to be proven in larger trials.\(^{40–64}\) However, the drug–drug interaction with PPIs might substantiate the exposure–response effect, hence the concomitant use of PPIs and crystalline dasatinib should be cautioned when using dasatinib dosages not specified in the prescription information. The AUC following XS004 and omeprazole was estimated slightly higher than following XS004 alone, however the results indicate that a ratio of 90% or less is statistically unlikely. Hence, a drug–drug interaction like the one described for the original crystalline formulation of dasatinib, where the AUC is decreased by 40%–60% when co-administered with omeprazole can be excluded.\(^{4,12,13}\) A 15% lower XS004 $C_{\text{max}}$ observed with omeprazole co-medication is not considered to be clinically significant.\(^{18}\)

PPI medication is not the only reason for gastric pH increase. The gastric milieu can also be influenced by other acid regulating medicines, by food intake,\(^{65}\) by diseases of the gastrointestinal system,\(^{66,67}\) and the dynamic gastrointestinal physiology.\(^{38,69}\) All these aspects can have an impact on gastric pH and accordingly on TKI uptake and contribute to the substantial intra- and inter-patient variability, an effect which could be avoided by an alternative formulation such as XS004. In healthy adults, the pH in gastric content in fasted state usually ranges between 2 and 3.\(^{68,69}\) However, the fasted-state pH in the stomach may still be highly variable due to concomitant intake of water with the pharmaceutical product diluting the gastric content for a short time, differences in basal acid gastric secretion, local stomach differences, buffer capacity, ionic strength, bile salts, gastric emptying, and retroperistalsis that causes back transfer of bile acid and neutralizing bicarbonate into the stomach.\(^{68,70,71}\) Other factors to consider are disease conditions such as atrophic gastritis that reduces parietal cells that result in achlorhydria and hypochlorhydria. The estimated prevalence of atrophic gastritis is up to 15% in US populations and may be greater in specific populations.\(^{72}\)

In conclusion, we have demonstrated that co-medication of PPI and TKIs is common in CML patients and that even in dasatinib-treated patients, where PPI use should be avoided, many patients are prescribed and takes such drugs. Furthermore, we observed a poorer survival of patients with co-medication of dasatinib and PPIs. Based on previously published data,\(^{4,12,13}\) we conclude that co-medication with PPIs will impact the bioavailability of dasatinib for a significant proportion of the patients. Our study further demonstrates that XS004, a new ASD formulation of dasatinib, maintains the bioavailability of the active pharmaceutical ingredient when co-administered with PPIs and the original tablet formulation (Sprycel\textsuperscript{®}).

\section*{Pharmacokinetic parameters of dasatinib following oral dosing of XS004 alone and with concomitant oral dosing of omeprazole.}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
Parameter (unit) & XS004 (control) & XS004 + omeprazole (test) & Ratio test/control (%) & 90% confidence interval & Intrasubject CV (%) \\
\hline
$C_{\text{max}}$ (ng/mL) & 138.4 & 118.6 & 85.7 & 67.2–109.2 & 42.1 & 0.3 \\
AUC$_{\text{0–24}}$ (h * ng/mL) & 426.3 & 455.1 & 106.8 & 90.3–126.3 & 28.5 & 0.5 \\
AUC$_{\text{inf}}$ (h * ng/mL) & 433.6 & 466.3 & 107.5 & 91.0–127.1 & 28.4 & 0.5 \\
\hline
\end{tabular}
\caption{Five-year OS associated with TKI and PPI co-medication.}
\end{table}

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\hline
\end{tabular}
\caption{Pharmacokinetic parameters of dasatinib following oral dosing of XS004 alone and with concomitant oral dosing of omeprazole.}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
Parameter (unit) & XS004 (control) & XS004 + omeprazole (test) & Ratio test/control (%) & 90% confidence interval & Intrasubject CV (%) \\
\hline
$C_{\text{max}}$ (ng/mL) & 138.4 & 118.6 & 85.7 & 67.2–109.2 & 42.1 & 0.3 \\
AUC$_{\text{0–24}}$ (h * ng/mL) & 426.3 & 455.1 & 106.8 & 90.3–126.3 & 28.5 & 0.5 \\
AUC$_{\text{inf}}$ (h * ng/mL) & 433.6 & 466.3 & 107.5 & 91.0–127.1 & 28.4 & 0.5 \\
\hline
\end{tabular}
\caption{Pharmacokinetic parameters of dasatinib following oral dosing of XS004 alone and with concomitant oral dosing of omeprazole.}
\end{table}

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PPI, proton pump inhibitors; TKI, tyrosine kinase inhibitors.

\textsuperscript{*}Adjusted for age, sex, year of diagnosis, use of anti-coagulants, and Charlson Comorbidity Index.
with acid regulating agents, including PPIs and that the co-medication of XS004 and PPIs is compatible.

AUTHOR CONTRIBUTIONS
In the Registry study, Gunnar Larfors and Leif Stenke designed and acquired the data. Gunnar Larfors analyzed the data. Gunnar Larfors, Leif Stenke, Hans Lennernäs, Per Andersson, Charlotta Liljebris, and Magnus Brisander interpreted the data.

In the Drug–Drug interaction study, Per Andersson, Charlotta Liljebris, and Magnus Brisander designed and acquired the data. Magnus Brisander and Hans Lennernäs analyzed the data. Gunnar Larfors, Leif Stenke, Hans Lennernäs, Per Andersson, Charlotta Liljebris, and Magnus Brisander interpreted the data.

Gunnar Larfors, Magnus Brisander, and Hans Lennernäs drafted the work. All authors participated in revising the work critically and contributed with important intellectual content and approved the final version of the work for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT
Gunnar Larfors reports consultancy and research funding for Xspray. Magnus Brisander reports consultancy and equity for Xspray. Hans Lennernäs reports part of advisory board for Vicore, consultancy for Xspray and Vicore and equity for Xspray, AstraZeneca, Novo Nordisk, Medivir Nanoligica and LIDDS, and research funding for Vicor and AstraZeneca. Leif Stenke reports consultancy for Xspray. Per Andersson, Gérald Jesson, and Charlotte Liljebris are employees of Xspray and holds equity in Xspray.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES


