ORIGINAL PAPER

Efficacy and safety of Afalaza in men with symptomatic benign prostatic hyperplasia at risk of progression: a multicenter, double-blind, placebo-controlled, randomized clinical trial

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Introduction In order to investigate the efficacy and safety of Afalaza in men with benign prostatic hyperplasia (BPH) at risk of progression, this multicenter, double-blind, placebo-controlled, randomized clinical trial was performed. Derived by technological treatment of antibodies to prostate-specific antigen (PSA) and endothelial nitric oxide synthase (eNOs), Afalaza was previously proved to modulate its molecular targets. The mechanism of action of the drug is associated with the modulating effect of the antibiodies (RA-Abs) on the molecular targets (PSA and eNOS) by way of conformational changes.
Material and methods A total of 249 patients aged 45–60 years with BPH and moderate lower urinary tract symptoms (LUTS), total prostate volume (TPV) ≥30 cm^3, Qmax 10–15 ml/s, and serum PSA<4 ng/ml were randomly assigned to receive either Afalaza (n = 125) or placebo (n = 124) for 12 months. Changes in BPH/LUTS symptoms (according to the International Prostate Symptom Score), Qmax, TPV, PSA, BPH clinical progression, occurrence of acure urinary retention (AUR) events or BPH-related surgery were estimated as the study endpoints.
Results IPSS mean change was -3.7 ±3.0 (95% CI -4.3 to -3.2) after 12 months of Afalaza (vs. -2.9 ±2.4; 95% CI -3.3 to -2.4 in placebo; p = 0.02). Qmax growth was 2.5 ±4.3 ml/s (vs. 1.4 ±3.3 in placebo; p = 0.049), TPV reduced by 11.8 ±16.0% (vs. 6.5 ±14.7%; p = 0.01, and PSA remained unchanged. Afalaza therapy resulted in a significant decrease in the total sum of BPH progression symptoms (p = 0.01). The maximum effect of Afalaza was registered after 12 months without a tendency to form a 'plateau'. During the study, no patients experienced AUR or BPH-related surgery.
Conclusions A 12-month course of Afalaza therapy is effective and safe for patients with BPH. The results of end points measurements revealed asignificant advantage of Afalaza compared to placebo in the overall symptoms benefit and a decline in the risk of BPH progression.
ClinicalTrials.gov: NCT01716104.

INTRODUCTION

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) are a prevalent condition in aging men [1, 2]. Untreated BPH is complicated by acute urinary retention (AUR), urinary tract infection, renal insufficiency and other disorders [3]. BPH progression hasa

substantial impact on the social and functional domains of life.

LUTS deterioration is one of the most frequent BPH progression events. AUR emergence is an urgent symptom related to disease progression [3, 4, 5]. The risk of AUR significantly increases as LUTS severity rises to >7 points according to the International Prostate Symptom Score (IPSS) or American Urological Association Symptom Index (AUA-SI) [4, 5]. Prostate volume >30 cm³, serum prostate-specific antigen (PSA) ≥1.4 ng/ml, maximum uroflow rate (Qmax) <12 ml/s are known to be risk factors for AUR and the need for BPH related surgery [5]. These factors are considered as BPH progression symptoms [3, 5, 6, 7].

Preventive treatment that will hamper prostatic hyperplasia and alleviate urinary tract obstruction is a difficult task. The symptoms of emerging BPH are managed by 5-α-reductase inhibitors (5-ARIs), and/or α-adrenoblockers (ABs) [8–12]. Type-5 phosphodiesterase (PDE5) inhibitors, antimuscarinics, and β3-adrenoreceptor agonists can also be used in treatment [8, 13]. Prolonged regimens may lead to adverse events (AEs) and complications [8, 14, 15]. For BPH management, Afalaza therapy can be used [16]. It is a medicinal product containing released-active forms [17, 18] of antibodies (RA-Abs) to prostate-specific antigen (PSA) [19, 20] and endothelial nitric oxide synthase (eNOS) [21, 22]. The pharmacological activity of the medication is associated with the RA-Abs modulating effect on their molecular targets (PSA and eNOS) by way of conformational changes [17, 18]. RA-Abs to PSA modifies the activity of endogenous PSA [19, 20], enhancing its regulatory effect on metabolic and functional processes in the prostate [23, 24]. RA-Abs to eNOS targets eNOS [21, 22] and stimulates production of NO involved in a range of metabolic processes, oxidative stress reactions, maintenance of circulation homeostasis, as well as in the regulation of inflammation processes [25]. The present study was conducted to investigate therapeutic and secondary preventive efficacy and safety of 12-month long Afalaza therapy in men with BPH at risk of progression.

MATERIAL AND METHODS

Study overview

The international, multicenter, double-blind, placebo-controlled, randomized, parallel-group clinical trial was performed between 02/Nov/2012 and 09/Nov/2016 in 15 medical institutions in Russia and in 1 institution in the Ukraine. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and was approved by the institutional review boards. Signed informed consent was obtained from all participants prior to enrollment. In compliance with regulatory requirements (local/national rules) the protocol of the study was submitted and approved by the Ministry of Healthcare of the Russian Federation. The study was registered in the international database ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01716104).

The study consisted of two phases: 1 – screening for up to 1 week; 2 – treatment and follow-up for 12 months. During the screening period, the patients were examined by an urologist, transrectal ultrasound (TRUS), uroflowmetry, and laboratory tests were performed (Visit 1). Eligible patients were randomized into Group 1 (Afalaza) or Group 2 (placebo) on Visit 2. During the study, the patients paid five more visits to the medical center: after 1, 3, 6, 9, and 12 months. Patient examination, therapy control and compliance assessment were performed at every visit.

Patient selection

The study included men aged 45–60 years old with BPH and associated LUTS persisting for more than 3 months, IPSS ranging 8–15 points, total prostate volume (TPV) >30 cm³, Qmax varying 10–15 ml/s; voided volume between 125 and 350 ml; post-void residual urine volume <100 ml, and serum PSA <4 ng/ml. The inclusion criteria were very precise and restricted in order to prove the efficacy of Afalaza monotherapy in prevention of disease progression, to provide comparability of the two groups, to mitigate risks for patients on placebo-therapy during 12-month participation in the clinical trials, and guarantee non-exclusion for them.

The exclusion criteria were a history of invasive or surgical treatment for BPH, AUR in the previous 3 months, suspected prostate cancer, urolithiasis, neurogenic lower urinary tract dysfunction, bladder diverticulum, urinary tract infection, urethral stricture, bladder neck sclerosis, severe concomitant pathology, renal or hepatic failure, history of 5-ARIs use.

Patient assessment

In the screening period (one week) the patients were examined to prove that BPH (not any other condition) caused lower urinary tract symptoms (LUTS) including bladder outlet obstruction (BOO) symptoms.

IPSS questionnaire and Qmax were carried out at screening, after 1, 3, 6, and 12 months; TRUS

for TPV measurement was implemented at screening and every 3 months; serum PSA was measured at screening, after 6, and 12 months; hematology, blood chemistry, and urinalysis were checked at screening and after 12 months.

Moderate-to-severe symptoms (according to IPSS), depressed Qmax rate (<12 ml/s), enlarged prostate (>30 cm³) or elevated serum PSA (≥1.4 ng/ml) were considered as risk factors for BPH progression [4–7]. Each particular risk factor scored 1 point, its absence 0 point, thus maximum score equaled 4 points. Each risk factor change was estimated after 12 months. Increase in risk factor severity (symptom deterioration) in comparison with initial value added 1 point, lack of changes gave 0 point, and decrease (symptom benefit) meant minus 1 point. The total sum dynamics was used to make a conclusion about BPH progression (in case of the score increase) or retardation (in case of the score decrease).

Laboratory tests and AEs registration were performed to assess the safety of the treatment. AEs were categorized by organ system, preferable terms, severity, and treatment relatedness as determined by the urologist.

Randomization and blinding

After screening, the patients were assigned to Afalaza or placebo groups in a 1:1 ratio. Interactive voice/web response randomization system based on a random number generator was used for patients' randomization and investigational medicine assignment. Neither participants, nor investigators, trial centers staff, and the sponsor's project team were aware of the treatment group assignment throughout the duration of the study.

Manufacturing, packaging and labeling with unique identification codes of the double-blind medications (Afalaza or placebo/identical in shape and taste tablet containing excipients) were performed by OOO 'NPF' 'Materia Medica Holding'.

Treatment

Two Afalaza tablets were administered twice a day, 15 to 30 minutes before meals for 12 months; the tablets were kept in the mouth until completely dissolved. Each Afalaza tablet contains a mixture of affinity purified polyclonal antibodies to PSA (6 mg) and antibodies to eNOS (6 mg) in released-active form produced by the patented technology (US Patent 8,535,664 B2, 2013) in accordance with the applicable European Pharmacopeia requirements.

Placebo was administered according to Afalaza administration schedule.

The compliance with the study therapies was assessed at each visit according to the count of tablets returned by the patient.

The patients were allowed to use concomitant therapy excluding 5-ARIs, ABs, herbal extracts and other drugs for the treatment of BPH and urination disorders; testosterone hormones, PDE5 inhibitors, diuretics, neuroleptics, psychoanaleptics, nebivolol, long-acting nitrates. These medications were not permitted either within 3 months prior to study entry, and 5-ARIs were prohibited at any point previously.

Study end points and statistical analysis

The primary efficacy end point was BPH symptom alleviation in IPSS score at 1, 3, 6 and 12 months compared to the baseline. Changes in the Qmax, TPV, PSA, BPH-related health status (question 8 in the IPSS), and dynamics of the total sum of BPH progression symptoms were used as the secondary end points. AUR episodes and/or BPH related surgery were monitored during the study.

Statistical analysis was performed using SAS (Version 9.4) statistical software. Data of the full analysis set excluding the failure to satisfy major entry criteria (eligibility violations) were used for intention-to-treat (ITT) analysis. The sample size was calculated assuming the difference between changes in the average IPSS score after 12 months compared to the baseline in Afalaza group and in Placebo group would be 1.0 point; while the standard deviation (SD) would be 2.5 points. The power of statistical criteria was assumed to be 80%; the type I error was assumed to be <5%. The minimum required size for each group was 100 patients; at least 260 patients had to be included, taking into account the dropout rate (during the screening and the study period) set at 1.2 (20%) or greater.

To compare the results in two groups, Student's t-test was used for continuous variables, and the Holm adaptive method was used for multiple comparisons. The longitudinal data was analyzed with two-way analysis of covariance (ANCOVA; with the factors based on 2 levels for the Group and 4 levels for the Visit, and adjustment for covariates for Visit 1) using SAS PROC MIXED. The χ^2 criterion, Cochran-Mantel-Haenszel test, and Fisher's exact test were used to compare the proportions.

RESULTS

Patient demographics and baseline characteristics

A total of 260 patients were assessed for eligibility. Upon completion of the study screening, 11 patients

were excluded as they did not meet the inclusion criteria or did meet the exclusion criteria. In total, 249 patients were randomized to treatment: 125 of them into the Afalaza group and 124 into the Placebo group (Figure 1). Thirteen randomized patients (6 in Afalaza group and 7 in Placebo group) failed to satisfy major entry criteria (eligibility violations), so they were excluded from the full analysis set. The rest of the participants (n = 236) constituted the ITT set analyzed. Treatment outcomes in this set (119 patients in Afalaza group and 117 in Placebo group) were considered for ITT analysis of efficacy. Treatment safety in both groups was assessed in all patients who received at least one dose of Afalaza (n = 125) or placebo (n = 124).

Patients in both groups did not differ in demographic and baseline characteristics, including IPSS score, Qmax depression, prostate volume enlargement, PSA level, and total sum of the risk factors for BPH progression (Table 1).

Change in International Prostate Symptom Score

After 12 months, the IPSS mean decreased to 8.1 ±3.0 (95% confidence interval [CI] 7.5 to 8.6) in patients of the Afalaza group versus 8.6 ±2.5 (95% CI 8.1 to 9.0) in the Placebo group. ANCOVA revealed significant results for the Group factor (p = 0.001), for the Visit factor (p <0.0001), and for the Group-by-Visit interaction (p = 0.008). Thus, ANCOVA confirmed that IPSS decrease was more significant in the Afalaza group than in the Placebo group.

Final IPSS score decline from baseline in the Afalaza group was -3.7 ±3.0 versus -2.9 ±2.4 in the Placebo group (Figure 2). The Student's t-test has proved a significant IPSS decrease at each visit (1, 3, 6, and 12 months of treatment) for Afalaza patients compared to that of the Placebo group.

Maximum urinary flow rate

At 1 month follow-up, Qmax mean increase was higher for the Afalaza group in comparison to the Placebo group (Figure 3). Subsequent administration of Afalaza led to Qmax rise to 14.9 ±4.3 ml/s versus 14.0 ±3.2 ml/s in the Placebo group at 12 months follow-up. ANCOVA proved Qmax increase to be more significant in the Afalaza group than in the Placebo group (Group factor: p = 0.0004; Visit factor: p <0.0001; Group-by-Visit interaction: p = 0.0335). Total Qmax change confirmed its significant growing by the end of the 12 months for the Afalaza group, amounting to +2.5 ±4.3 ml/s (vs. +1.4 ±3.3 ml/sec in Placebo group; p = 0.049).
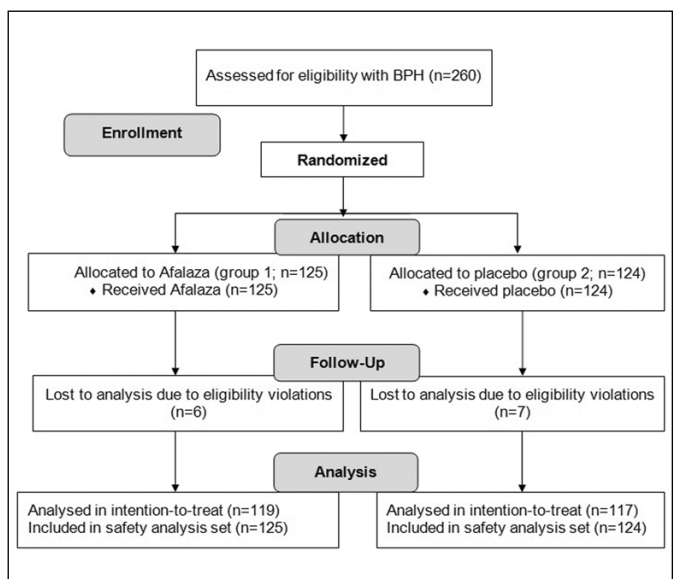
Total prostate volume

In the Afalaza group, mean TPV decreased by 3.0 ±6.3 cm³ after 3 months, by 4.5 ±6.6 cm³ after

Table 1. *Patient demographics and baseline characteristics*

|	Group		p-value
	Afalaza (n = 119)	Placebo (n = 117)	
Age (years)			
Median	55.1	54.8	0.90*
Minimum	45.0	45.4	
Maximum	60.9	60.9	
IPSS (M ±SD), points	11.8 ±2.0	11.4 ±1.8	0.16
Qmax (M ±SD), ml/s	12.4 ±1.5	12.6 ±1.4	0.48
Prostate volume (M ±SD), cm³	43.1 ±17.9	40.5 ±10.1	0.17
PSA (M ±SD), ng/ml	1.5 ±1.0	1.5 ±0.9	0.98
BPH-related health status (M ±SD), points	3.3 ±0.9	3.3 ±1.0	0.87
Total sum of the risk factors for BPH progression (M ±SD), points	2.8 ±0.7	2.8 ±0.7	0.61
Number of patients with at least one concomitant disease (n/%)	52/43.7	48/41.0	0.70**
Number of patients received at least one concomitant medication (n/%)	35/29.4	33/28.2	0.88**

*χ^2 Median One-Way Analysis. IPSS, Q_{max}, Prostate volume, PSA, BPH-related health status, and Total sum of the risk factors for BPH progression were analyzed by Student's t-test
**Fisher's exact test. IPSS – International Prostate Symptom Score; Q_{max} – maximum uroflow rate. PSA – prostate-specific antigen; BPH – benign prostatic hyperplasia
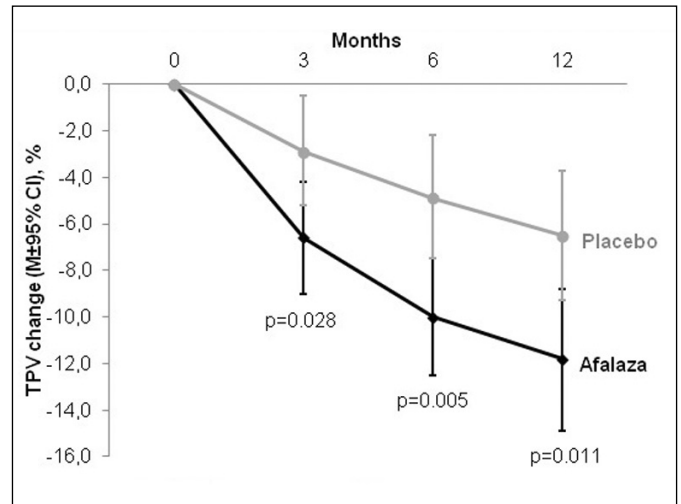
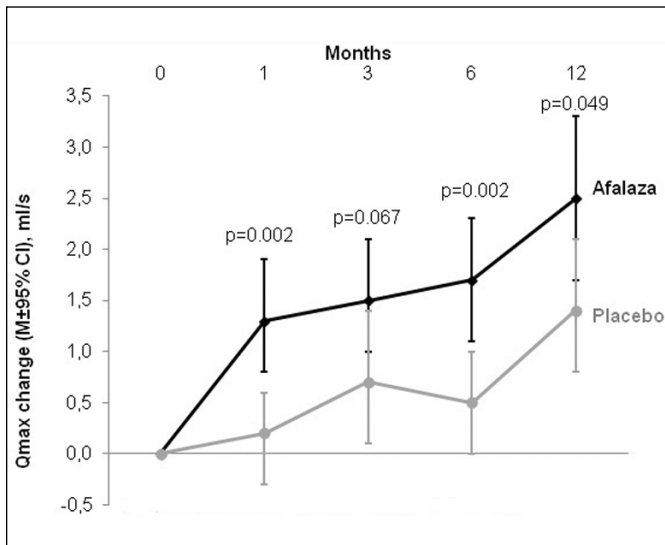

Figure 1. *Study design flow diagram.*
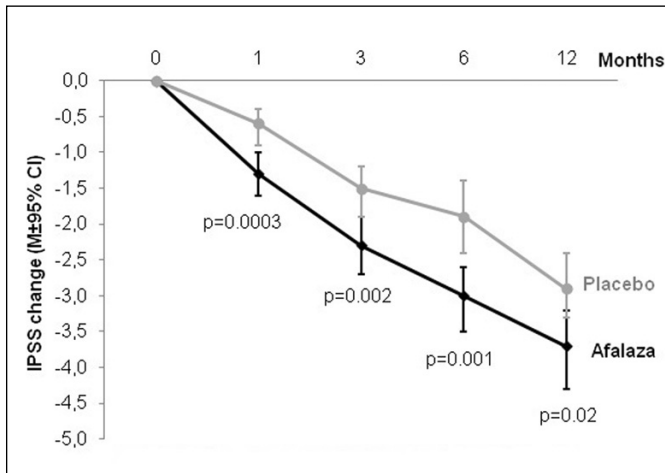
Figure 2. *Mean changes in International Prostate Sypmtom Score (IPSS) score during 12 months.*

Figure 4. *Mean changes in total prostate volume (%) during 12 months.*
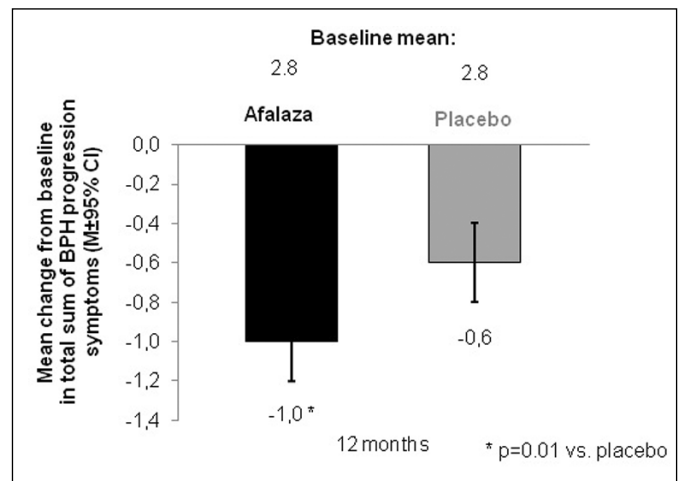

Figure 3. *Mean changes in Qmax during 12 months.*

Figure 5. *Mean changes in total sum of the risk factors for BPH progression during 12 months.*

6 months, and by 5.5 ±8.0 cm^3 after 12 months. In the Placebo group, as measured at the same time intervals, the mean TPV changes were -1.2 ±4.8 (p = 0.0195), -1.9 ±5.5 (p = 0.0019), and -2.5 ±5.7 (p = 0.0018) cm^3. Scored as the percentage of the initial volume, these values are presented in Figure 4. Student's t-test showed superiority for Afalaza over placebo in steady TPV reduction both in cm^3 and percentage units.

Prostate-specific antigen

The mean values of total PSA remained stable throughout the study in both groups (Table 2). ANCOVA proved that mean PSA did not differ between the two groups during the 12 months of treatment.

PSA increase was reported in 9 patients: 4 patients in the Afalaza group and 5 patients in the Placebo group (p = 0.54). All 9 patients fully completed their participation in the study and received further treatment.

Benign prostatic hyperplasia-related health status

In the Afalaza group, the IPSS question 8 score decreased from the baseline (-1.0 ±1.0; 95% CI -1.2 ÷ -0.8) and differed favorably and significantly from the Placebo group (-0.6 ±1.2; 95% CI -0.9 ÷ -0.4; p = 0.025). ANCOVA results confirmed the advantage of Afalaza over placebo in improving BPH-related health status throughout the 12 months of treatment (Group-by-Visit interaction: p = 0.04).

Table 2. *Serum prostate-specific antigena (ng/ml)*

Visit/Month	Afalaza N = 103	Placebo N = 105	Statistics	
			Student's t-test[b]	ANCOVA
1/Baseline	1.5 ±1.0 (1.3 ÷ 1.7)	1.5 ±0.9 (1.3 ÷ 1.7)	t = 0.03; p = 0.98	1) Group factor F = 0.16; p = 0.69;
5/6 months	1.6 ±1.1 (1.4 ÷ 1.8)	1.7 ±1,3 (1.4 ÷ 1.9)	t =-0.70; p = 0.48	2) Visit factor: F = 2.4; p = 0.09;
7/12 months	1.5 ±1,2 (1.2 ÷ 1.7)	1.6 ±1,2 (1.4 ÷ 1.8)	t =-0.44; p = 0.66	3) Group*bVisit: F = 0.09; p = 0.91

[a]Results are presented as M±SD (95% CI); [b]p-values are given taking into account the multiplicity of comparisons using Holm adaptive criterion; ANCOVA – two-way analysis of covariance with adjustment for covariate for Visit 1

Table 3. *Adverse events*

SOC / Adverse event	Afalaza (N = 125)	Placebo (N = 124)	p-value
Number of subjects reporting at least one AE*	25 (20.0)	29 (23.4)	0.54
Gastrointestinal disorders			
At least one event	4 (3.2)	5 (4.0)	0.75
Upper abdominal pain	1 (0.8)	0 (0.0)	1.00
Inguinal hernia	1 (0.8)	0 (0.0)	1.00
Diarrhea	1 (0.8)	0 (0.0)	1.00
Heartburn	0 (0.0)	1 (0.8)	0.50
Swollen tongue	0 (0.0)	1 (0.8)	0.50
Nausea	1 (0.8)	2 (1.6)	0.62
Exacerbation of chronic gastritis	0 (0.0)	1 (0.8)	0.50
General disorders			
At least one event	0 (0.0)	1 (0.8)	0.50
Asthenia	0 (0.0)	1 (0.8)	0.50
Infections and infestations			
At least one event	13 (10.4)	13 (10.5)	1.000
Gastroenteritis	0 (0.0)	1 (0.8)	0.50
Urinary tract infection	1 (0.8)	0 (0.0)	1.00
Herpes labialis	1 (0.8)	0 (0.0)	1.00
Upper respiratory tract infection	9 (7.1)	10 (8.0)	0.82
Acute bronchitis	1 (0.8)	0 (0.0)	1.00
Rhinitis	0 (0.0)	2 (1.6)	0.25
Pharyngitis	1 (0.8)	0 (0.0)	1.00
Investigations			
At least one event	4 (3.2)	4 (3.2)	0.54
Blood pressure increased	0 (0.0)	0 (0.0)	0.50
Free prostate-specific antigen increased	4 (3.2)	4 (3.2)	0.54
Musculoskeletal and connective tissue disorders			
At least one event	0 (0.0)	1 (0.8)	0.50
Chronic injury of the medial meniscus	0 (0.0)	1 (0.8)	0.50
Nervous system disorders			
At least one event	1 (0.8)	5* (4.0)	0.12
Headache	1 (0.8)	6 (4.8)	0.07
Respiratory, thoracic and mediastinal disorders			
At least one event	3 (2.4)	0 (0.0)	0.25
Vasomotor rhinitis	1 (0.8)	0 (0.0)	1.00
Throat irritation	1 (0.8)	0 (0.0)	1.00
Cough	1 (0.8)	0 (0.0)	1.00
Skin and subcutaneous tissue disorders			
At least one event	0 (0.0)	1 (0.8)	0.50
Contact dermatitis	0 (0.0)	1 (0.8)	0.50
Vascular disorders			
At least one event	3 (2.4)	1 (0.8)	0.62
Hypertensive crisis	2 (1.6)	1 (0.8)	0.54
Haemorrhoids	1 (0.8)	0 (0.0)	1.00

The results are presented as n (%). AE – adverse event; SOC – system-organ-class in accordance with Medical Dictionary for Regulatory Activities (MedDRA). *Differences in the number of patients with at least one AE and the total number of AEs in the group are due to the fact that in some patients there were 2, 3 or 4 AE registered. **In 1 patient from the Placebo group PSA was increased twice (after 6 and 12 months of therapy), but the investigator recorded this as 1 AE.

Total sum of risk factors for benign prostatic hyperplasia progression

In patients of the Afalaza group, the total sum of risk factors for BPH progression was reduced by -1.0 ±1.0 (95% CI -1.1 to -0.8) points after 12 months of treatment (Figure 5), which was considerably higher (p = 0.01) than in the Placebo group (-0.6 ±1.0; 95% CI -0.8 to -0.4).

Safety and tolerability

A total of 28 AEs in 25 (20.0%) patients of the Afalaza group and 35 AEs in 29 (23.4%) patients of the Placebo group were reported during the 12 months of treatment, without significant differences between the frequency of AEs related to systems-organ-classes (Table 3).

Twenty-one (75.0%) AEs in the Afalaza group were unrelated to the medication, in 1 (3.6%) the relationship was uncertain, and in 6 (21.4%) it was possible or probable including PSA increase(4 cases vs. 6 cases in placebo, p = 0.54), abdominal pain (n = 1), and herpes labialis (n = 1). In the Placebo group, relationship was absent in 26 (74.3%), uncertain in 4 (11.4%), possible or probable in 5 (14.3%) cases. A total of 75.0% AEs were mild and 25.0% AEs were moderate. The frequency of AEs relationship and severity did not differ in both groups (Tables 4, 5).

Hematology, blood chemistry, and urinalysis parameters exceeded the reference values neither at the enrollment nor at the end of the treatment.

Table 4. *Relationship between the drug and adverse events*

Relationship	Afalaza (N = 125)	Placebo (N = 124)	Statistics
Unrelated	21 (75.0)	26 (74.3)	
Uncertain	1 (3.6)	4 (11.4)	
Possible	3 (10.7)	1 (2.9)	CMH χ^2 = 0.048; p = 0.83◆
Probable	3 (10.7)	4 (11.4)	
Total	28 (100.0)	35 (100.0)	

The results are presented as n (%). ◆ CMH χ^2 – Cochran-Mantel-Haenszel χ^2 (modified for multiple comparisons)

Table 5. *Adverse events severity*

Severity	Afalaza (N = 125)	Placebo (N = 124)	Statistics
Mild	21 (75.0)	26 (74.3)	
Moderate	7 (25.0)	9 (25.7)	χ^2 = 0.004; p = 0.95▼
Total	28 (100.0)	35 (100.0)	

The results are presented as n (%).▼The results of frequency analysis (χ^2test).

The mean compliance rates in patients of Afalaza and Placebo groups were close to 100% without significant differences (p = 0.65).

There was no evidence of drug-to-drug interaction with medications administered concomitantly with Afalaza to treat comorbidities in BPH patients.

During the study ,no cases of AUR or BPH-related surgery were reported.

DISCUSSION

The 12-month Afalaza therapy improved LUTS, led to Qmax increase and TPV reduction in men with symptomatic BPH. The therapy effect manifested itself during the first three months, positive dynamics continued throughout the subsequent months and sustained until the end of 12 months. IPSS, Qmax and TPV improvement reached their maximum at the end of the therapy but did not reach a plateau. Serum PSA remained stable throughout the study.

To assess the risk of BPH progression, the proven risk factors were considered, comprising total IPSS, Qmax, TPV, and PSA level [3–7]. Afalaza therapy led to a significant reduction in total sum of BPH progression symptoms compared to placebo (p = 0.01). For 12 months of therapy none of the participants experienced AUR or conditions requiring surgery.

It may seem challenging to compare the results of this Afalaza study to any other long-term trials aimed to assess the effects of prolonged therapy on BPH-related symptoms and disease progression due to the presence of 5-ARIs and ABs as a common therapy practice [8–12]. In comparison, finasteride treatment in the 4-year PLESS study improved symptom score by 2.6 points (vs. 1.0 for placebo according to AUA-SI; p <0.001) [9]. The MTOPS study [11] showed that finasteride reduced the risk of symptomatic progression (defined as an increase in the AUA-SI ≥4 points) by 30% compared with placebo (p = 0.016).

5-ARIs exert an antiandrogenic effect by inhibiting the conversion of testosterone to dihydrotestosterone which leads to a decreased protein synthesis and prostate tissue involution. Afalaza has a completely different mechanism of action. Pharmacological activity of the medicine is associated with modulating effects [17, 18] on the PSA and eNOS via modification of its conformation. PSA is shown to stimulate reactive oxygen species generation in LNCaP, PC3 and DU145 cells [26]. PSA suppresses the growth and migration of endothelial cells by inhibiting endothelial cell response to the fibroblast growth factor 2 and vascular endothelial growth factor. They have the ability to cleave plasminogen, causing the release of biologically active angiostatin-like fragments and

can essentially slow the progression of the disease through this antiangiogenic activity [23]. eNOS is known to keep blood vessels dilated, control blood pressure, and have numerous other vasoprotective effects [25]. RA-Abs to PSA and eNOS synergistic action is assumed to result in prostate metabolism, circulation, and proliferation balance leading to the improvement of the urinary tract function. These effects were demonstrated in vivo and in clinical trials for each particular component of Afalaza: RA-Abs to PSA (active substance of Afalaza) [27, 28] and RA-Abs to eNOS (active substance of Impaza) [29, 30]. The comparison of the study results with data of international multicenter clinical trials examining the efficacy of the combined (5-ARI+AB) or mono-component (5-ARI /AB) [7, 9–12] treatment in BPH, highlights a positive benefit-risk balance of Afalaza therapy. The effective and safe effect that Afalaza exerts on the hyperplastic prostate is realized in prostate volume reduction and BPH symptoms relief. A gradual and augmenting activity of Afalaza achieved the maximum effect after 12 months. Cumulative BPH symptoms benefit, prostate volume reduction, Qmax rising without reaching a plateau within 12 months indicate that more prolonged Afalaza use may hamper BPH progression.

The positive therapeutic results of Afalaza were combined with a high level of safety. Afalaza neither increased, nor decreased serum PSA concentration. The simultaneous use of Afalaza with drugs of various classes did not lead to incompatibility reactions. Despite more moderate benefit compared to the routinely prescribed 5ARIs and/or ABs the advantage of Afalaza is obvious due to rare frequency of AEs related to the medicine.

The absence of patients with severe LUTS, huge prostate enlargement, severe concomitant diseases, and elderly age may be considered as study limitations. Its relatively short duration and small samples size did not allow to investigate further outcomes of Afalaza monotherapy. In addition, the effects of various Afalaza combinations with drugs for the treatment of BPH and urination disorders have not been evaluated.

CONCLUSIONS

The data from this 12-month study in men with moderate LUTS/BPH at risk of progression suggests sustainable symptoms benefits of Afalaza use. They are reflected in the IPSS and BPH-related health status improvement, Qmax growth, possible decline in the prostate enlargement, and alleviation of the total sum of the risk factors for BPH progression. The conclusions were based on the proved superiority over placebo. Afalaza provides a unique balance of efficacy and safety which favorably distinguishes this drug among others used to treat LUTS/BPH. The total sum of BPH progression symptoms decrease indicates the possibility of disease control achieving with long-term Afalaza therapy. This assumption requires confirmation in the additional studies in large populations using validated methods for assessing the function and structure of the prostate and urinary tract. To compare the efficacy and safety of Afalaza with standard medication is the next phase of the clinical development program.

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