Effect of a high-calorie, high-fat meal on the pharmacokinetics of oral nifurtimox in adults with chronic Chagas' disease

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Introduction

Nifurtimox (NFX) is one of only two treatments for patients with Chagas' Disease (CD); a 30 mg tablet suitable for age-appropriate dosing of pediatric CD patients has been developed recently. As NFX is a poorly soluble and highly permeable drug, food can have a considerable effect on its uptake from the GI tract. We therefore conducted a Phase I study to investigate this possible food effect, initially in adults.

Study design and methods

We investigated the pharmacokinetics (PK) and safety of 120 mg (four 30 mg tablets) administered to CD patients in the fasted and fed states. A randomised cross-over design without blinding was followed. The study was conducted at a single site in Argentina (NCT02606864).

Nifurtimox was administered to subjects who either had fasted for ≥10 hours or had received a high-fat, high-calorie meal ("American breakfast") within the 30 minutes before dosing. The subjects were then observed, with blood and urine sampling for PK, over 24 hours. A follow-up examination for safety took place 7–14 days later. After a wash-out period of at least 5 days the respective other treatment was administered. A follow-up examination for safety took place 7–14 days after the second treatment.

Study analysis

Plasma PK parameters designed to quantify the food effect were: area under the concentration–time curve from zero to infinity after single dose (AUC), AUC from time 0 to the last measurable data point (AUC(0-t_{last})), maximum observed drug concentration (C_{max}) and time to reach C_{max} (t_{max}). Bioequivalence criteria were applied to assess the food effect; complete absence of a food effect was defined as being found if the 90% confidence intervals (CIs) for all of the above criteria lay within the range 80–125%.

Additionally, the 24-hour AUC ($AUC_{(0-24)}$), terminal half-life ($t_{1/2}$), mean residence time (MRT), apparent total clearance (CL/F), and apparent volume of distribution (V_z/F) were calculated. Urine PK data were retained for separate exploratory analysis.

Study population

Of 39 adult CD patients screened, 36 were treated and 35 were evaluable for PK; the remaining patient withdrew consent after only one treatment.

The subjects' mean age was 33.9 years (range 26−45 years) and BMI was 26.3 kg/m^2 (SD 3.1 kg/m^2). Most (32; 89%) were female, most (33; 92%) were Hispanic or Latino, and all were Caucasian.

Results: Pharmacokinetics

Plasma concentration–time courses of NFX are summarised in Figure 1.

Figure 1: Geometric mean concentrations (geom. std. dev.) of nifurtimox in plasma for subjects in the fasted and the fed states.

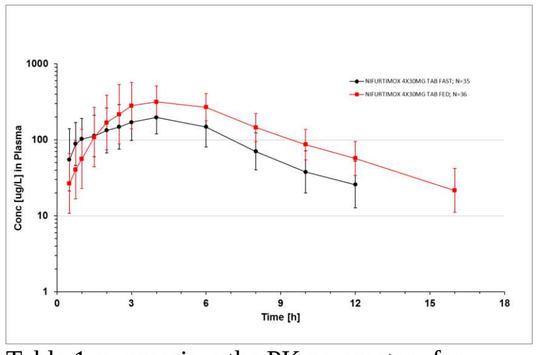

Table 1 summarises the PK parameters for 120 mg nifurtimox administered orally to the subjects in the fasted and fed states. Geometric means are shown with percentage coefficients of variation and ranges (for t_{max} median and range only).

Table 1: Pharmacokinetic parameters (geo. mean, %C.V.)

Parameter	Fasted	Fed
AUC [µg·h/L]	1480 / 40.4 (675 – 2900)	2530 / 21.3 (1510 – 4000)
AUC(0-t_{last}) [µg·h/L]	1390 / 40.6 (619 – 2770)	2390 / 21.7 (1370 – 3830)
AUC(0-24) [µg·h/L]	1460 / 39.7 (674 – 2870)	2500 / 21.4 (1460 – 3970)
CL/F [L/h]	81.2 / 40.4 (41.4 – 178)	47.4 / 21.3 (30.0 – 79.6)
C_{max} [µg/L]	277 / 36.7 (145 – 604)	465 / 33.4 (218 – 905)
MRT [h]	5.83 / 22.7 (3.65 – 10.1)	6.56 / 21.5 (4.73 – 10.6)
$t_{1/2}$ [h]	3.07 / 34.6 (1.59 – 7.16)	3.13 / 27.4 (1.77 – 6.23)
t_{max} [h]	3.00 (0.50 – 6.05)	4.00 (1.00 – 8.00)
V_z/F [L]	359 / 36.5 (196 – 792)	214 / 37.4 (99.2 – 574)

The bioavailability results are shown in Table 2.

Table 2: Bioavailability analysis

Parameter	Estimated ratio (%)	90% CI (%)
AUC	171	[154 ; 191]
$AUC_{(0-tlast)}$	172	[154 ; 192]
C_{max}	168	[150 ; 187]

Results: Safety

Five subjects (14%) reported at least 1 adverse event after treatment with nifurtimox (3 subjects fasted, 2 fed). All these events were gastrointestinal disorders (nausea, 2 subjects; abdominal pain and vomiting, 1 subject each) or headache (3 subjects). Most events were considered related to the study drug. The greatest severity was 'moderate' for the 3 subjects in whom onset was under fasted conditions and 'mild' for the 2 subjects with onset under fed conditions. There were no serious events. None of the AEs led to discontinuation. All AEs resolved.

Other safety data (laboratory, vital signs, ECG) yielded no clinically relevant abnormalities.

Conclusion

- Nifurtimox exposure was increased and its variability decreased by almost twofold (% C.V.) when a single oral dose of 120 mg nifurtimox was administered to subjects under fed conditions (high-calorie, high-fat meal) compared with fasted conditions.
- Peak concentrations were increased as well no difference in intersubject variability of C_{max} was associated with this change:
- With food, AUC, $AUC_{(0-tlast)}$, and C_{max} were increased by 71%, 72% and 68%, respectively.
- Food slightly increased the time to reach peak nifurtimox plasma concentrations, with a median t_{max} of 4 hours (fed) compared with 3 hours (fasted), suggesting a mildly reduced rate of absorption under fed conditions.
- Statistical analysis confirmed a pronounced, statistically significant food effect. The treatment was well tolerated, and there were no new safety findings.

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