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.

2. Synopsis

Date of report:	26 AUG 2015
Study title:	Open-label, randomized, single-dose cross-over study to assess bioequivalence between single 120 mg nifurtimox tablet and four 30 mg nifurtimox tablets administered orally, following high calorie/high fat meal to adult male and female patients suffering from chronic Chagas' disease and to determine the pharmacokinetics of nifurtimox tablets administered orally, in a form of aqueous slurry
Sponsor's study number:	16004
NCT number:	National Clinical Trial (NCT) number NCT01927224
EudraCT number:	Not applicable
Sponsor:	Bayer HealthCare
Clinical phase:	I
Study objectives:	**Primary:** To investigate the bioequivalence of the new 30 mg nifurtimox oral tablet formulation versus the marketed 120 mg oral tablet under fed conditions in adult male and female subjects suffering from chronic Chagas' disease and to characterize the pharmacokinetics of nifurtimox after ingestion of the dose as aqueous slurry (tablets disintegrated in tap water). **Secondary:** To assess the safety and tolerability, and to collect pharmacokinetic (PK) data on the renal excretion of nifurtimox.

Test drugs:	Nifurtimox (BAY a2502) 30 mg tablet (Group 1 & 2) Nifurtimox (BAY a2502) aqueous slurry from 30 mg tablet (Group 1) Nifurtimox (BAY a2502) 120 mg tablet (Group 2)
Name of active ingredient:	Nifurtimox
Dose:	120 mg (4 x 30 mg tablets, or aqueous slurry prepared by 4 x 30 mg tablets disintegrated in 1 to 2 mL tap water, or 1 x 120 mg tablet)
Route of administration:	Oral
Duration of treatment:	Single dose on 2 occasions (2-way cross-over design)
Reference Drug:	Not Applicable.
Indication:	Chagas' disease
Diagnosis and main criteria for inclusion:	Adult male and female subjects diagnosed with chronic Chagas' disease, aged 18 to 45 years, inclusive
Study design:	Open-label, randomized, single-dose, cross-over design, 2 groups
Methodology	Following satisfactory screening and pre-dose assessments, eligible subjects were enrolled to either Group 1 or Group 2. The study included 2 treatment periods for each subject. In each group, the subjects were randomized to one of 2 treatment sequences: AB or BA for Group 1 and AC or CA for Group 2. The single-dose treatments were as follows **Group 1:** Treatment A: 4 x 30 mg nifurtimox tablets Treatment B: 4 x 30 mg nifurtimox tablets disintegrated in tap water to form an aqueous slurry **Group 2:** Treatment A: 4 x 30 mg nifurtimox tablets Treatment C: 1 x 120 mg nifurtimox tablet The subjects remained at the study center until 24 hours after dosing. There was a washout period of ≥ 5 days and up to 10 days between dosing in both groups. All study drugs were administered under fed conditions (high fat, high calorie). A follow-up visit was conducted 7 to 14 days after the last study drug administration. Safety assessments were performed, and blood and urine samples were collected, at predefined time points relative to dosing. After the end of the study, the subjects were offered a treatment course with nifurtimox, if medically indicated.

Study center:	1 Center in Argentina	
Publication(s) based on the study (references):	None at the time of report creation.	
Study period:	First subject, first visit:	18 NOV 2013
	Last subject, last visit:	27 MAY 2014
	End of study	17 SEP 2014
Early termination	Not Applicable.	
Number of subjects:	Planned:	N = 36 (N = 12 in Group 1; N = 24 in Group 2)
	Randomized:	N = 37 (N = 13 in Group 1; N = 24 in Group 2); 1 subject withdrew before receiving study drug
	Analyzed:	N = 36 (N = 12 in Group 1; N = 24 in Group 2) More details are given in the section on study subjects below.
Criteria for evaluation Pharmacokinetics:	The primary PK variables were area under the concentration versus time curve from time 0 to the time of last measurable concentration ($AUC(0\text{-}t_{last})$) and maximum observed concentration (C_{max}) of nifurtimox. Secondary PK parameters were area under the concentration versus time curve from time 0 to infinity (AUC), C_{max} normalized to dose and body weight ($C_{max,norm}$), AUC normalized to dose and body weight (AUC_{norm}), area under the concentration versus time curve from time 0 to 48 hours post-dose (AUC(0-48)), time to reach C_{max} (t_{max}), half-life associated with the terminal slope ($t_{1/2}$), mean residence time (MRT), apparent total body clearance (CL/f), apparent volume of distribution during the terminal phase (V_z/F), amount excreted into urine from time 0 to infinity ($A_{E,ur}$), and renal body clearance (CLR), if applicable. (Urine data were not analyzed at the time of this report; see PK Evaluation section.)	
Safety:	Safety and tolerability assessments were adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms (ECGs), and physical examinations.	
Other:	Continuous 24-hour urine collections were performed for the determination of urine volume, creatinine concentration, and creatinine clearance (calculated using the Cockcroft-Gault equation). (Urine data were not analyzed at the time of this report; see PK Evaluation section.)	

Statistical methods:	All data were listed and summary tables were provided. The primary statistical analysis was the investigation of bioequivalence of the 2 tablet formulations administered in Group 2 (1 x 120 mg versus 4 x 30 mg tablets). The PK characteristics AUC(0-t_{last}) and C_{max} of nifurtimox were analyzed assuming log-normally distributed data. The logarithms of these characteristics were analyzed using an analysis of variance (ANOVA) including sequence, subject (sequence), period, and treatment effects. Based on these analyses, point estimates (least squares-means [LS-means]) and 90% confidence intervals (CIs) for the ratio "4 x 30 mg tablets/120 mg tablet" of nifurtimox AUC(0-t_{last}) and C_{max} were calculated by re-transformation of the logarithmic data using the intra-individual standard deviation (SD) of the ANOVA. Bioequivalence was assumed if all of the above 90% CIs fell in the acceptance interval of [0.8; 1.25]. A similar ANOVA was performed for the evaluation of nifurtimox tablets administered as whole tablets and as aqueous slurry (Group 1). Descriptive summary statistics were produced for safety data. The incidence of treatment-emergent adverse events (TEAEs) and drug-related AEs, respectively, was summarized by treatment using MedDRA terms, version 17.0.
Substantial protocol changes:	The study was conducted according to final Study Protocol from date 18 APR 2013, and included no substantial amendments.

Study subjects

A total of 39 subjects were enrolled (signed informed consent) and screened. Of these, 2 subjects were screen failures, and 37 subjects were randomized (13 subjects in Group 1, and 24 subjects in Group 2). However, 1 subject (Group 1) did not receive any study drug, because she decided to withdraw from the study. All of the 36 subjects who received study drug completed the study and the end-of-study follow-up, and all were included in the safety and PK analysis sets (12 subjects in Group 1, and 24 subjects in Group 2).

The overall mean age in Group 1 and Group 2 was 33.8 years and 32.4 years, respectively, and the overall mean BMI was 26.1 kg/m^2 and 24.4 kg/m^2, respectively. All 12 subjects in Group 1 were female, and 16 of the 24 subjects (66.7%) in Group 2 were female. All of the 36 subjects in both groups were white. The sequence groups within each group were well balanced.

Pharmacokinetic evaluation

Table 2-1 and Table 2-2 summarize the main PK parameters of nifurtimox as geometric means and %CV (with range) for Group 1 and Group 2, respectively. Table 2-3 and Table 2-4 provide the LS-means and two-sided 90% CIs for the primary PK parameters (AUC(0-t_{last}) and C_{max}) resulting from the ANOVA models for Group 1 and Group 2, respectively.

In Group 1, as an aqueous slurry, nifurtimox showed a comparable AUC(0-t_{last}) of 93% compared to the corresponding tablet formulation. The C_{max} data showed that the maximum nifurtimox plasma concentration was reduced by approximately 24% when administered as an aqueous slurry compared to the tablets. There was low variability in both PK parameters (geometric CV = 14%). There was no evidence for a relevant difference between both formulations.

In Group 2, the 120 mg tablet and 4 x 30 mg tablets were compared in order to evaluate whether bioequivalence could be demonstrated between the two treatments. Bioequivalence was tested for the ratio of "4 x 30 mg tablets / 120 mg tablet" of nifurtimox. For both parameters, bioequivalence was demonstrated with respect to the point estimates because they were within the predefined equivalence range of 80% to 125% for the 90% CIs.

Table 2-1: Pharmacokinetic parameters of nifurtimox in plasma in Group 1 (geometric mean / %CV [range]; PK analysis set, N = 12)

Parameter	Unit	Treatment A: 4 × 30 mg tablets (N = 12)			Treatment B: 4 × 30 mg aqueous slurry (N = 12)		
AUC	µg*h/L	2790 /	18.8	(2230 – 3970)	2630 /	21.8	(1750 – 3370)
AUC(0-t_{last})	µg*h/L	2670 /	19.2	(2090 – 3860)	2490 /	23.5	(1480 – 3120)
AUC(0-48)	µg*h/L	2790 /	18.8	(2230 – 3970)	2620 /	22.3	(1700 – 3370)
AUC_{norm}	µg*h/L	1490 /	15.3	(1220 – 1950)	1410 /	22.9	(887 – 2100)
C_{max}	µg/L	568 /	26.4	(380 – 900)	434 /	31.2	(200 – 596)
$C_{max,norm}$	kg/L	304 /	18.8	(239 – 417)	233 /	26.8	(126 – 329)
t_{max}[a]	hours	4.00		(2.00 – 6.00)	4.00		(2.00 – 8.00)
$t_{1/2}$	hours	3.30 /	11.6	(2.57 – 4.25)	3.61 /	37.3	(2.64 – 9.67)
CL/F	L/h	43.0 /	18.8	(30.2 – 53.8)	45.6 /	21.8	(35.6 – 68.7)
MRT	hours	6.17 /	14.2	(4.77 – 7.47)	6.82 /	20.6	(5.58 – 12.6)
V_Z/F	L	205 /	26.2	(112 – 274)	237 /	49.3	(168 – 959)

a Median (range).

Table 2-2: Pharmacokinetic parameters of nifurtimox in plasma in Group 2 (geometric mean / %CV [range]; PK analysis set, N = 24)

Parameter	Unit	Treatment A: 4 × 30 mg tablets (N = 24)	Treatment C: 1 × 120 mg tablet (N = 24)
AUC	µg*h/L	2670 / 25.8 (1620 – 4530)	2550 / 25.0 (1250 – 3960)
AUC(0-t_{last})	µg*h/L	2560 / 26.3 (1500 – 4440)	2450 / 25.6 (1170 – 3880)
AUC(0-48)	µg*h/L	2670 / 25.8 (1620 – 4530)	2550 / 25.0 (1250 – 3960)
AUC_{norm}	µg*h/L	1390 / 19.8 (819 – 1900)	1330 / 17.7 (989 – 1900)
C_{max}	µg/L	518 / 40.2 (178 – 828)	509 / 37.9 (200 – 874)
$C_{max,norm}$	kg/L	270 / 37.7 (122 – 506)	266 / 37.0 (116 – 524)
t_{max}[a]	hours	4.00 (2.00 – 6.00)	4.00 (2.00 – 6.00)
$t_{1/2}$	hours	2.63 / 23.1 (1.37 – 3.63)	2.85 / 30.2 (1.26 – 4.55)
CL/F	L/h	45.0 / 25.8 (26.5 – 73.9)	47.0 / 25.0 (30.3 – 96.0)
MRT	hours	6.65 / 16.4 (4.45 – 8.80)	6.43 / 17.8 (4.41 – 8.89)
V_Z/F	L	171 / 31.7 (104 – 302)	193 / 38.4 (85.6 – 484)

a Median (range).

Table 2-3: Point estimates (LS-means) and two-sided 90% CIs of selected PK parameters of nifurtimox in Group 1 (PK analysis set, N = 12)

Ratio	Parameter	Unit	N	Geometric %CV	Geometric LS-Mean Estimated Ratio (%)	90% CI (%)
4 x 30 mg aqueous slurry / 4 x 30 mg tablets	AUC(0-t_{last})	µg*h/L	12	13.75	93.19	[84.22 ; 103.13]
	C_{max}	µg/L	12	14.44	76.48	[68.77 ; 85.05]

Table 2-4: Point estimates (LS-means) and two-sided 90% CIs of selected PK parameters of nifurtimox in Group 2 (PK analysis set, N = 24)

Ratio	Parameter	Unit	N	Geometric %CV	Geometric LS-Mean Estimated Ratio (%)	90% CI (%)
4 x 30 mg tablets / 1 x 120 mg tablet	AUC(0-t_{last})	µg*h/L	24	11.19	104.73	[99.09 ; 110.68]
	C_{max}	µg/L	24	26.36	101.67	[89.41 ; 115.60]

No PK urine parameters are presented in this report; urine concentration data were not available because the validation work for the assay had not been completed at the time of this report. Therefore, the secondary objective relating to these data could not be addressed.

Safety evaluation

Exposure: In Group 1, 12 subjects received a single dose of 120 mg nifurtimox in 4 x 30 mg tablets and a single dose of 120 mg nifurtimox in an aqueous slurry. In Group 2, 24 subjects

received a single dose of 120 mg nifurtimox in 4 x 30 mg tablets and a single dose of 120 mg nifurtimox in a 120 mg tablet.

Adverse events (AEs): In Group 1, of the 12 treated subjects, 8 (66.7%) subjects reported at least 1 TEAE: 7 (58.3%) subjects following Treatment A (4 x 30 mg tablets) and 4 (33.3%) subjects following Treatment B (aqueous slurry). All TEAEs were considered by the investigator to be related to the study drug. The maximum intensity of the TEAEs was mild for 4 (33.3%) subjects and moderate for 4 (33.3%) subjects, overall. The most commonly reported TEAE, overall, was vomiting (reported by 6 [50.0%] subjects), followed by headache (5 [41.7%] subjects) and nausea (2 [16.7%] subjects). There were no notable differences between the two treatments.

In Group 2, of the 24 treated subjects, 9 (37.5%) subjects reported at least 1 TEAE: 5 (20.8%) subjects following Treatment A (4 x 30 mg tablets) and 5 (20.8%) subjects following Treatment C (1 x 120 mg tablet). All TEAEs were considered by the investigator to be related to the study drug. The maximum intensity of the TEAEs was mild for 7 (29.2%) subjects and moderate for 2 (8.3%) subjects, overall. The most commonly reported TEAEs, overall, were nausea and headache (reported by 4 [16.7%] subjects each), followed by abdominal pain (2 [8.3%] subjects) and vomiting (1 [4.2%] subject). There were no notable differences between the two treatments.

No subjects in either group experienced an SAE or a TEAE leading to study drug discontinuation. All TEAEs resolved.

Other safety data: The clinical laboratory, vital signs, and ECG data showed no overt clinically relevant differences between the study drug treatments, in either Group 1 or Group 2.

Overall conclusions

- The new 30 mg nifurtimox oral tablet formulation was bioequivalent to the marketed 120 mg nifurtimox oral tablet, under fed conditions, in adult male and female subjects with chronic Chagas' disease ($AUC(0\text{-}t_{last})$: 2450 µg*h/L and 2560 µg*h/L, respectively; C_{max}: 509 µg/L and 518 µg/L, respectively).
- Systemic exposure of nifurtimox after ingestion as an aqueous slurry (4 x 30 mg tablets disintegrated in tap water) was comparable to that of the 4 x 30 mg tablets ($AUC(0\text{-}t_{last})$: 2490 µg*h/L and 2670 µg*h/L, respectively). Peak exposure was reduced by approximately 24% following dosing with the aqueous slurry (C_{max}: 434 µg/L and 568 µg/L, respectively). There was no relevant difference between the two formulations.
- A single oral dose of 120 mg nifurtimox, administered as 4 x 30 mg tablets, an aqueous slurry made from 4 x 30 mg tablets, or 1 x 120 mg tablet, was well tolerated, and there were no new safety or tolerability findings.
- In the absence of differences in clinically relevant safety findings, the PK data show that the 30 mg tablet is a viable formulation for administration of nifurtimox in children.