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Study No: ARI10019
Title: A Double-Blind, Placebo Controlled, Randomized, Parallel Group Study To Investigate The Changes In The Corrected QT Interval Following Repeat Oral Doses Of GI198745 (dutasteride) In Healthy Male Volunteers.
Rationale: QT interval prolongation has been associated with a specific, potentially fatal polymorphic ventricular tachycardia termed torsade de pointes (TdP). In light of the unavailability of in vitro cardiac electrophysiology data, and limited clinical data from studies that were not designed to specifically to monitor QT intervals, it was deemed important to investigate the effect of repeat doses of dutasteride(Dut) on the QTc interval in healthy male volunteers.
Phase: I
Study Period: This study was initiated on 02 October 2000 and completed on 18 December 2001.
Study Design: This was a randomized, double-blind, repeat-dose, parallel group, placebo controlled, multicenter study.
Centres: Three in the US
Indication: None
Treatment: Subjects received placebo on Day -1 (baseline) and were randomized to one of the three following oral daily treatments: 0.5 mg Dut for 28 days (25 mg loading dose on Day 1), 5 mg Dut for 28 days (40 mg loading dose on Days 1-7), or placebo for 28 days.
Objectives: The primary objective of this study was to determine the effect of 0.5 mg and 5 mg doses of Dut administered daily for 28 days on the corrected QT (QTc) interval in healthy males. The secondary objectives were to assess the effect of 0.5 mg and 5 mg doses of Dut on serum dihydrotestosterone (DHT), testosterone (T) (free and total), and sex hormone binding globulin (SHBG) and to further investigate the safety and tolerability of Dut.
Statistical Methods: Sample Size Calculation. The purpose of the study was to determine whether there was strong evidence to suggest that dutasteride prolonged corrected QT interval. The following sample sizes were based on a one-sided significance level of 0.05. From previous GSK studies, a reasonable estimate of the standard deviation of the weighted mean for QTcF (corrected QT interval by Fridericia's formulae) is 12 msec. A sample size of 19 subjects in each dose group would provide 80% power to detect an increase of 10 msec in weighted mean of QTcF when dutasteride was compared to placebo. Therefore, a total of at least 90 subjects (30 per group) were to participate in the study to ensure meaningful interpretation of the results in case subjects prematurely discontinued.
ECG analysis. All ECG parameters including the corrected QT intervals were listed for each subject and summarized by dose group and assessment time. QTc were calculated by both Fridericia's and Bazett's formulae. Although the primary endpoint is based on Fridericia's formula, all of the analyses below were performed for both corrected intervals (QTcF and QTcB). The derived endpoints weighted mean QTc 0-12 hour and maximum QTc 0-12 hour were calculated for each subject for Day -1 (Baseline, placebo treatment), Day 1, and Day 28. The primary analysis compared Day 28 weighted mean QTcF interval between the dutasteride and placebo dose groups. This was performed using analysis of covariance (ANCOVA), including terms for dose group and site, with baseline (Day -1) weighted mean QTcF as the covariate. Estimates of the treatment effect were based on the difference between the least square means (SAS LSmeans) of the dutasteride dose group (test) compared to the placebo dose group

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(reference). This ANCOVA analysis was repeated for Day 28 weighted mean QTcB, maximum QTcF and maximum QTcB. Similarly, this analysis was also performed for Day 1 corrected QT intervals.

The safety population was intent-to-treat (ITT) population that included all subjects who received at least one dose of randomized study medication. This population was used for summarizing baseline characteristics, demographic, ECG, and safety information.

Study Population: Non-smoking, healthy male volunteers, between 18 and 60 years of age (inclusive), BMI between 19 and 29 kg/m<sup>2</sup> (inclusive). ECG QTc interval at screening was to be equal to or less than 450 msec and heart rate was to be greater than or equal to 50 bpm. Any subject with a screening ECG that was considered unsuitable for QT analysis (e.g., bundle branch block, invalid T wave vector, marked sinus arrhythmia) was not included in the study.

Number of Subjects:			
Planned N	90		
Dosed N	97		
Completed n (%)	89 (92)		
Total Number Subjects Withdrawn n (%)	2 (2)		
Withdrawn due to Adverse Events n (%)	2		
Withdrawn due to Lack of Efficacy n (%)	0		
Withdrawn for Other Reasons n (%)	0		
Demographics	Placebo	Dut 0.5 mg	Dut 5 mg
N (ITT)	34	31	32
Females: Males	0:34	0:31	0:32
Mean Age in Years (sd)	37.4 (11.1)	31.6 (9.4)	39.5 (12.6)
Mean BMI in kg/m <sup>2</sup> (sd)	25.74 (2.54)	25.01 (2.48)	25.64 (2.72)
White n (%)	12 (35)	9 (29)	9 (28)
Pharmacodynamics (PD) Endpoints:			
Serum DHT concentration	Mean serum DHT levels fell by >91% with the Dut 0.5 mg dose and >93% with the Dut 5 mg dose beginning with the first sample analyzed, Day 7, and was similar for the Day 14, 21, and 28 samples. Individual values showed some variation with minimal suppression still >78% from Day 14 onward. CV for the percent change was <4% after the second week of therapy for both doses. In the 0.5mg dose group, levels were returning to baseline during the follow-up period with a mean percent suppression of		

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	52% by Month 2 follow-up.
Serum Testosterone concentration	<p>Mean baseline serum total testosterone concentrations were lower in the placebo group compared to the Dut 0.5mg and 5mg dose groups. There was little change in the mean serum total testosterone levels of the placebo group (-0.4 to 7%). Increases in serum testosterone levels from baseline were observed in both the Dut 0.5mg (18 to 32%) and 5mg (14 to 27%) dose groups during the treatment period.</p> <p>Mean baseline serum free testosterone concentrations were lower in the placebo group compared to the Dut 0.5mg and 5mg dose groups. For the Dut 0.5mg dose group free testosterone ranged from 27 to 41% mean change from baseline during the treatment period. For the Dut 5mg dose group free testosterone ranged from 10 to 25% mean change from baseline during the treatment period.</p>

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Serum SHBG concentration	Mean baseline serum SHBG concentrations were lower in the placebo group compared to the Dut 0.5mg and 5mg dose groups. There was a slight decrease in serum SHBG levels mean percent change from baseline values in the placebo group (-2 to -9%). Increases in serum SHBG levels mean percent change from baseline values were observed in both the Dut 0.5mg (0 to 13%) and Dut 5mg (0 to 6%) dose groups during the treatment period.			
Safety results:				
Treatment comparison of least square means of weighted mean QTcF and QTcB intervals on Days 1 and 28 (ITT population)				
Weighted mean QTc interval	Dut treatment	Day	Treatment difference (ms) (90% CI)	
QTcF	0.5 mg	1	-0.07 (-2.36, 2.22)	
	5 mg		-0.75 (-3.01, 1.51)	
	0.5 mg	28	1.36 (-2.12, 4.84)	
	5 mg		0.02 (-3.31, 3.34)	
QTcB	0.5 mg	1	-1.30 (-3.99, 1.39)	
	5 mg		-1.35 (-4.01, 1.31)	
	0.5 mg	28	2.60 (-1.32, 6.53)	
	5 mg		-0.55 (-4.29, 3.18)	
Treatment comparison of least square means of maximum QTcF and QTcB intervals on Days 1 and 28 (ITT population)				
Maximum QTc interval	Dut treatment	Day	Treatment difference (ms) (90% CI)	
QTcF	0.5 mg	1	3.75 (0.41, 7.08)	
	5 mg		1.42 (-1.85, 4.70)	
	0.5 mg	28	0.43 (-4.25, 5.12)	
	5 mg		-1.99 (-6.44, 2.46)	
QTcB	0.5 mg	1	2.95 (-1.40, 7.29)	
	5 mg		0.64 (-3.64, 4.92)	
	0.5 mg	28	-1.89 (-7.99, 4.21)	
	5 mg		-5.03 (-10.79, 0.72)	
Frequency of categorical maximum changes in QTcF (Number and % subjects) (ITT population)				
Day	Treatment	0-30 ms (%)	30-60 ms (%)	>60 ms (%)
1	Placebo	32 (94)	0 (0)	0 (0)
	Dut 0.5 mg	31 (100)	0 (0)	0 (0)
	Dut 5 mg	29 (91)	1 (3)	0 (0)
28	Placebo	30 (91)	3 (9)	0 (0)
	Dut 0.5 mg	24 (89)	1 (4)	0 (0)
	Dut 5 mg	24 (77)	6 (19)	0 (0)
Frequency of categorical maximum changes in QTcB (Number and % subjects) (ITT population)				
Day	Treatment	0-30 ms (%)	30-60 ms (%)	>60 ms (%)
1	Placebo	32 (94)	2 (6)	0 (0)
	Dut 0.5 mg	30 (97)	1 (3)	0 (0)

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	Dut 5 mg	24 (75)	8 (25)	0 (0)
28	Placebo	23 (70)	10 (30)	0 (0)
	Dut 0.5 mg	22 (81)	4 (15)	1 (4)
	Dut 5 mg	26 (84)	5 (16)	0 (0)
Adverse Events:	Placebo	Dut 0.5 mg	Dut 5 mg	
N (ITT)	34	31	32	
No. subjects with AEs n (%)	16 (47)	18 (58)	16 (50)	
Most Frequent AEs n (%) in any dose group				
Headache	4 (12)	4 (13)	2 (6)	
Viral ear, nose & throat (ENT) infections	2 (6)	1 (3)	3 (9)	
Malaise & fatigue	2 (6)	1 (3)	1 (3)	
ENT infections	0 (0)	2 (6)	2 (6)	
Gastrointestinal signs & symptoms	1 (3)	1 (3)	1 (3)	
Throat & tonsil discomfort & pain	0 (0)	2 (6)	0 (0)	
Chest symptoms	0 (0)	0 (0)	2 (6)	
Upper respiratory inflammation	0 (0)	0 (0)	2 (6)	
Serious Adverse Events: No SAEs occurred during the 28-day treatment phase of the study				

Date Updated: 21-Dec-2004

Publications:

No Publications