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Study No: ARI10017
Title : A study to investigate the effect of GI198745 (dutasteride) on the pharmacokinetics of digoxin in healthy male volunteers.
Rationale: Dutasteride (dut) is a potent dual inhibitor of 5 alpha-reductase enzymes type 1 and 2 and is currently in Phase III clinical trials for the treatment of benign prostatic hyperplasia (BPH). Patients being treated for BPH may also receive digoxin for the treatment of congestive heart failure and atrial arrhythmias. Digoxin is primarily excreted unchanged in the urine, while dut is primarily excreted unchanged in the feces; a metabolic interaction is not anticipated. However, due to the lack of pre-clinical interaction data and the narrow therapeutic window of digoxin (0.5–2.0ng/mL), this interaction study was conducted to determine whether there was a clinically meaningful interaction of dut with digoxin, in healthy volunteers.
Phase: I
Study Period: 12 February 1999 - 18 June 1999
Study Design: This drug interaction study consisted of an open label digoxin treatment period followed by a randomized, double-blind, placebo-controlled, parallel-group treatment period.
Centres: One in the US
Indication: None
Treatment: Each subject received a daily dose of 0.25mg digoxin on Days 1–35. On Day 15, subjects received their randomized treatment of either a 25mg loading dose of dut Soft Gelatin Capsules or matching placebo, followed by daily doses of 0.5mg dut Soft Gelatin Capsules or matching placebo for Days 16–35. This was given concurrently with the daily dose of 0.25mg digoxin.
Objectives: The objective of this study was to evaluate the effects of daily dosing of dut Soft Gelatin Capsules on the steady-state pharmacokinetics of digoxin.
Statistical Methods: Sample size was determined by assuming an inter-subject standard deviation of 0.24 for log-transformed digoxin AUC and Cmax results. From this inter-subject deviation, it was concluded that 18 subjects (9 per treatment group on Day 35) would provide a greater than 80% power to assess equivalence (70-143%) for each parameter. This is based on the assumption that a 30% change in digoxin levels would be clinically significant. A total of 24 subjects were enrolled into the study on Day 1 to accommodate for dropouts. Analysis of covariance was used to compare digoxin pharmacokinetics on Day 35 between treatment groups (Dut/Digoxin and Pbo/Digoxin) using baseline (Day 14) pharmacokinetic values as a covariate. Parameters were log-transformed prior to analysis. Treatment ratios were estimated by exponentiating the difference in least squares means and the corresponding 90% confidence interval (CI). Equivalence within the clinically relevant range (difference of < 30%) was concluded if the 90% CI fell within 0.70 and 1.43 for AUC ₂₄ , Cmax and CLr ratios. Concentrations of Dut on Days 15, 16, 27, 30, 33, 35, 45, 95, 125, and 155 and digoxin results on Days 14 and 35 were listed in a descriptive statistical summary. The safety analysis population consisted of all volunteers who consented to the study and remained in the study beyond the baseline recordings. The pharmacokinetic population studied included all volunteers who completed the dosage regimen and procedures through the serial blood collection on Days 14 – 15 or Days 35 – 36.
Study Population: Healthy, non-smoking males between 18 and 50 years of age with a body mass index of 19 to 29 kg/m ² , weighing at least 55 kg and having an estimated creatinine clearance of >60 mL/min.

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Number of Subjects:				
Planned N	24			
Dosed N	24			
Completed n (%)	20 (83.3)			
Total Number Subjects Withdrawn n (%)	4 (16.7)			
Withdrawn due to Adverse Events n (%)	0			
Withdrawn due to Lack of Efficacy n (%)	0			
Withdrawn for Other Reasons n (%)	0			
Demographics	Placebo/Digoxin (n=12)		Dut/Digoxin (n=12)	
N (ITT)	12		12	
Females: Males	0 : 12		0 : 12	
Mean Age in Years (sd)	28 (8)		33 (11)	
Mean Weight in Kg (sd)	79.2 (9.5)		76.2 (10.2)	
White n (%)	8 (67%)		11 (92%)	
Pharmacokinetics (PK) Endpoints:				
Parameter	Day 14		Day 35	
	Placebo/Digoxin (n=11)	Dut/Digoxin (n=9)	Placebo/Digoxin (n=11)	Dut/Digoxin (n=9)
AUC ₀₋₂₄ (ng.h/mL) Mean (SD)	17.04 (3.59)	17.58 (2.53)	15.67 (4.18)	16.97 (5.74)
C _{max} (ng/mL) Mean (SD)	1.77 (0.40)	1.78(0.30)	1.65 (0.30)	1.78 (0.47)
C _{min} (ng/mL) Mean (SD)	0.48 (0.12)	0.53 (0.09)	0.44 (0.16)	0.43 (0.20)
t _{max} (h) Mean (Range)	1.00 (1.0-1.5)	1.00 (0.5-1.5)	1.00 (0.5-2.0)	1.00 (1.0-1.5)
CL _r (mL/min) Mean (SD)	121.93 (27.30)	137.80 (36.69)	114.68 (38.49)	110.46(21.46)
CL _{po/F} (mL/min) Mean (SD)	254.29 (51.90)	241.81 (38.18)	286.19 (87.59)	288.00 (161.04)
Safety results:				
Adverse Events (AE):	Pre- randomization Placebo/ Digoxin	Pre- randomization Dut/ Digoxin	Post- randomization Placebo/ Digoxin	Post- randomization Dut/ Digoxin
N (ITT)	12	12	12	12
No. subjects with AEs n (%)	4 (33)	7 (58)	6 (50)	7 (58)
Most Frequent Adverse Events Affecting >1				

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Subject/Group				
Headaches	1 (8)	3 (25)	1 (8)	3 (25)
Viral ear, nose, and throat infections	0	3 (25)	2 (17)	1 (8)
Throat and tonsil discomfort & pain	0	2 (17)	1 (8)	2 (17)
Nasal signs and symptoms	1 (8)	0	0	2 (17)
Nausea and vomiting	0	0	1 (8)	2 (17)
Serious Adverse Events: There were no serious adverse events reported during this study				

Date Updated: 21-Dec-2004

Publications:

No Publications