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<b>Study No:</b> ARIA1001		
<b>Title:</b> An Investigation of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of GI198745 (dutasteride), an Inhibitor of the 5-Alpha Reductase Enzyme, In Healthy Adult Males		
<b>Rationale:</b> Dutasteride (Dut) is a new chemical entity, not previously administered to humans. This study was conducted to provide critical information regarding the safety, tolerability, pharmacokinetics and pharmacodynamics of GI198745 in healthy adult male subjects, in order to provide the basis for subsequent decisions regarding the development of the compound.		
<b>Phase:</b> I		
<b>Study Period:</b> 31 October 1994 - 18 April 1995		
<b>Study Design:</b> This was a first-in-man, single-blind, active and placebo (Pbo) -controlled, randomised, parallel-group, escalating-dose study consisting of 2 parts: Part I: single escalating-dose evaluation of Dut, placebo, or finasteride (Fin) in healthy adult male subjects. Part II: based on results of Part I, evaluated a repeat dose (daily for 7 days) of Dut, placebo or finasteride. The highest Dut doses were expected to safely produce maximal lowering of serum dihydrotestosterone (DHT). The number of subjects per treatment group was expected to provide 80% power in detecting 60% differences in DHT concentrations (CV% = 30%) between Dut treatment and placebo groups. 12 Lead ECG measurements were performed at screening, pre-dose (Day 1), pre-dose (Day 7), 4 and 24 hours and 28 days post dosing (Day 7) in both parts of the study. Pre-dose (Day 1) has been used throughout as the baseline measure. The paper ECG recordings provided were recorded at 25 mm/sec and 10 mm/mv. The R-R and QT intervals were manually measured on up to three consecutive complexes of lead II as on the majority of ECGs this was the only lead recorded in rhythm format. If the QT was not measurable on lead II then the second choice lead was V2. The chosen lead was then used for all ECGs for the same subject. The preceding R-R interval for each of the respective measured QT intervals was used for the calculation of the corrected QT interval (QTcB and QTcF) for each individual complex. These values were then averaged to give the average QT, QTcB and QTcF.		
<b>Centres:</b> One in the UK		
<b>Indication:</b> None		
<b>Treatment:</b> Part 1: subjects were randomised to receive Dut, Pbo or finasteride (Fin). Eight separate treatment groups were studied: 1 subject from each group received placebo, one received Fin (5 mg) and 4 subjects received Dut (doses ranging from 0.01 mg to 40.0 mg). Safety data from each treatment group were reviewed before administration of study drug to the next treatment group. Based on the results of Part I, 2 parallel groups received a 1.0mg dose of Dut (expected to safely produce a 90% reduction in serum DHT concentrations), or a 20.0mg dose (expected to safely produce a maximal suppression in serum DHT concentrations) daily for 7 days. Within each group four subjects received Dut, two received finasteride and one received placebo.		
<b>Objectives:</b> The primary study objectives were to investigate: the safety and tolerability of Dut, effects of Dut on serum DHT, and the pharmacokinetic characteristics of Dut.		
<b>Statistical methods:</b> Pharmacodynamic analysis: The analysis of DHT and testosterone (T) focused on the change from baseline. Treatment groups were compared in terms of the change from baseline DHT and T serum concentrations in terms of logarithmically transformed data using general linear model. Pairwise comparisons of each treatment group with placebo and finasteride were performed using t-tests from the general linear model. The relationship between Dut dose and the effect of Dut on DHT concentrations was evaluated by fitting a sigmoidal E <sub>max</sub> model with a baseline effect to the maximum percent decrease from baseline in DHT observed with increasing dose. Pharmacokinetic analysis: Noncompartmental pharmacokinetic analysis of concentration time data was performed using standard techniques. AUC, C <sub>max</sub> , t <sub>max</sub> , and terminal elimination half-life were calculated. Linearity between AUC and C <sub>max</sub> and administered Dut dose was assessed. The parameters were analysed using analysis of variance (ANOVA) models, allowing for dose effects (Part I) and dose and day effects (Part II). Both ln-transformed and untransformed analyses were carried out. Descriptive statistics (median, range, mean, standard deviation, %CV, geometric mean, geometric least squares means, and 95% confidence intervals) of pharmacokinetic parameters and dose-normalized parameters were computed by dose (Part I) or by dose and study day (Part II). Analysis of t <sub>max</sub> was performed on untransformed data using the Kruskal-Wallis test. (Part I) and the Wilcoxon Rank Sum test (Part II). The analysis of the ECG data was exploratory only		
<b>Study Population:</b> Healthy male subjects aged between 20 and 65 years, weighing <120 kg and within +25% of ideal body weight for height and frame.		
<b>Number of Subjects</b>	<b>Part I</b>	<b>Part II</b>
Planned N	N/A	N/A
Dosed N	48	15
Completed n (%)	48 (100)	14 (93)

Withdrawn n (%)	0 (0)					1 (7)				
Withdrawn due to other reasons						1 (7)				
<b>Demographics</b>	<b>PART I</b>									
	<b>Pbo</b>	<b>Dut dose (mg)</b>								<b>Fin. 5mg</b>
		<b>0.01</b>	<b>0.1</b>	<b>1.0</b>	<b>2.5</b>	<b>5.0</b>	<b>10.0</b>	<b>20.0</b>	<b>40.0</b>	
N (ITT)	8	4	4	4	4	4	4	4	4	8
Females: Males	0:8	0:4	0:4	0:4	0:4	0:4	0:4	0:4	0:4	0:8
Mean Age in Years (sd)	34.9 (10.01)	49.8 (5.19)	47.5 (7.77)	42.0 (5.60)	40.3 (15.35)	23.8 (4.92)	37.8 (15.26)	32.3 (13.18)	40.8 (10.97)	32.9 (8.87)
Mean Weight in Kg (sd)	74.8 (9.22)	80.0 (18.26)	67.4 (8.55)	82.5 (3.48)	74.5 (4.72)	79.4 (8.66)	72.8 (5.91)	70.7 (11.41)	78.4 (7.61)	73.7 (11.57)
White n (%)	6 (75)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	8 (100)
	<b>PART II</b>									
N (ITT)	15									
Females: Males	0:15									
Mean Age in Years (sd)	27.3-34.3 [range: 21-47]									
White n (%)	14 (100)									

<b>Pharmacokinetic (PK) Endpoints:</b>						
<b>Non-compartmental PK parameters Median (Min-Max)</b>						
<b>PART I</b>						
<b>Dut dose (mg)</b>	<b>t<sub>max</sub> (hours)</b>	<b>C<sub>max</sub> Dose-normalized (ng/mL) per mg</b>	<b>AUC<sub>last</sub> Dose-normalized (ng.hr/mL) per mg</b>	<b>AUC<sub>∞</sub> Dose-normalized (ng.hr/mL) per mg</b>	<b>Half-life (days)</b>	
0.01	N/A	N/A	N/A	N/A	N/A	
0.1	1.0 (1.0-2.0)	4.9 (4.6-8.8)	26 (14-36)	39 (20-65)	0.3 (0.2-0.8)	
1.0	1.0 (1.0-3.0)	5.7 (4.3-6.0)	138 (131-297)	164 (138-308)	2.5 (1.5-3.1)	
2.5	2.0 (1.0-3.0)	5.0 (2.4-10.5)	369 (249-686)	393 (276-715)	4.3 (3.8-5.0)	
5.0	2.0 (1.0-4.0)	4.3 (3.2-7.4)	471 (365-669)	489 (371-706)	4.9 (3.4-5.5)	
10	2.0 (1.0-4.0)	6.0 (5.1-6.9)	1187 (645-1240)	1411 (734-1815)	10.8 (9.4-16.1)	
20	1.5 (1.0-2.0)	3.8 (2.6-5.1)	905 (779-1605)	992 (962-1888)	13.7 (8.0-21.1)	
40	1.0 (1.0-2.0)	4.2 (2.4-5.8)	635 (474-643)	681 (500-816)	8.6 (6.4-13.6)	
<b>PART II</b>						
<b>Dut dose (mg)</b>	<b>t<sub>max</sub> (hours)</b>	<b>C<sub>max</sub> Dose-normalized (ng/mL) per mg</b>	<b>Accumulation C<sub>max</sub> Day7/Day1</b>	<b>AUC<sub>(0-24)</sub> Dose-normalized (ng.hr/mL) per mg</b>	<b>Accumulation AUC Day7/Day1</b>	<b>Half-life (days)</b>
1.0, Day 1	2.0 (1.0-2.0)	6.4 (5.6-11.7)	N/A	71 (64-77)	N/A	N/A
1.0, Day 7	2.0 (1.0-2.0)	18.4 (15.8-19.2)	2.7 (1.5-3.4)	334 (308-368)	4.9 (4.0-5.4)	4.8 (3.4-8.6)
20.0, Day 1	2.0 (1.0-3.0)	6.5 (5.7-8.0)	N/A	78 (69-95)	N/A	N/A
20.0, Day 7	1.5 (0.5-6.0)	16.1 (13.9-18.0)	2.7 (1.8-2.7)	327 (292-370)	4.1 (3.9-4.5)	9.9 (6.9-25.7)
<b>Pharmacodynamic (PD) Endpoints:</b>						
PART I: Mean serum DHT decreased soon after dosing with Dut and reached a nadir within 48-72 hours of dosing. Dosing with Dut resulted in dose related decreases in serum DHT with a pronounced decrease at doses at or above 1mg. At doses of 5, 10, 20 and 40mg the maximum percent decrease from baseline in DHT concentrations averaged 86.7%, 88.7%, 92.4% and 94.7%, respectively. The duration of the effect on DuT increased with increasing dose. Following administration of doses <5mg Dut, DHT concentrations tended towards baseline within 4 weeks; following administration of doses ≥10mg DHT concentrations remained suppressed at 4 weeks, with a gradual return to baseline by 8-12 weeks postdose. Following administration of a single 5mg dose of Fin, DHT concentrations decreased to nadir levels at 12 hours after dosing and returned to baseline values within 2 weeks.						
PART II: Serum DHT decreased soon after dosing with Dut achieving an approximate 80% decrease from baseline within 8-48 hours after dosing. The duration of the effect on DHT increased with increasing dose. Following administration of 1mg Dut, DHT concentrations returned to baseline within 8 weeks; following administration of 20mg Dut, DHT concentrations remained suppressed up to 8 weeks following last administration. The duration of effect of Fin was shorter than the doses of Dut, based on comparisons with Pbo. Multiple dosing with Dut resulted in significant decreases in serum DHT at both doses (1mg and 20mg), with a maximum decrease at the 20mg dose. The maximum mean percent decrease from baseline in DHT was 90% and 97% following dosing with 1mg and 20mg, respectively.						
<b>ECG Endpoints Evaluated:</b> QT interval, weighted mean QT using Fridericia's correction (QTcF), weighted mean QT using Bazett's correction (QTcB), maximum QTcF and maximum QTcB, number and percent of subjects with change in QT, QTcF, QTcB from baseline which were <30 msec, 30 to 60msec, and >60msec.						

Part 1											
Actual values (ms): average of 3 measurements [Mean (SD)]											
	Assess-ment time	Pbo n=8	Dut dose (mg)								Fin n=8
			0.01 n=4	0.1 n=4	1.0 n=4	2.5 n=4	5.0 n=4	10.0 n=4	20.0 n=4	40.0 n=4	
QTcB	Screening	387.5 (18.2)	405.3 (9.1)	383.0 (14.5)	394.0 (21.2)	382.3 (11.6)	399.8 (15.2)	386.0 (14.8)	394.0 (19.9)	403.3 (30.4)	396.0 (22.9)
	Pre-Dose	397.3 (18.8)	402.5 (10.1)	393.0 (13.6)	385.8 (8.9)	378.3 (9.7)	393.0 (13.2)	391.0 (18.4)	384.5 (20.9)	411.0 (29.1)	390.9 (12.1)
	Pre-Last Dose	---	---	---	---	---	---	---	---	---	---
	4h Post Dose	381.9 (20.4)	407.8 (15.5)	383.5 (19.8)	384.5 (11.8)	376.8 (13.5)	387.3 (14.5)	389.3 (15.0)	394.5 (15.3)	398.8 (21.8)	379.4 (19.7)
	24 h Post Dose	382.6 (17.7)	400.0 (9.2)	376.3 (12.4)	389.0 (3.2)	373.8 (16.7)	390.8 (11.4)	380.8 (17.2)	387.0 (19.6)	399.0 (19.7)	381.6 (18.9)
	Follow up	390.5 (14.3)	407.5 (11.4)	390.0 (13.9)	393.8 (2.2)	386.3 (7.8)	388.8 (5.6)	387.3 (15.2)	399.0 (24.9)	405.5 (24.0)	385.6 (20.9)
	QTcF	Screening	386.4 (20.5)	405.3 (4.3)	384.0 (18.8)	396.3 (18.6)	383.5 (16.1)	389.3 (12.8)	389.8 (12.1)	393.0 (10.3)	398.0 (22.8)
	Pre-Dose	384.6 (22.6)	399.8 (6.2)	387.3 (14.5)	382.8 (11.4)	375.8 (17.9)	384.3 (12.4)	387.0 (18.4)	373.5 (13.2)	396.0 (29.0)	388.5 (10.7)
	Pre-Last Dose	---	---	---	---	---	---	---	---	---	---
	4h Post Dose	388.5 (21.4)	410.8 (8.6)	393.8 (23.9)	396.3 (13.9)	384.0 (9.8)	385.3 (4.6)	398.3 (17.0)	393.3 (5.2)	404.3 (13.5)	390.6 (14.9)
	24 h Post Dose	381.5 (17.2)	402.0 (6.6)	384.3 (18.1)	397.5 (9.9)	378.3 (14.8)	382.5 (7.4)	389.0 (14.4)	385.8 (6.6)	404.5 (13.4)	388.4 (13.9)
	Follow up	382.6 (17.4)	405.0 (12.9)	387.5 (16.9)	391.5 (4.4)	389.5 (8.4)	387.5 (9.0)	389.5 (16.2)	395.5 (15.3)	402.5 (15.6)	384.8 (22.1)
QT	Screening	384.6 (33.6)	405.8 (9.2)	386.3 (29.1)	401.3 (32.6)	386.3 (28.9)	371.3 (45.9)	398.5 (17.6)	391.5 (24.1)	388.8 (10.8)	392.9 (33.4)
	Pre-Dose	361.5 (40.0)	394.3 (19.8)	375.5 (22.9)	377.0 (20.3)	372.0 (37.2)	367.0 (22.0)	380.0 (34.6)	352.0 (7.0)	367.3 (29.6)	384.9 (32.1)
	Pre-Last Dose	---	---	---	---	---	---	---	---	---	---
	4h Post Dose	402.6 (36.9)	417.0 (8.9)	415.3 (32.8)	421.3 (19.3)	399.3 (14.8)	382.0 (15.1)	416.5 (25.0)	392.0 (31.3)	416.5 (7.9)	414.6 (21.1)
	24 h Post Dose	379.9 (26.6)	406.3 (14.1)	400.5 (31.0)	415.0 (23.7)	386.8 (17.0)	366.8 (16.9)	407.0 (28.7)	385.3 (33.7)	416.3 (16.6)	402.4 (10.9)
	Follow up	367.9 (26.8)	400.0 (16.5)	382.3 (26.0)	387.0 (11.5)	397.0 (15.4)	385.0 (17.1)	394.5 (25.0)	390.3 (36.0)	397.5 (18.2)	384.1 (38.0)
Part II											
Actual values (ms): average of 3 measurements [Mean (SD)]											
	Assessment time	Pbo n=2	Dut 1.0mg n=4	Dut 20.0mg n=4	Fin 5mg n=4						
QTcB	Screening	387.5 (7.8)	387.3 (12.6)	389.5 (11.8)	399.5 (21.7)						
	Predose (D1)	368.0 (7.1)	397.0 (12.6)	395.0 (24.6)	388.8 (7.6)						
	Pre-last dose (D7)	388.0 (7.1)	384.3 (21.0)	383.0 (25.6)	383.8 (10.9)						
	4h postdose (D7)	384.5 (10.6)	387.5 (17.2)	378.3 (21.4)	378.5 (7.0)						

	24h postdose (D7)	387.0 (4.2)	383.3 (12.9)	383.8 (17.7)	376.3 (10.9)								
	Follow up	392.0 (0.0)	396.3 (11.7)	384.5 (24.7)	392.0 (23.4)								
QTcF	Screening	386.5 (13.4)	379.0 (20.4)	384.3 (6.9)	398.0 (11.0)								
	Pre-dose (D1)	367.0 (17.0)	379.0 (13.8)	385.8 (22.3)	383.8 (14.9)								
	Pre-last dose (D7)	393.5 (10.6)	386.8 (18.2)	388.8 (26.1)	388.5 (11.7)								
	4h postdose (D7)	388.0 (7.1)	390.3 (18.0)	385.0 (20.9)	385.0 (5.9)								
	24h postdose (D7)	390.0 (4.2)	383.0 (12.7)	386.8 (19.1)	379.3 (13.3)								
	Follow up	389.0 (7.1)	382.3 (14.7)	379.5 (21.4)	384.8 (15.8)								
QT	Screening	385.5 (24.7)	364.3 (42.3)	374.0 (15.5)	396.3 (30.5)								
	Pre-dose (D1)	366.0 (36.8)	346.0 (16.5)	367.8 (21.1)	375.0 (41.2)								
	Pre-last dose (D7)	405.0 (18.4)	392.8 (16.9)	400.8 (34.0)	399.0 (17.5)								
	4h postdose (D7)	396.0 (0.0)	396.0 (23.4)	399.3 (25.8)	398.3 (3.9)								
	24h postdose (D7)	396.0 (5.7)	382.8 (17.1)	393.3 (30.3)	384.8 (17.5)								
	Follow up	382.0 (21.2)	355.3 (26.3)	369.5 (18.6)	372.0 (33.5)								
<b>Change from Predose (ms): average of 3 measurements [Mean (SD)]</b>													
	Assessment time	Placebo n=2	Dut 1.0mg n=4	Dut 20.0mg n=4	Finasteride 5mg n=4								
QTcB	Pre-last dose (D7)	20.0 (0.0)	-12.8 (8.6)	-12.0 (6.3)	-5.0 (13.7)								
	4h postdose (D7)	16.5 (3.5)	-9.5 (8.8)	-16.8 (6.9)	-10.3 (12.0)								
	24h postdose (D7)	19.0 (2.8)	-13.8 (5.5)	-11.3 (6.9)	-12.5 (7.0)								
	Follow up	24.0 (7.1)	-0.8 (18.3)	-10.5 (4.9)	3.3 (17.3)								
QTcF	Pre-last dose (D7)	26.5 (6.4)	7.8 (4.6)	3.0 (5.9)	4.8 (15.6)								
	4h postdose (D7)	21.0 (9.9)	11.3 (7.9)	-0.8 (5.9)	1.3 (11.9)								
	24h postdose (D7)	23.0 (12.7)	4.0 (3.9)	1.0 (6.4)	-4.5 (17.5)								
	Follow up	22.0 (9.9)	3.3 (16.6)	-6.3 (7.5)	1.0 (10.9)								
QT	Pre-last dose (D7)	39.0 (18.4)	46.8 (9.0)	33.0 (13.6)	24.0 (33.0)								
	4h postdose (D7)	30.0 (36.8)	50.0 (11.0)	31.5 (9.1)	23.3 (38.0)								
	24h postdose (D7)	30.0 (31.1)	36.8 (6.3)	25.5 (15.1)	9.8 (44.0)								
	Follow up	16.0 (15.6)	9.3 (20.3)	1.8 (13.6)	-3.0 (9.9)								
<b>Change from Predose (ms): categorized change frequency [number of subjects]</b>													
	Assess-ment time	Placebo n=2			Dut 1.0mg n=4			Dut 20.0mg n=4			Finasteride 5mg n=4		
		<30	30- 60	≥60	<30	30- 60	≥60	<30	30- 60	≥60	<30	30 - 60	≥60
QT	Pre-last dose (D7)	1	1			3	1	2	2		3		1
	4h post-dose (D7)	1	1			3	1	3	1		2	1	1
	24h post-dose (D7)	1	1			4		3	1		2	1	1
	Follow up	2			4			4			4		

		<30	30-60	≥60	<30	30-60	≥60	<30	30-60	≥60	<30	30-60	≥60
QTcB	Pre-last dose (D7)	2		4		4		4					
	4h post-dose (D7)	2		4		4		4					
	24h post-dose (D7)	2		4		4		4					
	Follow up	2		4		4		4					
QTcF	Pre-last dose (D7)	1	1	4		4		4					
	4h post-dose (D7)	2		4		4		4					
	24h post-dose (D7)	1	1	4		4		4					
	Follow up	2		4		4		4					
<b>Maximum change from predose (ms) [Mean (SD)]</b>													
		Placebo n=2		Dut 1.0mg n=4		Dut 20.0mg n=4		Finasteride 5mg n=4					
QTcB		24.5 (6.4)		-7.8 (21.5)		-18.3 (5.9)		-0.5 (21.7)					
QTcF		27.0 (7.1)		12.3 (14.2)		-6.8 (9.5)		-4.0 (21.0)					
QT		41.0 (21.2)		54.5 (10.2)		35.8 (10.1)		14.8 (47.3)					
<b>Categorized change from predose frequency [number of subjects]</b>													
		Placebo n=2		Dut 1.0mg n=4		Dut 20.0mg n=4		Finasteride 5mg n=4					
QTcB	<30ms	2		4		4		4					
	30-60ms												
QTcF	<30ms	1		4		4		4					
	30-60ms	1											
QT	<30ms	1				2		1					
	30-60ms	1		2		2		2					
	≥60ms			2				1					
<b>Safety</b>													
<b>Most Frequent Adverse Events Affecting &gt;1 Subject/Group Part I</b>													
		Placebo		Dut (all doses)				Fin					
	N (ITT)	8		32				8					
	No. subjects with AEs n (%)	6 (75)		19 (59)				6 (75)					
	Headache	3 (38)		6 (19)				4 (50)					
	Cough	1 (13)		2 (6)				1 (13)					
<b>Most Frequent Adverse Events Affecting &gt;1 Subject/Group Part II</b>													
		Pbo		DUT 1mg		DUT 20 mg		Fin					
	N (ITT)	3		4		4		4					
	No. subjects with AEs n (%)	1 (33)		4 (100)		3 (75)		2 (50)					
	Headache	0 (0)		2 (50)		0 (0)		0 (0)					
<b>Serious Adverse Events, n (%) [# considered by the investigator to be related, possibly related, or probably related to study medication]:</b>													
Part I: There were no serious adverse events reported during this period of the study.													
Part II: One serious adverse event of hematemesis was reported by a subject (1mg DUT) on study day 37; 30 days after discontinuation of the study drug. The event was considered by the investigator as unlikely to be related to the study drug.													
<b>Publications:</b>													
No publication.													

Date Updated: 11-May-2005