



Study to evaluate the Effect of Fatty meals on Nilotinib drug levels in Patients with Chronic Myeloid Leukemia-CP

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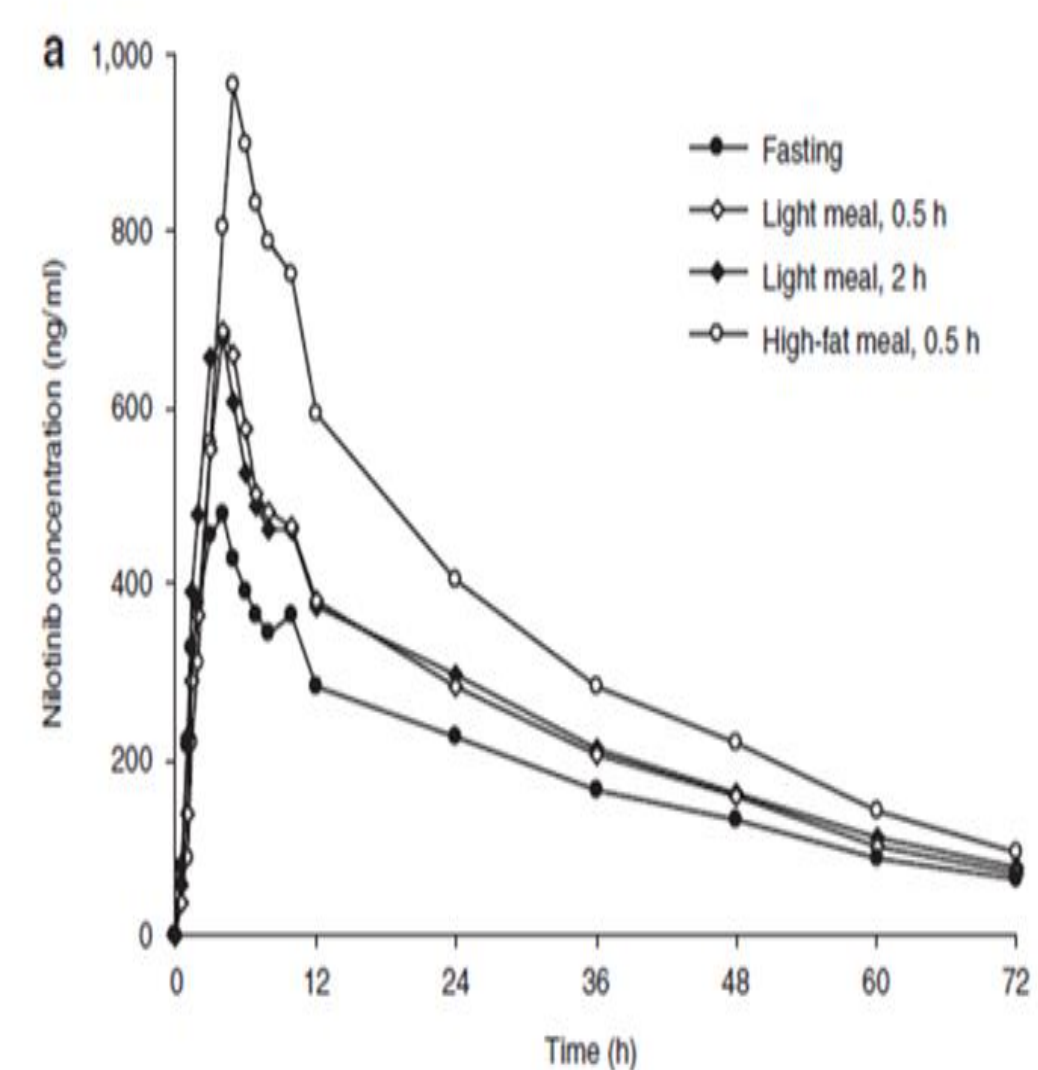


Introduction

Nilotinib is approved as a first line drug in patients of CML-CP.

The dose of 300 mg BD is approved in CML-CP and 400 mg BD in CML-AP recommended in a fasting state.

Background



PK parameter	Fasting N= 44	Light meal 0.5 hr prior N= 20	High Fat meal 0.5 hr prior N= 44
C max (ng/ml)	508	743	1068
AUC (ng-h/ml)	13,662	17,154	24,416

A study, among 48 healthy volunteers, following a single dose of nilotinib 400 mg, the systemic exposure of nilotinib increased when given with food. The highest effect was observed with high-fat meal with the AUC and Cmax increasing 82% and 112%, respectively. For a light meal, the increases in AUC and Cmax were 33% and 55%, respectively.

Study Rationale

Nilotinib taken with food increases drug peak concentration and AUC.

This can lead to decrease in dose required to produce a clinical benefit.

Objective

To determine increase in drug levels when nilotinib is administered with low fat meals.

Study Design

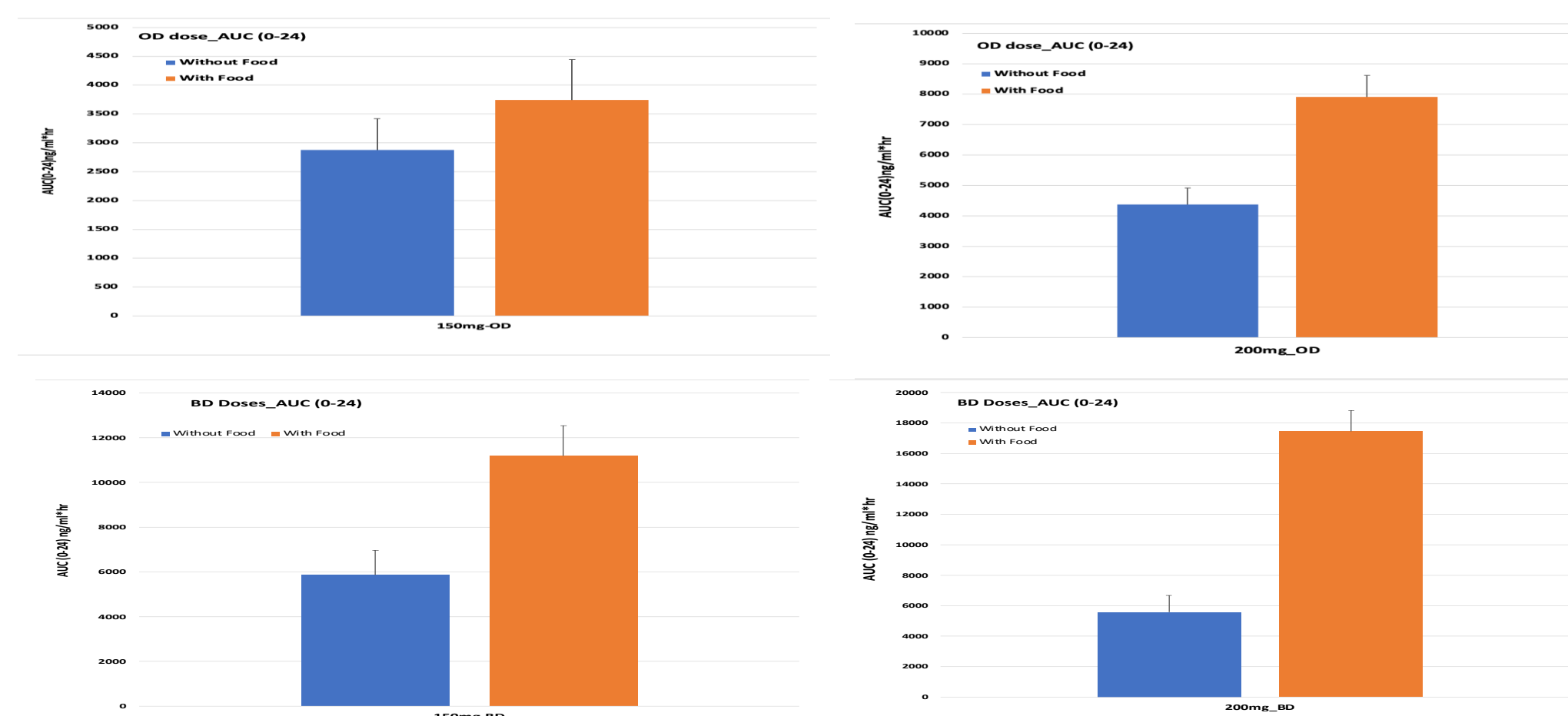
- Single center, open label, pharmacokinetic study
- 1. 150 mg OD X 7 days f/b with food X 7 days
- 2. 200 mg OD X 7 days f/b with food X 7 days
- 3. 150 mg BD X 7 days f/b with food X 7 days
- 4. 200 mg BD X 7 days f/b with food X 7 days
- 5. 300 mg BD X 7 days empty stomach

Food = 2 slices of bread + 10 gm of Butter (**Low Fat Meal**)

- Blood samples for drug levels will be taken on 0,1, 2, 3,4, 6, 8, 10, 12, 16, 20 and 24 hours on day 1 of dosing
- At 0 and 3 hours interval On day 8
- Drug levels were detected by Liquid Chromatography- Mass Spectroscopy.

Study Results

Cohort	AUC (ng*hr/ml)		C max (ng/ml)	
	Fasting State	Fed State	Fasting State	Fed State
150 mg OD (N= 6)	2878 (896- 4324)	3739 (1583-6046)	303 (108-517)	323 (151-561)
200 mg OD (N=6)	4373 (1693-9165)	7914 (2129-16203)	551 (189-1360)	833 (210-2209)
150 mg BD (N=4)	5865 (2976- 8583)	11179 (5361- 14476)	524 (206-834)	805 (596- 1081)
200 mg BD (N=5)	5581 (3956-6747)	17447 (9828-30462)	312 (155-521)	822 (292-1836)



Cohort	AUC ratio		C max		P- value
Nilotinib 150 mg OD	30 %	1.3	6.6%	1.06	P= .11
Nilotinib 200 mg OD	80%	1.8	51%	1.5	P= 0.02
Nilotinib 150 mg BD	90%	1.9	53.6%	1.53	P= 0.04
Nilotinib 200 mg BD	212%	3.12	163 %	2.63	P=0.03

Discussion

	Boons et al (2)	Our Study
Patient Population	Already on nilotinib Majority > 1 year Were in MMR	Newly Diagnosed patients
Dose levels	Single 200 mg BD	4 doses
Food Specified	None variable	Kept uniform
Study design	Home Based	Hospital
Sampling	Dried blood Spot method	Fresh venous samples
Analysis	Done differently for both doses 12 hour interval	Done combined 24 hour
Results	Non Inferior	Significant Food Interaction

Limitations:

- Limited Sample Size
- Food effects were not studied in 300 mg BD arm.
- Not designed for bioequivalence.

Conclusion

- Nilotinib had a significant dose dependent food interaction.
- Higher Doses had more increase in AUC, Cmax.
- 150 mg BD had 90% increase in AUC with low fat meal and can be used for further bioequivalence studies.

References

- Tanaka C et al. Clinical pharmacology & Therapeutics 2010; 87 (2): 197- 203.
- Boons et al. Eur J Haematol. 2020;105:148–155