

<b>Study No.:</b> ARI40001 -Open-Label		
<b>Title:</b> A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Study to Compare the Efficacy of dutasteride/GI198745 0.5mg od Versus Finasteride 5mg od for 12 Months in the Treatment of Subjects with Benign Prostatic Hyperplasia (BPH), Followed by an Optional 24 Months Open-Label Phase (Report on Open-Label Treatment Phase)		
<b>Rationale:</b> The open-label study extension gave an opportunity to gather data on the longer-term safety and tolerability of dutasteride (Dut) monotherapy and the effects of switching from finasteride (Fin), as well as offering subjects the option of receiving Dut treatment for up to a further 24 months, which was expected to prevent possible prostate growth and disease regression.		
<b>Phase:</b> IIIb		
<b>Study Period:</b> 10 Nov 1998 - 6 Feb 2003		
<b>Study Design:</b> Open-label extension phase of randomised double-blind, double-dummy, parallel group study.		
<b>Centres:</b> 36 investigators in 8 countries: Brazil, Canada, Czech Republic, Mexico, Norway, Portugal, Slovakia and Ukraine.		
<b>Indication:</b> BPH		
<b>Treatment:</b> Upon completion of the 12-month double-blind phase, eligible subjects previously administered Dut (Dut/Dut group) or Fin (Fin/Dut group) were enrolled in the open-label treatment extension phase in which subjects received Dut 0.5 mg once daily for 24 months. The total duration of the study including the double-blind period for subjects who took part in the open-label extension was 41 months and a follow-up visit was conducted 4 months after the final dose of study medication.		
<b>Objectives:</b> To assess the safety and tolerability of an extended period of repeat, once-daily doses with Dut 0.5 mg.		
<b>Primary Outcome Variable:</b> As this was an open-label extension of a 12-month study, the primary outcome variable was safety.		
<b>Secondary Outcome Variable:</b> Not applicable		
<b>Study Population:</b> Subjects were males, $\geq 50$ years of age, with a diagnosis of BPH (according to medical history and physical examination including a digital rectal examination), American Urology Association Symptoms Index $\geq 12$ at baseline, a urinary flow rate $\leq 15$ mL/sec with a minimum voided volume $\geq 125$ mL, prostate volume $\geq 30$ cm <sup>3</sup> as determined by transrectal ultrasound. Subjects were excluded if they had a post-void residual volume $>250$ mL or a serum prostate-specific antigen (PSA) $<1.5$ ng/mL or $>10$ ng/mL.		
<b>Statistical Methods:</b> Sample size was determined by those subjects who completed the 1-year double blind study in the countries that elected to participate in the open-label phase. Since the objective of the open-label phase was to assess the safety and tolerability of the single treatment dutasteride 0.5mg, there was no treatment difference hypothesis and no inferential statistical analyses in terms of treatment groups.		
The primary population of subjects summarized was the Open-Label Intent-to-Treat which consisted of all subjects enrolled in the open-label phase (after completing the 12 month double-blind phase) and who received at least one dose of study treatment during the open-label phase.		
<b>Number of Subjects:</b>	<b>Dut/Dut</b>	<b>Fin/Dut</b>
Planned N	636	636
Randomised N for double-blind study: Double-blind ITT population	813	817
Completed double-blind study n (%)	719 (88.4)	735 (90.0)
Withdrawn double-blind study n(%)	94 (11.6)	82 (10.0)
Started open-label study N: Open-label ITT population	222	226
Completed open-label study n (%)	188 (84.7)	183 (81.0)
Withdrawn from open-label study n (%)	34 (15.3)	43 (19.0)
Withdrawn due to Adverse Events n (%)	13 (6%)	21 (9%)
Withdrawn due to Lack of Efficacy n (%)	na	na
Withdrawn for other reasons n (%)	21 (9%)	22 (10%)
<b>Demographics</b>	<b>Dut/Dut</b>	<b>Fin/Dut</b>
N (ITT)	222	226
Females: Males	0:222	0:226
Mean Age in Years (SD)	67.0 (7.36)	67.0 (7.21)
Mean Weight in kg (SD)	79.2 (12.60)	78.6 (12.12)
White n (%)	201 (90.5)	200 (88.5)

<b>Primary Efficacy Results:</b> The primary outcome for the open-label phase was safety. See adverse events reported below.		
<b>Safety Results:</b> Adverse events were coded and grouped by body system. AE and SAE incidences reported are for the open-label period.		
<b>Most Frequent Adverse Events – On Therapy</b>	<b>Dut/Dut</b>	<b>Fin/Dut</b>
N (Open-Label ITT)	n=222	n=226
Subjects with AEs during open-label phase, n (%)	100 (45)	100 (44)
Hypertension	14 (6)	15 (7)
Viral respiratory infections	9 (4)	6 (3)
Impotence	8 (4)	6 (3)
Urinary tract hemorrhage	8 (4)	2 (<1)
Musculoskeletal pain	7 (3)	9 (4)
Arthralgia and articular rheumatism	7 (3)	2 (<1)
Abdominal discomfort and pain	6 (3)	4 (2)
Nausea and vomiting	5 (2)	1 (<1)
Disorders of lipid metabolism	5 (2)	8 (4)
Myocardial infarction	5 (2)	2 (<1)
Dizziness	5 (2)	2 (<1)
Viral ear nose and throat infections	6 (3)	9 (4)
Headaches	4 (2)	6 (3)
Angina pectoris	4 (2)	5 (2)
Altered (decreased) libido	0	5 (2)
Skin rashes	0	4 (2)
<b>Serious Adverse Events - On-Therapy</b>		
	<b>Dut/Dut</b>	<b>Fin/Dut</b>
<b>Subjects with SAEs during open-label phase, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]</b>	21 (9) [2]	26 (12) [1]
Myocardial infarction	5 (2) [1]	2 (<1) [0]
Embolisms	1 (<1) [0]	1 (<1) [1]
Cerebrovascular accidents	1 (<1) [0]	1 (<1) [0]
Cardiac failure	1 (<1) [0]	1 (<1) [0]
Arterial stenosis and arteriospasm	0	1 (<1) [0]
Coronary artery disorders	1 (<1) [0]	0
Angina pectoris	0	1 (<1) [0]
Atrioventricular block	0	1 (<1) [0]
Gastrointestinal herniae	2 (<1) [0]	0
Primary malignant gastrointestinal neoplasia	0	2 (<1) [0]
Nausea and vomiting	1 (<1) [0]	0
Gastrointestinal ulcers	1 (<1) [1]	0
Gastric ulcers	1 (<1) [0]	0
Duodenal ulcers	1 (<1) [1]	0
Urinary retention	0	2 (<1) [0]
Renal impairment	0	1 (<1) [0]
Urinary tract signs and symptoms	0	1 (<1) [0]
Urinary calculi	1 (<1) [0]	0
Primary malignant urinary neoplasia	0	1 (<1) [0]
Fractures	1 (<1) [0]	2 (<1) [0]
Injuries	1 (<1) [0]	1 (<1) [0]
Delayed healing of wounds	0	1 (<1) [0]
Wounds and lacerations	1 (<1) [0]	0
Primary malignant male reproductive neoplasia	1 (<1) [0]	3 (1) [0]
Prostate disorders	0	1 (<1) [0]
Infections	1 (<1) [0]	0
Anaphylactic reactions and allergic shock	0	1 (<1) [0]

Non-specific conditions	0	1 (<1) [0]
Primary malignant neoplasia	0	1 (<1) [0]
Viral neurological infections	0	1 (<1) [0]
Dizziness	1 (<1) [0]	0
Motor dysfunction	0	1 (<1) [0]
Respiratory disorders	0	1 (<1) [0]
Pleura disorders	0	1 (<1) [0]
Primary malignant lower respiratory neoplasia	0	1 (<1) [0]
Cholecystitis	0	1 (<1) [0]
Hepatobiliary symptoms	1 (<1) [0]	0
Cholelithiasis	1 (<1) [0]	0
Muscle atrophy weakness and tiredness	1 (<1) [0]	0
Benign musculoskeletal neoplasia	1 (<1) [0]	0
Hematological disorders	0	1 (<1) [0]
Decreased white cells	0	1 (<1) [0]
Diabetes mellitus	0	1 (<1) [1]
Ocular pressure disorders	0	1 (<1) [0]
Eustachian tube labyrinth and vestibule disorders	1 (<1) [0]	0
<b>Subjects with fatal SAEs during open-label phase, n (%) [considered by the investigator to be related, possibly related, or probably related to study medication]</b>	<b>3 (1.4) [1]</b>	<b>5 (2.2) [0]</b>
Septicaemia	1 (0.5) [0]	0
Acute myocardial infarction	1 (0.5) [1]	0
Myocardial infarction	1 (0.5) [0]	1 (0.5) [0]
Unstable angina pectoris	0	1 (0.5) [0]
Prostate cancer	0	1 (0.5) [0]
Neutropenia	0	1 (0.5) [0]
Renal insufficiency	0	1 (0.5) [0]
Pancytopenia	0	1 (0.5) [0]
Head trauma	0	1 (0.5) [0]
Lung cancer diagnosed	0	1 (0.5) [0]
Heart failure	0	1 (0.5) [0]

Conclusion:

Once daily treatment with dutasteride 0.5mg for up to 3 years resulted in an expected level of adverse events related to sexual function such as impotence, decreased libido and ejaculation disorders. As in previous dutasteride studies, there was a low incidence of gynaecomastia and prostate cancer. No notable new adverse events appeared over time and many of the events decreased in frequency in the third year of treatment compared to the previous two years.

Date Updated: 22-Dec-2004

Publications:

No Publication