Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Date of study report:	28 NOV 2016
Study title:	Non-blinded, randomized, single center, single dose, cross-over study to assess the effect of a high calorie/high fat meal on the pharmacokinetics of four 30 mg nifurtimox tablets taken orally by adult male and female patients suffering from chronic Chagas' disease
Sponsor's study number:	16005
NCT number:	NCT02606864
EudraCT number:	Not applicable
Sponsor:	Bayer
Clinical phase:	Phase 1
Study objectives:	The **primary objective** of the study was to investigate the effect of a high calorie / high fat meal on the PK of nifurtimox in adult male and female subjects suffering from Chagas' disease. The **secondary objective** was to investigate safety and tolerability.
Test drug:	Nifurtimox (BAYa2502) 30 mg tablet
Name of active ingredient(s):	Nifurtimox
Dose:	120 mg (4 x 30 mg tablets)
Route of administration:	Oral
Duration of treatment:	Single dose on 2 days with a washout period of at least 5 days in between.
Reference drug:	Not applicable
Indication:	Chagas' disease
Diagnosis and main criteria for inclusion:	**Key inclusion criteria** were: • Male and female subjects with chronic Chagas' disease • Age 18 to 45 years (inclusive).
Study design:	Single center, open label, randomized, single dose, 2-way cross-over design

Methodology:	The study comprised a screening period, 2 treatment periods, and a follow-up period for each subject. Following satisfactory screening and predose assessments, eligible subjects were randomized to one of 2 treatment sequences (A-B or B-A). • Treatment A: single dose of 120 mg nifurtimox (4 x 30 mg tablets) under fasted conditions • Treatment B: single dose of 120 mg nifurtimox (4 x 30 mg tablets) under fed conditions (high calorie / high fat breakfast) The subjects remained at the study site until 24 hours after dosing in each treatment period. There was a washout period of at least 5 days between the 2 treatments in each subject. A follow-up visit was performed 7 to 14 days after the second treatment. Safety assessments were performed, and pharmacokinetic (PK) blood samples were collected at 16 predefined time points up to 24 hours postdose for measurement of nifurtimox in plasma. PK urine sampling was also performed for measurement of urinary concentrations of nifurtimox and potentially present metabolites on an exploratory, optional basis, if possible (4 collection intervals up to 24 hours postdose). After the end of the study, the subjects were offered further treatment, if medically indicated.
Study center(s):	One centre in Argentina
Publication(s) based on the study (references):	None at the time of report creation
Study period:	**Study Start Date:** 16 DEC 2015 **Study Completion Date:** 04 AUG 2016
Early termination:	Not applicable
Number of subjects:	**Planned:** 36 **Analyzed:** 35 / 36

Criteria for evaluation

Efficacy: Not applicable

Safety: **Secondary variable** was the number of participants with adverse events.

Other variables for the assessment of safety and tolerability were clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.

Clinical pharmacology: **Primary variables** defined to quantify the food effect were the following PK parameters for nifurtimox analyzed in plasma:

- Area under the concentration versus time curve from zero to infinity after single dose (AUC);
- AUC from time 0 to the last data point above the lower limit of quantitation (AUC(0-t_{last});
- Maximum observed drug concentration of nifurtimox in plasma (C_{max}); and
- Time to reach C_{max} (t_{max}).

Other variables were the following PK parameters: area under the concentration versus time curve from time 0 to 24 hours postdose (AUC(0-24)), half-life associated with the terminal slope ($t_{1/2}$), mean residence time (MRT), apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F) of drug calculated after extravascular dose administration.

PK urine data collected for exploratory, optional assessment will be presented in a separate report.

Statistical methods:	All data were listed and summary tables were provided. The PK characteristics AUC, AUC(0-t_{last}), and C_{max} of nifurtimox were analyzed assuming log-normally distributed data. The logarithms of these characteristics were analyzed using analysis of variance (ANOVA) including sequence, subject (sequence), period, and treatment effects. Based on these analyses, point estimates (least squares-means [LS-means]) and exploratory 90% confidence intervals (CIs) for the ratios "fed/fasted" were calculated by re-transformation of the logarithmic data using the intra-individual standard deviation (SD) of the ANOVA. Bioequivalence criteria were applied to assess the food effect quantitatively, assuming complete absence of a food effect, if all of the above 90% CIs completely fell into the acceptance interval of 80% to 125%.
Substantial protocol changes:	The study was conducted according to final study protocol Version 2.0 from 18 MAY 2015, and included no substantial amendments.

Subject disposition and baseline

A total of 39 subjects were enrolled (signed informed consent) and screened. Of these, 3 subjects were screen failures, and 36 subjects were randomized and received at least 1 dose of study drug (18 subjects in Sequence A−B and 18 subjects in Sequence B−A). Of the 36 randomized subjects, 35 completed the study and 1 subject discontinued (withdrew consent after first treatment) and did not receive a second dose of study drug. All 36 randomized subjects who received at least 1 dose of nifurtimox were included in the safety analysis set; the 35 subjects who received both doses of nifurtimox (i.e., a single dose of 120 mg under both fasted and fed conditions) were included in the PK analysis set.

The overall mean age was 33.9 years (range: 26−45 years), and the overall mean (SD) BMI was 26.31 (3.10) kg/m^2 (safety analysis set). The majority of subjects were female (32 subjects, 88.9%) and Hispanic or Latino (33 subjects, 91.7%). All subjects were white. The sequence groups were well balanced in terms of demographic and baseline characteristics. Demographic statistics for the PK analysis set were very similar to those for the safety analysis set.

Pharmacokinetic evaluation

The tables below summarize the main PK parameters of nifurtimox as geometric means and percentage coefficient of variation (CV) (with range), and present the LS-means and two-sided 90% CIs for the primary PK parameters (AUC, AUC(0-t_{last}), and C_{max}), resulting from the ANOVA model.

Food increased the AUC of nifurtimox by 71%, AUC(0-t_{last}) by 72%, and C_{max} by 68%. The 90% CIs of all ratios (fed/fasted) were not included in the range 80% to 125%, indicating a food effect. Food also slightly delayed the median t_{max} from 3 to 4 hours.

Parameter	Units	Treatment A		Treatment B	
		n	Geometric mean/%CV (range)	n	Geometric mean/%CV (range)
AUC	µg*h/L	35	1480/40.4 (675-2900)	35	2530/21.3 (1510-4000)
AUC(0-t_{last})	µg*h/L	35	1390/40.6 (619-2770)	35	2390/21.7 (1370-3830)
AUC(0-24)	µg*h/L	35	1460/39.7 (674-2870)	35	2500/21.4 (1460-3970)
CL/F	L/h	35	81.2/40.4 (41.4-178)	35	47.4/21.3 (30.0-79.6)
C_{max}	µg/L	35	277/36.7 (145-604)	35	465/33.4 (218-905)
MRT	h	35	5.83/22.7 (3.65-10.1)	35	6.56/21.5 (4.73-10.6)
$t_{1/2}$	h	35	3.07/34.6 (1.59-7.16)	35	3.13/27.4 (1.77-6.23)
t_{max}[a]	h	35	3.00 (0.50-6.05)	35	4.00 (1.00-8.00)
V_z/F	L	35	359/36.5 (196-792)	35	214/37.4 (99.2-574)

A = Single oral dose of 120 mg (4 x 30 mg tablets) BAY a2502 (nifurtimox) under fasted conditions.
B = Single oral dose of 120 mg (4 x 30 mg tablets) BAY a2502 (nifurtimox) under fed conditions.
a Data are presented as median (range).

Parameter	Units	n	Geometric CV (%)	Estimated Ratio (%)	90% Confidence Interval (%)	95% Prediction Interval (%)
AUC	µg*h/L	35	27.0	171	[154 ; 191]	[78.9 ; 372]
AUC(0-t_{last})	µg*h/L	35	27.3	172	[154 ; 192]	[78.7 ; 376]
C_{max}	µg/L	35	28.3	168	[150 ; 187]	[74.6 ; 376]

Safety evaluation

Exposure: A total of 35 subjects received 2 single doses of 120 mg nifurtimox (4 x 30 mg tablets). One subject received 1 single dose of 120 mg nifurtimox only (4 x 30 mg tablets) due to discontinuation after first treatment.

Adverse events: Five subjects (13.9%) reported at least 1 TEAE (3 subjects [8.6%] after nifurtimox under fasted conditions, and 2 subjects [5.6%] after nifurtimox under fed conditions). All TEAEs were gastrointestinal disorders (abdominal pain [1 subject], nausea [2 subjects], or vomiting [1 subject]) or headache (3 subjects). The majority of events were considered by the investigator as related to study drug. The maximum intensity of the TEAEs was moderate for all 3 subjects who had an AE after nifurtimox under fasted conditions, and mild for the 2 subjects who had an AE after nifurtimox under fed conditions. There were no deaths or other SAEs, and no subjects had a TEAE leading to discontinuation. All TEAEs resolved.

Other safety data: The clinical laboratory, vital signs, and ECG data showed no clinically significant findings. Two cases of QTc increase > 60 ms that occurred 1.5 – 2.5 h after dosing, were judged to be without clinical relevance by the investigator.

Overall conclusions

- Nifurtimox exposure was increased when a single oral dose of 120 mg nifurtimox (4 x 30 mg tablets) was administered under fed conditions (high calorie / high fat meal) compared with fasted conditions: AUC, AUC(0-t_{last}), and C_{max} were increased by 71%, 72%, and 68%, respectively, with food.

- Food slightly increased the time to reach peak nifurtimox plasma concentrations, with a median t_{max} of 4 hours (fed) versus 3 hours (fasted), suggesting a mildly reduced rate of absorption under fed conditions.

- Statistical analysis confirmed that the tablet formulation investigated in this study shows a pronounced, statistically significant food effect.

- A single oral dose of 120 mg nifurtimox, administered as 4 x 30 mg tablets, was well tolerated, and there were no new safety or tolerability findings. Two cases of QTc increase > 60 ms that occurred 1.5 – 2.5 h after dosing, were judged to be without clinical relevance by the investigator.