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Study No.: ARIF 4010
Title: Multicentre, randomized, placebo-controlled, double-blind, parallel-group, phase IIIB clinical trial evaluating the efficacy of dutasteride in the prevention of bleeding related to prostate transurethral resection in subjects presenting with BPH.
Rationale: Benign Prostatic Hyperplasia (BPH) is a progressive disease basically characterized by low urinary tract symptoms (LUTS), an increased prostate volume, and a decreased peak urinary flow rate. Although pharmacological treatment has obtained some encouraging results during the last years, surgical treatment, especially transurethral resection of the prostate (TURP), remains the most used methodology in the medical management of this disease and its complications. Nevertheless, TURP is associated with peri- and post-operative complications such as urinary retention, excessive bleeding requiring transfusion, and clot retention. The aim of this study is to evaluate whether pre-treatment with dutasteride (DUT) prevents or reduces peri- and post-operative bleeding associated with TURP, and decreases the prostatic micro-vessel density by a reduction of the activity of androgen-controlled growth factors responsible for angiogenesis.
Phase: IIIB
Study Period: 2 September 2002 to 19 February 2004
Study Design: A multicentre, randomized, double-blind, parallel-group, placebo-controlled, study
Centres: 10 centres in France
Indication: BPH
Treatment: DUT 0.5mg, daily oral administration and matching placebo (PBO) for 4 weeks.
Objectives To evaluate peri-operative bleeding prevention related to TURP in subjects with BPH previously treated for 4 weeks with DUT compared to the PBO group.
Primary Outcome/Efficacy Variable: Haemoglobin quantity (grams [g]) measured in the irrigation fluid obtained at the end of TURP surgery (precisely at the time of resectoscope withdrawal), related to the peri-operative resected prostatic mass (g).
Secondary Outcome/Efficacy Variables: Rate of subjects transfused during post-operative period Rate of subjects who experienced a macroscopic hematuria during the post-operative period Haemoglobin quantity dosed in the irrigation fluid per gram of resected prostate, divided by the time of surgery (in minutes) Percent change of International Prostate Symptom Score (IPSS) score between visits 1 and 2, visits 1 and 3, and visits 2 and 3, Description of relevant histologic modifications and of micro-vascular density in both DUT and PBO groups.
Statistical Methods: The efficacy analysis was performed on the Full Analysis Set (FAS) population. The FAS consisted of all randomized subjects who received ≥ 1 dose of study medication and for whom ≥ 1 efficacy criteria was available. Subjects who discontinued before surgery were not included in the FAS analysis because they had no efficacy assessments. Quantitative data: The normality hypothesis was analysed using the Shapiro-Wilk test. If the normality was accepted, a Student t test was performed to compare treatment groups, and variance equality was tested using the Fisher test. If the normality was rejected, a non-parametric test (Wilcoxon) was performed. Qualitative data: Chi-square test or Fisher's exact test for qualitative nominal data, the Fisher's exact test was used instead of the Chi-square test when ≥ 1 expected frequency was < 5 . Wilcoxon Rank Sum test for ordinal data with > 5 categories. Ordinal variables were compared with a Jonckheere-Terpstra test when there were < 5 categories, with a Wilcoxon test either.
Study Population: Subjects aged > 50 years, diagnosed with BPH [according to medical history and clinical examination with a digital rectal examination (DRE)] having a prostate volume > 30 cc (confirmed by ultrasonography), and an indication for TURP. Subjects with one of the following were excluded : history or evidence of prostate cancer or prostate cancer discovered recently, previous prostate surgery (including balloon dilatation, thermotherapy and stent replacement) or any other invasive BPH treatment, not controlled BP as a Systolic Blood Pressure (SBP) ≥ 220 mmHg or a Diastolic Blood Pressure (DBP) ≥ 120 mmHg, bacterial prostatitis or chronic urinary tract infection within the last 12 months, history of aggregation abnormality, history of hepatic impairment, subjects under anti-aggregant treatment, except antithrombotics as the low molecular weight heparin (Fragmine [®] , Fraxiparine [®] , Lovenox [®]) at prophylactic doses

administred during post-intervention period, subjects using any other drug interfering with the hemostasis process (concerning platelet anti-aggregants, the exclusion window is reduced to 10 days before the TURP and 4 days after this intervention), BPH-related phytotherapy and finasteride within 6 months prior to study entry, concurrent use of treatment with androgenic properties (including finasteride) or anabolic steroids.		
Number of Subjects:	DUT	PBO
Planned, N	30	30
Randomised, N	35	28
Completed, n (%)	31 (88.57)	27 (96.42)
Total Number Subjects Withdrawn, n (%)	4 (11.42)	1 (3.57%)
Withdrawn Due to Adverse Events, n (%)	1 (2.85)	0
Withdrawn Due to Lack of Efficacy, n (%)	0	0
Withdrawn For Other Reasons, n (%)	3 (8.57)	1 (3.57)
Demographics	DUT	PBO
N (ITT)	32	27
Males	32	27
Mean Age, years (SD)	68 (7.9)	65 (7.5)
Caucasian, n (%)	31 (96.87)	27 (100)
Primary Efficacy Results:		
Haemoglobin Quantity (g) by Resected Prostate Shaving Weight (g)	DUT N=32	PBO N=27
Mean (SD)	1.944 (1.816)	1.401 (1.021)
Median	1.221	1.300
Minimum; Maximum	0.26;7.52	0.11;3.74
p-value	0.382	
Secondary Outcome Variable(s):		
	DUT	PBO
Rate of Subjects Transfused During Post-operative Period, n (%)	1 (3)	0
Rate of Subjects With a Macroscopic Hematuria During the Post-Operative Period, n (%)	27(87)	22 (85)
Haemoglobin Quantity (g) In Post-operative Fluid Per Gram of Resected Prostate / Time of Surgery (minutes)	0.0443	0.0338
Difference between treatments	0.0105	
95% Confidence Interval (CI)	-0.0045;0.0255	
p-value	0.167	
Percent Change of IPSS Score Between Visits 1 and 2 (SE) Mean IPSS score at Visit 1 (SD)	0.0 (5.4) 19.3 (6.6)	1.0 (5.8) 18.3 (7.5)
Adjusted Mean Percent Change of IPSS Score Between Visits 1 and 3 (SE)	-11.1 (0.9)	-9.8 (1.0)
Difference Between Treatments (SE)	-1.28 (1.31)	
95% CI	-3.91;1.35	
p-value	0.332	
Percent Change of IPSS Score Between Visits 2 and 3 ((SE)	-11.6 (8.5)	-10.5 (9.3)
Description of Relevant Histologic Modifications		
Description of Micro-vascular Density (SD)	17.3 (6.5)	17.9 (5.0)
Safety Results: Treatment period was defined from the first drug intake to the last drug intake included.		
	DUT N=35	PBO N=28
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	5 (14)	3 (11)
Abdominal pain	1 (3)	0
Diarrhea	1 (3)	0
Vomiting	1 (3)	0
Blood clot	1 (3)	0
Dysuria	0	1 (4)

Bradycardia	0	1 (4)
Chest pain	0	1 (4)
Gout	1 (3)	0
Jaw pain	0	1 (4)
Sciatica	1 (3)	0
Pain pharynx	0	1 (4)
Serious Adverse Events - On-Therapy		
n (%) [n considered by the investigator to be related to study medication]		
	DUT N=35	PBO N=28
Subjects with non-fatal SAEs, n (%)	0	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:

The differences between groups concerning TURP bleeding and reduction in microvascular density were not statistically significant ($p=0.382$ and $p=0.167$, respectively). Adverse events were reported in 5 (14%) subjects in the DUT group, and 3 (11%) subjects in the PBO group. No fatal or non-fatal serious adverse events were reported.

Publications:

No Publication

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