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Study No: ARI10016
Title: A Double-Blind, Randomized, Placebo-Controlled Study to Determine the Effect of GI198645 (dutasteride) Dose for 21 Days on the Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Male Volunteers.
Rationale: Patients with benign prostatic hyperplasia (BPH) may receive other concomitant medications such as warfarin (War). Because both War and dutasteride (Dut) are both highly bound to plasma proteins (approximately 99% each), there was a potential for alteration of unbound War concentrations when these medications were co-administered. Due to the narrow therapeutic window of War, and the lack of formal pharmacokinetic and pharmacodynamic information from Phase III subjects, this clinical study was conducted to substantiate the lack of interaction observed in in vitro studies.
Phase: I
Study Period: 12 Feb 1999 – 09 Apr 1999
Study Design: Open-label warfarin treatment lead-in phase followed by a randomized, double-blind, placebo-controlled, parallel group phase.
Centres: 1 center in the US
Indication: None
Treatment: During the lead-in phase, all subjects received War 5 mg daily on Days 1–3, followed by titration of the daily War dose on Days 4–10 to achieve and maintain a stable International Normalized Ratio (INR) of 1.5–2.0, followed by a fixed daily dose of War (determined from the previous titration period) on Days 11–14. Following completion of the lead-in phase, subjects received, in addition to the fixed dose of War, a single loading dose of 25 mg Dut on Day 15, followed by daily doses of 0.5 mg Dut on Days 16–35, or a single loading dose of 25 mg matching Dut placebo (Pbo) on Day 15, followed by daily doses of 0.5 mg matching Pbo on Days 16–35.
Statistical Methods: PT values measured on day 15 (prior to warfarin dosing), and on day 35 (prior to warfarin dosing) were used to assess drug interaction effects. PT values (untransformed) on day 35 were compared between treatments (warfarin + GI198745/Dut versus warfarin + placebo) using an analysis of covariance (ANCOVA) model, taking into account variation due to treatment effects, and using the PT value obtained on day 15 (i.e. baseline) as the covariate. The least squares mean (LSMean) was calculated for each treatment. To compare the treatment groups, the difference in LSMeans and the associated 90% confidence interval (CI) were expressed as a proportion of the reference treatment LSMean. Warfarin and placebo was considered the reference treatment. The absence of significant pharmacodynamic drug interaction was concluded if this 90% CI fell within the 80%-120% interval.
Log transformed pharmacokinetic parameters (except tmax) for each warfarin enantiomer on day 35 were compared between treatments using an ANCOVA model where the parameter estimate obtained on day 14 (baseline) was used as the covariate). The geometric LSMean was calculated for each parameter for each treatment. To compare the treatment groups, the 90% CI for the difference in the LSMean between the test and the reference treatment was computed for each parameter. If the 90% CI for AUC24 fell between 80% and 125%, and the 90% CI for Cmax and Cmin fell between 70% and 144% then equivalence, no interaction, was assumed.
Objectives: The primary objective was to evaluate the effect of multiple doses of Dut Soft Gelatin Capsules on the pharmacodynamics (i.e., prothrombin time (PT) values) of War in

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healthy male volunteers. The secondary objective was to evaluate the effect of multiple doses of Dut Soft Gelatin Capsules on the steady-state pharmacokinetics of War.				
Study Population: Healthy male volunteers aged 21 to 55 years inclusive, weighing at least 55 kg with a body mass index between 19 and 29 kg/m ² inclusive.				
Number of Subjects:	War + Dut		War + Pbo	
Planned N	12		12	
Dosed N	11		12	
Completed n (%)	11 (100)		12 (100)	
Total Number Subjects Withdrawn N (%)	0		0	
Withdrawn due to Adverse Events n (%)	0		0	
Withdrawn due to Lack of Efficacy n (%)	0		0	
Withdrawn for Other Reasons n (%)	0		0	
Demographics	War + Dut		War + Pbo	
N (ITT)	12		12	
Females: Males	0:12		0:12	
Mean Age in Years (sd)	37 (11)		35 (10)	
Mean Weight in Kg (sd)	86.5 (10.2)		78.7 (12.4)	
White n (%)	10 (83)		10 (83)	
Pharmacokinetic (PK) Results:				
R-Warfarin PK parameters	War + Dut		War + Pbo	
	Day 14 (n=11)	Day 35 (n=11)	Day 14 (n=12)	Day 35 (n=12)
Dose-normalized (1 mg dose -DN) AUC ₂₄ (ng.h/mL), mean (SD)	2415 (642)	2272 (670)	3075 (670)	2837 (571)
DN-C _{max} (ng/mL), mean (SD)	140 (28)	147 (38)	175 (27)	164 (26)
DN-C _{min} (ng/mL), mean (SD)	79.0 (25.3)	77.9 (27.4)	102 (23.9)	93.4 (20.5)
t _{max} (h), median (min-max)	1.00 (0.5–3.0)	0.50 (0.5–1.5)	0.50 (0.5–1.5)	1.00 (0.5–12.0)
CL _{po} /F (L/h), mean (SD)	0.436 (0.089)	0.467 (0.101)	0.340 (0.074)	0.370 (0.099)
Treatment comparisons	War + Dut		War + Pbo	
DN-AUC ₂₄ (ng.h/mL)				

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Geometric least squares (LS) mean	2476		2490	
Treatment comparison	0.99			
90% CI	(0.89, 1.10)			
DN-Cmax (ng/mL)				
Geometric LS mean	160		147	
Treatment comparison	1.09			
90% CI	(0.97, 1.22)			
DN-Cmin (ng/mL)				
Geometric LS mean	84.8		80.6	
Treatment comparison	1.05			
90% CI	(0.93, 1.18)			
tmax (h)				
Geometric LS mean	0.50		1.00	
Treatment comparison (Hodges-Lehmann estimate of median difference)	0.50			
90% CI	(0–0.50)			
S-Warfarin PK parameters	War + Dut		War + Pbo	
	Day 14 (n=11)	Day 35 (n=11)	Day 14 (n=12)	Day 35 (n=12)
DN-AUC24 (ng.h/mL), mean (SD)	1852 (697)	1831 (735)	1910 (588)	1797 (479)
DN-Cmax (ng/mL), mean (SD)	117 (34)	128 (34)	126 (22)	120 (24)
DN-Cmin (ng/mL), mean (SD)	56.6 (23.7)	60.5 (32.2)	58.2 (21.6)	53.2 (18.3)
tmax (h), median (min–max)	1.00 (0.5–2.0)	0.50 (0.5–1.5)	0.50 (0.5–1.5)	1.00 (0.5–1.5)

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CLpo/F (L/h), mean (SD)	0.601 (0.186)	0.615 (0.205)	0.578 (0.205)	0.601 (0.188)
Treatment comparisons	War + Dut		War + Pbo	
DN-AUC24 (ng.h/mL)				
Geometric LS mean	1752		1703	
Treatment comparison	1.03			
90% CI	(0.94, 1.12)			
DN-Cmax (ng/mL)				
Geometric LS mean	129		113	
Treatment comparison	1.14			
90% CI	(1.04, 1.26)			
DN-Cmin (ng/mL)				
Geometric LS mean	54.7		49.3	
Treatment comparison	1.11			
90% CI	(1.01, 1.22)			
tmax (h)				
Geometric LS mean	0.50		1.00	
Treatment comparison (Hodges- Lehmann estimate of median difference)	0			
90% CI	(0-0.50)			
Pharmacodynamic (PD) Results:				
	War + Dut		War + Pbo	
War PD Parameters	Day 14 (n=11)	Day 35 (n=11)	Day 14 (n=12)	Day 35 (n=12)
PT (sec), mean (SD)	16.7 (1.6)	15.6 (1.7)	16.8 (1.1)	14.8 (0.8)
INR, mean (SD)	1.6 (0.3)	1.4 (0.3)	1.6 (0.2)	1.2 (0.1)
Treatment comparison	War + Dut		War + Pbo	
PT (sec)				
Geometric LS	15.6		14.8	

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mean		
Treatment comparison	1.06	
90% CI	(1.01, 1.10)	
Safety Results:		
Most Frequent Adverse Events (AEs) Affecting >1 Subject/Group - On Treatment Post-Randomization	War + Dut (n=11)	War + Pbo (n=12)
Subjects with AEs, n (%)	6 (55)	6 (50)
Nasal signs & symptoms	3 (27)	1 (8)
Throat & tonsil discomfort & pain	0	2 (17)
Headaches	2 (18)	1 (8)
Serious Adverse Events (SAEs) - On Treatment n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]		
	War + Dut (n=11)	War + Pbo (n=12)
Subjects with Non-fatal SAEs, n (%)	0	0
Subjects with Fatal SAEs, n (%)	0	0

Date Updated: 21-Dec-2004

Publications:

No Publications