ORIGINAL ARTICLE

Food-effect study of nilotinib in chronic myeloid leukaemia (NiFo study): Enabling dose reduction and relief of treatment burden

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Abstract

Objectives: Taking advantage of its food-dependent bioavailability, the present study investigated the effect of a reduced dose taken with real-life meals on the pharmacokinetics (PK) of nilotinib in chronic myeloid leukaemia (CML) patients.

Methods: Nilotinib was taken fasted (300 mg BID, days 1-4) or with real-life meals (200 mg BID, days 5-11). Rich sampling (days 1, 3, 8, 11) allowed for non-compartmental PK analysis. Nilotinib exposure ($AUC_{0-12 h}$ -C_{min} -C_{max}) and its intra- and interpatient variability were compared between the two regimens. Adverse events were recorded by means of a patient diary and ECG monitoring.

Results: Fifteen patients aged 40-74 years participated. Nilotinib PK following 200 mg BID taken with a meal strongly resembled that of 300 mg BID taken fasted (C_{min} percentile (P)10-P90: 665-1404 ng/mL and 557-1743 ng/mL, respectively). Meals delayed nilotinib absorption. Intra- and interpatient variability were not increased by intake with meals. Nilotinib with food was well tolerated.

Conclusion: With support of therapeutic drug monitoring, the use of a reduced 200 mg nilotinib dose with real-life meals seems feasible and safe. Future (confirmatory) studies should further explore the usefulness of nilotinib dosing together with food, including the relationship with treatment efficacy as well as long-term effects on quality of life.

Clinical Trial Registration: NTR5000 (Netherlands Trial Register, www.trialregister.nl).

KEYWORDS
chronic myeloid leukaemia, food effect, nilotinib, pharmacokinetics, treatment burden

1 | INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant disease of the haematopoietic stem cell, characterised by a massive accumulation of myeloid cells in blood, bone marrow and spleen. If treated inadequately, within a few years chronic phase CML transforms into a fatal blast crisis.[1,2] Treatment of CML has been revolutionised since 2001 by the introduction of the tyrosine kinase inhibitor (TKI) imatinib, which gives excellent disease control and complete cytogenetic remissions in the majority of cases.[3] Second generation TKIs like nilotinib and dasatinib, induce a more robust response and have been found to offer better protection than imatinib against disease progression.[4,5] Therefore, these TKIs are now preferred over imatinib as first-line treatment of patients with intermediate and high-risk chronic phase CML.[1,2]

The efficacy and safety of nilotinib treatment have been established.[5] After 5 years of treatment, 77% of the patients achieved a major molecular response as compared to 60% of those treated with imatinib.[5] Although nilotinib use can be considered generally safe, it may cause potentially serious side effects like pancreatitis, QT-interval prolongation and peripheral arterial occlusive disease.[6-8] In this respect, high peak plasma concentrations (C_{max}) particularly have been associated with hyperbilirubinemia and QT interval prolongation.[9-11]

The recommended dose of nilotinib as first-line treatment of chronic phase CML is 300 mg twice daily (BID), approximately 12 hours apart. Food should not be consumed 2 hours before the dose is taken and for at least 1 hour thereafter.[6] This regimen attempts to circumvent problems caused by the variable bioavailability of nilotinib[9-11] which as such substantially increases when it is taken together with food.[9] However, even if nilotinib is taken without food considerable variability has been observed with regard to the area under the concentration-time curve (AUC) and the C_{max} and trough concentrations (C_{min}).[9-11] Furthermore, in healthy volunteers the intake of a standardised high-fat meal 0.5 hours before nilotinib dosing resulted in a 112 and 82% increase in C_{max} and AUC, respectively, whereas a light meal only resulted in a 55 and 29% increase, respectively.[9] In CML patients the increase in the AUC was 50% after a high-fat meal.[9] In both healthy volunteers and patients the elimination half-life was not affected by the variations in diet.[9] Thus, taking the effect of food into account, use of the recommended dosing regimen might imply that the daily dose is unnecessarily high. Consequently, treatment costs are also higher than necessary. Moreover, the complexity of the nilotinib dosing regimen is a considerable burden for patients[12,13] as they need to bring forward or delay their breakfasts and evening meals and are required to stay fasted for no less than 6 hours per day. Clearly, these requirements do not fit very well into daily life rhythm. The planning of medication intake and food consumption is therefore restrictive and requires strict discipline. This may substantially contribute to medication non adherence.[12,14,15] Although in most patients TKIs effectively reduce disease burden and prevent the disease to progress, a significant number of patients does not attain an acceptable response.[1,2] Indeed, non adherence

What is the new aspect of your work?

- The increased absorption of nilotinib in the presence of food may be used as a means to reduce the dose of nilotinib and improve intake conditions.

What is the central finding of your work?

- Nilotinib PK following the reduced dose taken with a real-life meal strongly resembled that of the recommended standard dose of nilotinib taken fasted.

What is (or could be) the specific clinical relevance of your work?

- Supported and secured by therapeutic drug monitoring (TDM), replacement of the recommended dose under fasting conditions by a reduced nilotinib dose (200 mg BID) with a real-life meal substantially increases the nilotinib dosing regimen's implementability in clinical practice. Importantly, intake of a reduced dose taken with a meal may also substantially reduce treatment costs.

has been identified as a major reason underlying TKI treatment ineffectiveness.[16]

In order to simplify the nilotinib dosing regimen while reducing CML treatment costs and taking advantage of the food dependent bioavailability of nilotinib, in the present study we investigated the effect of real-life meals on the pharmacokinetics (PK) of nilotinib in chronic phase CML patients. Aiming to improve their quality of life while maintaining effectiveness and safety of treatment, the intake of nilotinib with medium-fat food was expected to increase the bioavailability of nilotinib by approximately 50% allowing the daily dose to be reduced by about a third.[9] Hence, the objective of the present study was to explore whether nilotinib at a reduced dose of 200 mg BID administered with food is dose equivalent with nilotinib 300 mg BID administered under fasting conditions as recommended. Since it increases the regimen's implementability in clinical practice, the study thereby focuses on the effect of real-life meals, instead of standardised (high-fat) meals. Safety and quality of life (QoL) were also evaluated.

2 | METHODS

2.1 | Study design

A clinical pharmacology study with a one-group pretest-posttest design (Figure 1) was conducted in chronic phase CML patients on treatment with nilotinib at a dose of 300 mg BID as recommended. Patients were asked to take a lower nilotinib dose (200 mg BID)
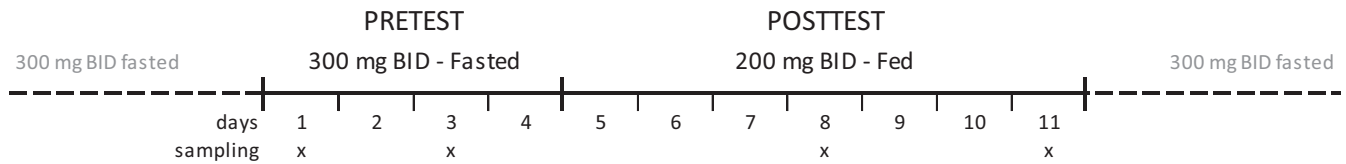
FIGURE 1 Study design of the NiFo study

simultaneously with their meals for a period of 7 days. Data were collected between December 2015 and August 2017 at the Amsterdam University Medical Centres (UMC) (location VUmc, Amsterdam). The study was approved by the Medical Ethics Review Committee of Amsterdam UMC (2014.579) and has been conducted in accordance with the Declaration of Helsinki and the Dutch Medical Research Involving Human Subjects Act (WMO). All patients provided written informed consent. The study was registered in the Netherlands Trial Register under number NTR5000.

2.2 | Study population

Chronic myeloid leukaemia patients were eligible if they were ≥18 years of age, were in chronic phase, had been treated at least for 3 months with nilotinib and had responsive disease.

2.3 | Treatment administration

Nilotinib 300 mg BID administered under fasting conditions (*reference treatment*) was compared with nilotinib at a reduced dose of 200 mg BID under fed conditions (*test treatment*)(Figure 1). For the fasted regimen, patients were asked to take nilotinib as recommended on an empty stomach, that is, no food was allowed for at least 2 hours predose and at least 1 hour postdose. For the fed regimen, patients were asked to take a reduced dose of nilotinib (200 mg BID) shortly after a meal for a period of 7 days. Food intake was not standardised in order to increase implementability in daily practice. However, to ensure an increased bioavailability of nilotinib, a breakfast consisting of at least the equivalent of one sandwich or one unit yogurt with cereals was required. The evening meal should comprise at least the equivalent of a regular meal made up from meat, fish or substitute, with potatoes, rice or noodles, and vegetables. This was verified by the research nurse (YH) or the researcher (CB) prior to study start. In case a meal seemed insufficient, patients were instructed to increase their food intake. In order to get insight into the effects of a high-fat meal on the PK of low-dose nilotinib and its safety, on the final day of the 7-day period of fed intake (day 11), patients took nilotinib in the evening with a relatively high-fat meal (>30 g fat). Total fat content of consumed meals, as registered by the patient in a diary, was scored by the researcher (JH) and a dietician (1 = very low-fat [<5 g], 2 = low-fat [5-10 g], 3 = medium-fat [10-20 g], 4 = high-fat [20-30 g] and 5 = very high-fat [>30 g]).

2.4 | Blood sampling

Blood sampling was performed by the patients at home by means of a validated dried blood spot (DBS) sampling method.[17] Patients received verbal and written instructions and practiced DBS sampling under supervision of the research nurse and investigator. Briefly, capillary blood was obtained by means of a finger prick using an automatic lancet device (BD Microtainer Contact-Activated Lancet, Pink, BD Diagnostics). The first drop was discarded and the next drops were collected to fill an 8-mm premarked circle on the sampling paper (WhatmanTM, FTATM DMPK-C (WB129243, GE Healthcare, VWR International BV). DBS samples were allowed to dry 2 hours at room temperature and were subsequently packed in sealable plastic minibags for shipping to the Amsterdam UMC (location VUmc, Amsterdam). Samples were stored at 4°C until analysis by means of a previously published nilotinib assay method.[17]

Sampling was performed on days 1 and 3 during fasted intake (days 1-4) and on days 8 and 11 during fed intake (days 5-11). Sampling time points for PK analysis were 1, 2, 3, 4, 6, 9 and 12 hours after the morning dose and 1, 2, 3, 4 and 12 hours after the evening dose. Patients self-recorded their nilotinib intake and blood sampling times in a diary.

2.5 | Pharmacokinetic analysis

The following PK parameters were determined on the basis of the plasma concentration-time profiles of nilotinib on days 1, 3, 8 and 11: AUC from time 0 to 12 h ($AUC_{0-12 h}$), C_{min}, C_{max} and time to C_{max} (t_{max}). The C_{min}, C_{max} and t_{max} values were obtained directly from the observed concentration-time data without interpolation. $AUC_{0-12 h}$ was calculated using the linear trapezoidal method. The protocol failed to include a blood sample at time 0 of each sampling day. This sample was added as a protocol amendment for the last 3 of 15 patients. For the remaining 12 patients, the missing C_{min} values at time 0 were imputed with the observed C_{min} values from the samples taken 12 hours after the evening dose for the corresponding sampling days.

2.6 | Safety assessment

Holter-ECG monitoring (Multichannel Holter ECG Recorder H2, Fysiologic ECG Services BV, Amsterdam, Netherlands) with emphasis on conduction times was performed at days 5-8 and 11. Adverse

Events (AEs) were measured by means of a diary. Patients were asked to report daily during the study period on occurrence of the following symptoms: headache, nausea, skin rash, itching, myalgia and fatigue (1 = not at all, 2 = a little bit, 3 = rather, 4 = a lot, 5 = very much).

2.7 | Quality of life

QoL was evaluated using the validated 30-item EORTC QLQ-C30 questionnaire[18] supplemented by the CML-specific 24-item module EORTC QLQ-CML24,[19] prior to study start and at day 11. Each item was scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The scales and single item raw scores were transformed into a score ranging from 0 to 100. A higher score indicates better health, functioning and satisfaction, or denotes more pain and symptoms.

2.8 | Data analyses

Data were processed using Microsoft Office Excel 2010 and analysed using SPSS version 22 for Windows (IBM Corp). To summarise patients' characteristics and nilotinib PK parameters, means (standard deviation) for continuous variables and frequencies (percentages) for categorical variables were calculated. Intra- and interpatient variability in nilotinib PK was expressed as the average coefficient of variation (CV%). The 90% confidence interval (CI) for the ratio of geometric means (GMR) between *test* and *reference treatment* was determined for $AUC_{0-12 h}$, C_{min} and C_{max}. QoL differences between the two regimens were tested with the non-parametric Wilcoxon signed-rank test.

3 | RESULTS

3.1 | Patient characteristics

A total of 15 patients with chronic phase CML, nine females and six males, participated in the study (mean age: 58.6 ± 12.0 years). Patient characteristics are listed in Table 1. All patients completed the study.

3.2 | Pharmacokinetics of nilotinib

The arithmetic mean concentration-time profiles of nilotinib 300 mg administered under fasting conditions or nilotinib 200 mg administered under fed conditions are shown in Figure 2. The corresponding PK parameters are presented in Table 2 and intra- and interpatient variability (CV%) in Table 3. Intra- and interpatient variability were not increased by intake with real-life meals. The proposed target C_{min} of 469 ng/mL[20] was achieved in 53/55 (96%) occasions following

TABLE 1 Patient characteristics

	N = 15
Age, range, M ± SD (years)	40-74, 58.6 ± 12.0
Female gender, n (%)	9 (60%)
Higher level of education, n (%)	8 (53%)
Years since CML diagnosis, range, M ± SD	1-16, 4.9 ± 3.9
Duration of use, range, M ± SD (months)	17-75, 42.0 ± 18.8
First-line treatment	11 (73%)
Molecular response	
MR[4.5]	2 (13%)
MR[4]	10 (67%)
MMR	3 (20%)

Abbreviations: M, Mean; MMR, Major MR; MR, Molecular Response; SD, Standard deviation.

200 mg taken with a meal and in 55/58 (95%) occasions following 300 mg fasted (missings excluded).

3.3 | Dose equivalence

Following the oral administration of 300 mg nilotinib in the fasted condition, the concentration of nilotinib peaked at a median time (t_{max}) of 2 hours (Table 2). The median t_{max} of nilotinib was delayed by 4 to 5 hours if the drug was administered at the lower dose with food. As shown in Figure 2 and Table 2, the mean plasma concentrations of nilotinib were generally lower when taken at the lower dose level with food. The geometric mean values of $AUC_{0-12 h}$, C_{min} and C_{max} of nilotinib following a morning dose were decreased by 11%, 12% and 10% respectively. The 90% CIs of the GMRs of nilotinib $AUC_{0-12 h}$, C_{min} and C_{max} were 81% to 98% (P = .045), 84% to 92% (P = .001), and 80% to 102% (P = .148) respectively. All limits of the 90% CIs of the GMRs for all of the comparisons fell within the equivalence limits of 80%-125%. Following an evening dose, the $AUC_{0-12 h}$ and C_{max} were decreased by 16% and 20%, with 90% CIs of 73% to 97% (P = .053) and 68% to 93% (P = .019). The geometric mean value of C_{min} was increased by 6% (90% CIs: 92 to 122%, P = .487). The 90% CIs of the C_{min} fell within the equivalence limits of 80%-125%. The $AUC_{0-12 h}$ and C_{max} were below the lower limit of dose equivalence.

Morning meals were low-fat meals [5-10 g]. Evening meals were medium-fat meals [10-20 g] on day 8 and high-fat meals [>30 g] on day 11. Nilotinib exposure was somewhat higher if the drug was taken with a medium- to high-fat meal as compared to a low-fat meal. There was no difference in nilotinib exposure between intake with medium-fat and high-fat meals.

3.4 | Safety

Clinically significant changes in ECG parameters were not observed. None of the measured QTc values was >480 ms and there were no
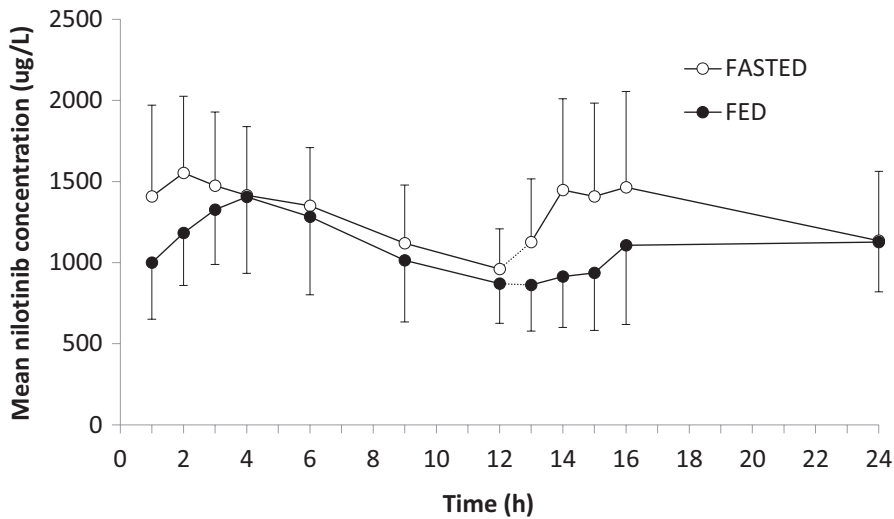
FIGURE 2 Mean (± SD) plasma concentrations of nilotinib over time following oral administration of 200 mg taken with a real-life meal (fed) and 300 mg fasted (N = 15)

TABLE 2 Mean nilotinib pharmacokinetic parameters following oral administration of 200 mg taken with a real-life meal and 300 mg fasted (N = 15)

	300 mg fasted[a]	200 mg fed[a]	Treatment ratio[b]
Morning dose			
$AUC_{0-12\,h}$ (ng*h/mL)	16 066 (4153) (9483-21146)	14 170 (3083) (9186-18751)	0.89 (0.81-0.98)
C_{min} (ng/mL)	1018 (260) (669-1399)	908 (242) (552-1244)	0.88 (0.84-0.92)
C_{max} (ng/mL)	1719 (463) (1134-2408)	1536 (334) (1009-2056)	0.90 (0.80-1.02)
t_{max} (h)	2 (2-3)	4 (3-6)	NA
Evening dose			
$AUC_{0-12\,h}$ (ng*h/mL)	16 436 (6730) (8980-27678)	13 444 (3820) (7473-19058)	0.84 (0.73-0.97)
C_{min} (ng/mL)	1207 (639) (475-2134)	1174 (326) (724-1636)	1.06 (0.92-1.22)
C_{max} (ng/mL)	1791 (706) (941-2919)	1384 (373) (754-1872)	0.80 (0.68-0.93)
t_{max} (h)	2 (2-4)	5.5 (4-12)	NA
Irrespective of timing			
$AUC_{0-12\,h}$ (ng*h/mL)	16 239 (5265) (9381-24283)	13 807 (3394) (8929-19071)	0.86 (0.77-0.96)
C_{min} (ng/mL)	1112 (430) (557-1743)	1040 (256) (665-1404)	0.97 (0.89-1.05)
C_{max} (ng/mL)	1750 (562) (1048-2621)	1457 (326) (928-1911)	0.85 (0.75-0.96)
t_{max} (h)	2.8 (2.0-3.5)	5.8 (4.8-7.5)	NA

Abbreviations: AUC, area under curve; CI, confidence interval; C_{max}, peak plasma concentration; C_{min}, trough plasma concentration; GMR, geometric mean ratio; t_{max}, time to C_{max}.
[a]Values shown are arithmetic means (standard deviation)(percentiles 10-90). t_{max} values are medians (quartiles 1-3).
[b]Geometric mean ratio [fed condition/fasting condition] (90% Confidence Interval) presented.

increases relative to intake under fasting conditions of >60 ms in any patient. The most frequently reported AEs were fatigue, myalgia and headache, occurring in 53% (8 of 15), 40% (6 of 15) and 33% (5 of 15) of patients during fasted intake respectively. Most patients reported their symptoms as mild. The frequency of these AEs was similar for the two dosing regimens.

3.5 | Quality of life

The results of the EORTC QLQ-C30 and EORTC QLQ-CML24 questionnaires are listed in Table S1. The median and quartiles are displayed for the two measurements. The score on symptom burden was significantly different (P = .021). Nine patients (60%) reported

TABLE 3 Intra- and interpatient variability of nilotinib following oral administration of 200 mg taken with a real-life meal and 300 mg fasted (N = 15)

	CV% of $AUC_{0-12 h}$	CV% of C_{min}	CV% of C_{max}
Intra-patient variability			
Fasting condition (*m*)	13.8%	14.3%	14.5%
Fasting condition (*e*)	13.1%	15.8%	15.0%
Fed condition (*m*)	16.7%	14.3%	20.5%
Fed condition (*e*)	17.0%	17.6%	16.3%
Inter-patient variability			
Fasting condition (*m*)	28.4%	29.0%	28.8%
Fasting condition (*e*)	42.3%	55.8%	40.6%
Fed condition (*m*)	26.0%	30.5%	28.1%
Fed condition (*e*)	31.4%	31.2%	31.1%

Note: Fasting condition, standard dose of nilotinib (300 mg BID) taken under fasting conditions as recommended.

Fed condition, a reduced dose of nilotinib (200 mg BID) taken with a real-life meal.

Abbreviations: AUC, area under curve; C_{max}, peak plasma concentration; C_{min}, trough plasma concentration; CV%, Coefficient of variation; *e*, evening dose; *m*, morning dose.

a lower symptom burden after 7 days of fed intake as compared to the symptom burden reported during fasted intake. In two patients (13%) the score was higher, and in four patients (27%) the score was unchanged. No other significant differences between QoL parameters were observed.

4 | DISCUSSION

The present study evaluated the effects of real-life food consumption on the PK of nilotinib in chronic phase CML patients. The standard dose of nilotinib (300 mg BID) taken under fasting conditions as recommended, was compared with a reduced dose (200 mg BID) taken with a real-life meal. Nilotinib PK following the reduced dose taken with a real-life meal strongly resembled that of the recommended standard dose of nilotinib taken fasted. The meals delayed the absorption of nilotinib depending on their fat content. Regardless of the dosing regimen nilotinib was generally well tolerated. The patient-reported symptom burden was lower after intake of the reduced dose with food.

By examining the PK of a lower nilotinib dose taken with a real-life meal, to our knowledge this is the first study that uses the increased absorption of nilotinib in the presence of food as a means to reduce the dose of nilotinib and improve intake conditions. In line with previous observations,[9] real-life food intake substantially increased nilotinib exposure. Dose equivalence was complete in terms of C_{min}, the parameter commonly used to associate nilotinib exposure with treatment efficacy.[9-11,20,21] Moreover, average nilotinib C_{min} morning and evening values obtained in the present study,

both in the fasted (1018 and 1207 µg/L) and fed states (908 and 1174 µg/L), were all well within the range of average/median C_{min} values that have been previously reported (774-1260 µg/L).[9-11] The C_{min} values were above the proposed target of 469 ng/mL[10] in 96% and 95% of occasions following 200 mg taken with a real-life meal and 300 mg fasted respectively. However, these findings should be interpreted with caution due to differences in the clinical scenario of these studies and the limited evidence yet available of an exposure-response relationship of nilotinib.[10,11,20] Nevertheless, in line with the results of a recent review,[20] which concluded that TDM of nilotinib is promising, the use of nilotinib at a reduced dose under fed conditions therefore seems a feasible treatment option in CML clinical practice.

In accordance with the literature,[9,22,23] in the present study the intake of nilotinib with a meal delayed the absorption of nilotinib. This effect has been contributed to an increase in the dissolution rate of nilotinib or delayed gastric emptying.[9,22] The substantial prolongation of the median t_{max} (5.5 hours) observed after evening intake of the reduced dose together with a medium-fat meal might explain the lower $AUC_{0-12 h}$ and C_{max} values. As compared to values in the fasted state, the $AUC_{0-12 h}$ and C_{max} obtained after morning intake of the reduced dose with a low-fat breakfast were decreased by 11% and 10% respectively. Following evening intake together with a medium-fat meal the decrease was more pronounced (16% and 20% respectively). As the result, for these parameters full dose equivalence between the two dosing regimens was not achieved. However, since the protocol did not include sampling time points between 5 and 11 hours after nilotinib intake in the evening, C_{max} was possibly not reached within 4 hours after nilotinib intake in the evening (the latest sampling time point before morning C_{min}). Accordingly, the evening $AUC_{0-12 h}$ and C_{max} values obtained under fed conditions were lower than those obtained under fasted conditions.

When comparing a light meal with a high-fat meal, the increase in the nilotinib absorption was more pronounced with a high-fat meal.[9] In the present study, nilotinib exposure was slightly higher if nilotinib was taken together with a medium- to high-fat meal as compared to a low-fat meal. The fat content of the meals consumed at the evening intake of nilotinib was higher than that of the meals used in the morning (>10 g vs 5-10 g respectively). This could explain why, relative to values in the fasted state, C_{min} was increased by 6% after intake of the reduced dose with food in the evening and decreased by 12% after intake of the reduced dose with food in the morning. The difference in bioavailability associated with the morning and evening doses has been observed previously.[10] It was explained by factors such as the presence of residual food or diurnal variation.[10] Nevertheless, considering the long half-life of nilotinib of 17 hours,[6] it is expected that variability in nilotinib exposure due to variabilities in the fat content of the meals it is taken with, is limited and clinically irrelevant. Furthermore, the protocol included a high-fat meal at the evening dose on day 11. Nilotinib blood levels observed after this meal did not differ with those after a medium-fat meal indicating that taking a lower nilotinib dose with a high-fat meal is not hazardous. A measure to assure safety when implementing the

alternative dosing regimen in clinical practice is the use of therapeutic drug monitoring (TDM) which can be performed relatively easily if the DBS blood sampling method is used.[24] Importantly, TDM on the basis of DBS will also be highly useful in optimising treatment conditions of patients using nilotinib according to the recommended dosing regimen.[24]

There are certain strengths and limitations of this study that need to be mentioned. A major strength is that the effect of real-life meals, instead of standardised (high-fat) meals, has been examined. This increases the regimen's implementability in clinical practice. A second strength is that in the present study four concentration-time curves of each patient were collected. A limitation is that no samples were collected between 5 and 11 hours after the evening dose. However, given the already considerable burden of study participation as such, these samples that had to be taken at night, were not included in the protocol. Second, DBS were obtained by patient self-sampling which as such has not been validated. However, 95% of the samples were suitable for analysis. This percentage is considerably higher than the percentages reported previously and seem due to the adequate and comprehensive sampling instruction.[24] Third, the 7-day study period may have been too short to permit firm conclusions on the resemblance of the two regimens. However, it is expected that steady state is achieved after four half-lives. Considering the half-life of nilotinib of 17 hours,[6] the 7-day study period was expected to be sufficient. Fourth, the burden of study participation (ie sequential DBS sampling, completing diaries, medical visits for ECGs) may have prevented to observe a QoL improvement.

In conclusion, with the support of TDM on the basis of DBS blood sampling, the use of a reduced nilotinib dose (200 mg BID) with a real-life meal seems feasible and safe, notably because dose equivalence with the recommended daily dose of nilotinib (300 mg BID) under fasted conditions was achieved in terms of C_{min}. The C_{min} values observed in the present study were also well in the range of those reported to be associated with nilotinib treatment efficacy.[9-11] Therefore, reducing the daily dose of nilotinib by a third to 200 mg seems a suitable starting point when prescribing the twice daily intake of nilotinib with food. Future (confirmatory) studies should further explore the usefulness of nilotinib dosing together with food. In these studies, the relationship with treatment efficacy should be established as well as the long-term effect on QoL parameters. Nilotinib treatment costs are high. In the case that the long-term use of unnecessary high doses can be avoided, the implementation of regimens using lower nilotinib doses taken with food will substantially reduce drug expenditures. In addition to optimising chronic phase CML treatment with nilotinib, the strategy followed in the present study can also be applied to various other expensive oral anticancer agents of which the bioavailability markedly improves when they are taken with food, but which are now taken fasted.

CONFLICT OF INTEREST

JJWM Janssen is an advisory board member for Abbvie, Incyte, Jazz Pharmaceuticals and Pfizer, and has received research support funding from Novartis and Bristol Myers Squibb and speaker's fees from Incyte and Pfizer. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CB, JJ, ES, NH, and JH designed the study. CB and YH recruited patients and collected data. RV performed the sample analysis. CB and AZ were involved in data analysis. CB drafted the manuscript and JJ, AZ, ES, NH, and JH critically revised the manuscript. All authors gave the final approval of the manuscript to be published. JH was the principal investigator.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.