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A randomised, placebo-controlled, multicentre, Phase 2 clinical trial to evaluate the efficacy and safety of GV1001 in patients with benign prostatic hyperplasia

Kyong Tae Moon*, Tag Keun Yoo*, Se Yun Kwon†, Ji Yong Ha‡, Seok Soo Byun§, Jang Hwan Kim¶, Jae Il Chung**, Tae Hyoung Kim††, Hong Sang Moon‡‡, Sang Jae Kim§§ and Kyung Seop Lee†

*Department of Urology, Eulji General Hospital, Eulji University School of Medicine, Seoul, †Department of Urology, Dongguk University Gyeongju Hospital, Dongguk University College of Medicine, Gyeongju, ‡Department of Urology, Keimyung University School of Medicine, Daegu, §Department of Urology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, ¶Departments of Urology, Yonsei University College of Medicine, Seoul, **Department of Urology, Busan Paik Hospital, Inje University, Busan, ††Department of Urology, College of Medicine, ChungAng University, ‡‡Department of Urology, Hanyang University College of Medicine, Seoul, Korea, and §§Teloid Inc., Los Angeles, CA, USA

Objectives

To evaluate the efficacy and safety of three dosing schemes of GV1001 in patients with benign prostatic hyperplasia (BPH).

Patients and methods

Eligible patients were men aged ≥50 years, with an International Prostate Symptom Score (IPSS) of ≥13, maximum urinary flow rate (Q_{max}) of 5–15 mL/s, post-void residual urine volume (PVR) of ≤200 mL, and prostate volume of ≥30 mL. After a 4 week run-in period, patients were randomly assigned to one of three treatment schedules: Group 1, GV1001 0.4 mg, 2-week interval; Group 2, GV1001 0.56 mg, 2-week interval; Group 3, GV1001 0.56 mg, 4-week interval) or placebo (Group 4). The eligible patients were administered GV1001 or placebo, for a total of seven intradermal injections that were administered at 2-week intervals at weeks 0, 2, 4, 6, 8, 10, and 12. Treatment continued for 12 weeks, and efficacy was evaluated at weeks 4, 8, 12, 13, and 16. Safety was evaluated throughout the 16-week period. The primary efficacy variable was change from baseline (CFB) in total IPSS. Secondary endpoints were CFB in Q_{max}, PVR, prostate volume, International Index of Erectile Function score, plasma testosterone level, dihydrotestosterone level, and prostate-specific antigen level.

Results

A total of 161 patients were included (Group 1, $n = 41$; Groups 2–4, $n = 40$). Most patients (88.8%) received all planned doses of the study treatment. At week 13, a statistically significant difference in the mean CFB in IPSS was seen in GV1001 treatment Groups 1 and 2 vs the control group for the full analysis population (−3.5 [control] vs −7.2 and −6.8 in Groups 1 and 2, respectively; both $P < 0.05$). There were also statistically significant differences in CFB at weeks 8, 12, 13, and 16 in treatment Groups 1 and 2 vs control in the per-protocol population. There was a statistically significant reduction in prostate gland volume at week 16 vs control in all treatment groups (0.8 [control] vs −4.6, −2.5, and −4.2 mL in Groups 1–3, respectively; all $P < 0.05$). There were no statistically significant differences found in other secondary outcome measures. Adverse event (AE) reporting was similar across all four groups. No treatment-emergent AEs were considered to be related to the study drug.

Conclusions

The results indicate that GV1001 was effective and well tolerated, and may provide potential beneficial effects in patients with BPH. Compared with medical therapies that require daily dosing, the convenient dosing regimen of GV1001 may provide greater patient adherence. Further investigation of these observations will require large-scale clinical evaluation.

Keywords

GV1001, benign prostatic hyperplasia, intradermal injection therapy, lower urinary tract symptoms, #UroBPH

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Introduction

BPH is one of the most common diseases associated with ageing in men, resulting in LUTS that can compromise overall heath and quality of life [1]. Several population-based studies have reported the prevalence of symptomatic BPH to be 23–40% of men in their 60s and 31–56% of men in their 70s [2–4]. Although a range of treatment options are available, α-adrenergic blockers and 5α-reductase inhibitors are most commonly used [5]. Both can achieve excellent efficacy, but are associated with a variety of side-effects, such as dizziness, orthostatic hypotension, retrograde ejaculation, loss of libido, and erectile dysfunction [6]. Surgical treatment may be considered if the patient is unresponsive to medical therapy, or has BPH-associated complications such as bladder stones, recurrent urinary retention, persistent BPH-related bleeding, and diminished renal function [7]. Widely used surgical techniques include TURP, holmium laser enucleation of the prostate (HoLEP), prostate laser vaporisation, and simple prostatectomy (open, laparoscopic, or robotic) [8]. However, surgery carries the risk of postoperative complications, such as bleeding, urethral stricture, retrograde ejaculation, and incontinence [9–11]. The disadvantages and potential side-effects associated with current medical and surgical approaches mean that an outstanding need for an improved therapeutic modality remains, and identification and investigation of new approaches for the treatment of BPH are ongoing.

The investigational agent, GV1001, was first developed as a vaccine for use as active immunotherapy of cancers expressing telomerase (e.g., pancreatic cancer and prostate cancer) [12–15]. Subsequently, *in vivo* studies have demonstrated efficacy in alleviating BPH symptoms by reducing the size of the prostate gland. Based on these findings, GV1001 has been assessed in experimental models of BPH [16], in which the progression of BPH appeared to be halted by the addition of GV1001, with the weight of prostate glands in treated animals returning to within normal range, whereas that in untreated animals did not. Moreover, histological observations after administration of dihydrotestosterone (DHT) plus GV1001 or DHT alone revealed that the DHT-induced proliferation of the dorsal, lateral, and ventral prostate gland was suppressed by the addition of GV1001.

The mechanism of action of GV1001 has been proposed to be through its dual activity as a GnRH inhibitor and 5α-reductase inhibitor. The GnRH antagonist activity has been established by co-immunoprecipitation assay, demonstrating an interaction between GV1001 and the GnRH receptor, which was abolished by pre-treatment with anti-GnRH receptor antibody [15]. In addition, a reporter assay exploiting the cyclic adenosine monophosphate responsive element (a deoxyribonucleic acid motif regulated upon GnRH receptor activation) demonstrated a GV1001-specific response. GV1001 also inhibits the expression of 5α-reductase [16]. In a model of BPH in Sprague-Dawley rats, the level of 5α-reductase mRNA decreased in rats treated with GV1001, whereas mRNA levels were upregulated in untreated rats. The upregulation was effectively attenuated by the addition of GV1001 in a dose-dependent manner. Although detailed analyses of the mechanism of action of GV1001 at the molecular level are still underway, it is considered that GV1001 acts through these two mechanisms to alleviate BPH by reducing the size of the prostate gland. As such, GV1001 has potential as an alternative treatment modality for patients with BPH.

Patients and Methods

Study Design

This was a multicentre, randomised, placebo-controlled, Phase 2 clinical study of patients with BPH. The study was conducted across eight sites in the republic of Korea between June 2015 and June 2016. The study consisted of a 4-week screening period, a 4-week run-in/washout period (during which patients received two doses of placebo), a 12-week treatment period, and an evaluation visit at week 13; finally, a close-out visit was conducted at week 16. Patients were randomised to one of four study groups, comprising three treatment groups: Group 1, GV1001 0.4 mg at 2-week intervals; Group 2, GV1001 0.56 mg at 2-week intervals; Group 3, GV1001 0.56 mg at 4-week intervals; and a placebo group (0.9% normal saline, Group 4). Patients were assigned to the study groups on a 1:1:1:1 basis. Efficacy evaluation was conducted at weeks 4, 8, 12, 13, and 16; safety evaluation was conducted throughout the 16-week period. Patients, but not investigators, were blinded to the treatment assignment throughout the study period.

Written, informed consent was obtained from all patients before screening. The clinical trial protocol and consent forms were approved and monitored by the local Institutional Review Boards at each site and by the Korean Ministry of Food and Drug Safety. An external trial monitor was enlisted to protect the rights and well-being of the participants, to verify the accuracy of the trial data, and to guarantee that the trial was conducted in compliance with the 2010 CONsolidated Standards of Reporting Trials (CONSORT) guidelines and the protocol approved according to Good Clinical Practice (GCP) guidelines.

Patient Inclusion and Exclusion Criteria

This study enrolled men with BPH aged ≥50 years. During the screening period, patients were required to meet the following criteria: prostate gland volume of >30 mL as detected by TRUS [17]; moderate-to-severe LUTS (total IPSS of ≥13); and maximum urinary flow rate (Q_{max}) of 5–15 mL/s measured when urine volume was at least 125 mL. PSA levels were required to be <10 ng/mL; biopsy testing was performed

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in patients with PSA levels 4–10 ng/mL to confirm the absence of prostate cancer. The post-void residual urine volume (PVR) was required to be ≤200 mL. Eligibility was re-examined at the randomisation visit. Exclusion criteria were as follows: hypersensitivity to any ingredients of GV1001, history or evidence of prostate cancer, previous prostatic surgery or radiation therapy, 5α-reductase inhibitor use within 6 months prior to entry, use of drugs similar to LHRH, and severe medical conditions that may affect the conduct of the study (e.g., chronic heart failure, difficult-to-control diabetes, mental disorders, drug or alcohol abuse, liver dysfunction, and kidney hypofunction).

Assessment of Outcomes

The primary efficacy variable was change from baseline (CFB) in total IPSS at weeks 4, 8, 12, 13, and 16. The secondary efficacy variables were CFB in the following variables: volume of prostate gland detected by TRUS at week 16, PSA level at weeks 13 and 16, Q_{max}, International Index of Erectile Function (IIEF), PVR, and testosterone and DHT levels at weeks 4, 8, 12, 13, and 16.

The safety variables were evaluation of adverse events (AEs), changes in clinical laboratory tests (haematology, blood biochemistry, and urine analysis), changes in body measurements and vital signs, electrocardiogram (ECG) test, and physical examination. The severity of adverse events was determined by Common Terminology Criteria for Adverse Events v.4.03. Safety was evaluated throughout the 16-week study period.

Statistical Analysis

For assessment of efficacy, the primary analysis was performed for the full analysis set (FAS) and conducted for all variables at each time point. For the primary efficacy assessment of the IPSS, one-way ANOVA was used for assessing differences amongst treatment groups at weeks 4, 8, 12, 13, and 16. If the difference amongst groups at a specific visit was statistically significant ($P < 0.05$), each of the study groups was compared with the control group using a two-sample *t*-test or Wilcoxon rank-sum test. Missing IPSSs were imputed by the last observation carried forward (LOCF) method. All safety analyses were conducted based on the safety set, which comprised all patients who received the study drug at least once after randomisation. For secondary efficacy and safety assessments, no imputation was performed for missing data.

Results

Baseline Patient Characteristics

Patient disposition is summarised in Fig. 1. After screening, 161 patients were randomised to one of the four study groups and 140 patients completed the study (completion rate, 87.0%). The reasons for study discontinuation were withdrawal of consent (16 patients), protocol deviation (three), and nondrug-related treatment-emergent AEs (TEAEs, two). The lowest study completion rate was found in the control group (77.5%), due to a higher rate of consent withdrawal (17.5%). There were no significant differences amongst the groups in baseline characteristics related to BPH (Table 1). All the study groups were well balanced allowing for 1:1:1:1 randomisation.

Primary Endpoint

IPSSs over the course of the study are summarised in Table 2. IPSSs were lower in all three of the treatment groups at 4, 8, 12, 13, and 16 weeks compared with baseline levels; sustained decreases were seen during weeks 4–13, and a trend towards a sustained decline in IPSS was seen amongst the three treatment groups.

In the FAS analysis, the IPSS CFB at week 13 was −7.2 and −6.8 in Study Groups 1 and 2, respectively. A statistically significant difference was seen between these values and CFB in the control group (−3.5; Fig. 2A). Other differences between treatment groups and the control group seen at other time points (weeks 4, 8, 12, and 16) did not reach statistical significance. In the per-protocol set (PPS) analysis (Fig. 2B), the IPSS CFB in Groups 1 and 2 vs control was statistically significant from weeks 8 to 16. In Group 3, the CFB vs control did not reach statistical significance.

Secondary Endpoints

Prostate Gland Volume

Prostate gland volume examined at week 16 showed a statistically significant decrease in all treatment groups vs control (Fig. 3A). The mean CFB in prostate gland volume was −4.6, −2.5, and −4.2 mL in Groups 1, 2 and 3, respectively.

Q_{max}

There were no statistically significant differences in mean CFB in Q_{max} between the study groups, although a notable trend towards improvement in mean CFB in Q_{max} was seen from weeks 4 to 16 in all treatment groups (Fig. 3B). At week 4, the mean CFB in Q_{max} in Study Groups 1, 2, and 3 was 2.1, 2.4, and 1.2 mL/s, respectively; by week 13, the CFB had improved to 4.40, 3.25, and 2.75 mL/s, respectively. At week 16, 4 weeks after cessation of the study drug, levels had begun to decline compared with the last visit on week 13.

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Fig. 1 Flow chart of patient disposition.

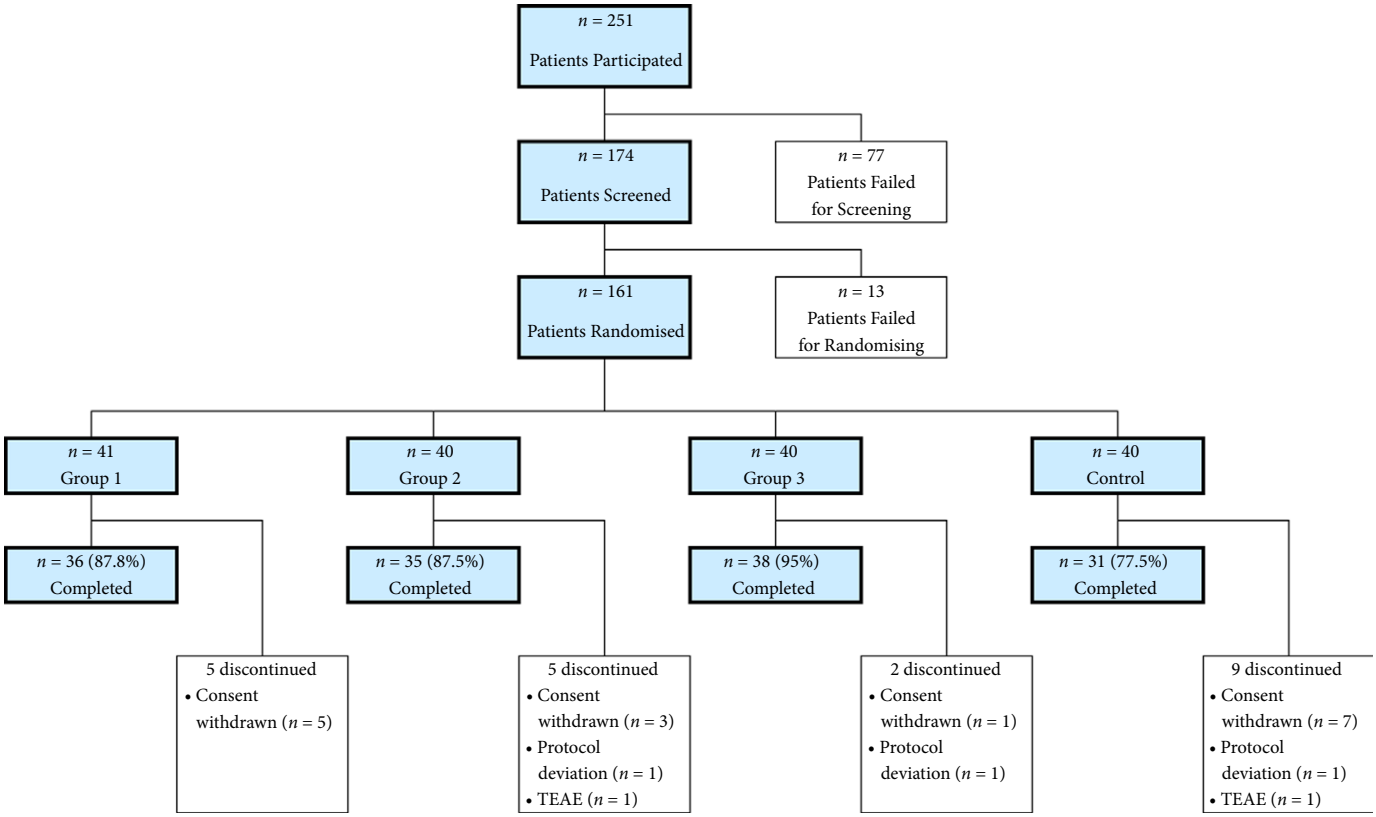

Table 1 Baseline characteristics of the PPS population*.

Variable	Group 1	Group 2	Group 3	Control
Number of patients	36	35	38	31
Mean (SD)				
Age, years	65.0 (7.5)	64.6 (9.9)	64.7 (8.8)	64.6 (8.2)
BMI, kg/m^2	25.2 (2.7)	24.5 (2.9)	24.3 (2.9)	24.8 (2.7)
IPSS	18.8 (0.9)	20.0 (0.9)	18.2 (0.6)	19.9 (0.9)
Prostate volume, mL	45.2 (2.2)	39.7 (1.9)	40.3 (2.0)	44.0 (2.5)
Q_{max}, mL/s	10.3 (0.4)	10.9 (0.4)	10.8 (0.4)	9.9 (0.5)
PVR, mL	38.3 (5.7)	42.4 (8.2)	46.3 (7.7)	43.5 (7.9)
Serum PSA level, ng/mL	1.9 (0.3)	1.8 (0.4)	1.6 (0.2)	1.7 (0.3)
IIEF score	33.9 (3.2)	24.6 (2.6)	35.5 (3.3)	29.0 (3.0)
Serum testosterone level, ng/mL	4.8 (0.3)	4.3 (0.2)	4.7 (0.2)	4.7 (0.3)
Serum DHT level, pg/mL	311.3 (30.2)	323.0 (34.4)	294.2 (46.5)	351.2 (47.3)

**There were no statistically significant differences between any of the variables and groups.*

Table 2 Change in total IPSS in the FAS and PPS groups.

		Mean (SD) IPSS					
		Baseline	4 weeks	8 weeks	12 weeks	13 weeks	16 weeks
Group 1	FAS (*n* = 41)	18.83 (0.89)	14.56 (0.99)	13.41 (0.99)	12.02 (0.92)	11.63 (1.01)	11.85 (1.00)
	PPS (*n* = 36)	19.14 (0.99)	13.97 (1.05)	12.57 (1.02)	11.31 (0.91)	10.91 (1.03)	11.23 (1.03)
Group 2	FAS (*n* = 40)	20.03 (0.88)	16.98 (1.02)	14.93 (1.13)	13.98 (1.21)	13.23 (1.17)	14.08 (1.29)
	PPS (*n* = 35)	20.35 (1.03)	16.68 (1.24)	14.48 (1.41)	13.29 (1.42)	12.77 (1.43)	13.52 (1.58)
Group 3	FAS (*n* = 40)	18.18 (0.64)	14.98 (0.96)	13.98 (1.11)	13.30 (0.95)	12.65 (1.07)	13.08 (1.24)
	PPS (*n* = 38)	17.92 (0.58)	14.35 (0.87)	13.41 (1.11)	12.76 (0.94)	12.05 (1.07)	12.51 (1.28)
Control	FAS (*n* = 40)	19.88 (0.91)	17.18 (1.06)	17.08 (1.08)	16.33 (1.09)	16.38 (1.20)	16.80 (1.25)
	PPS (*n* = 31)	19.70 (1.07)	16.54 (1.29)	17.46 (1.37)	16.36 (1.37)	16.36 (1.56)	17.07 (1.61)

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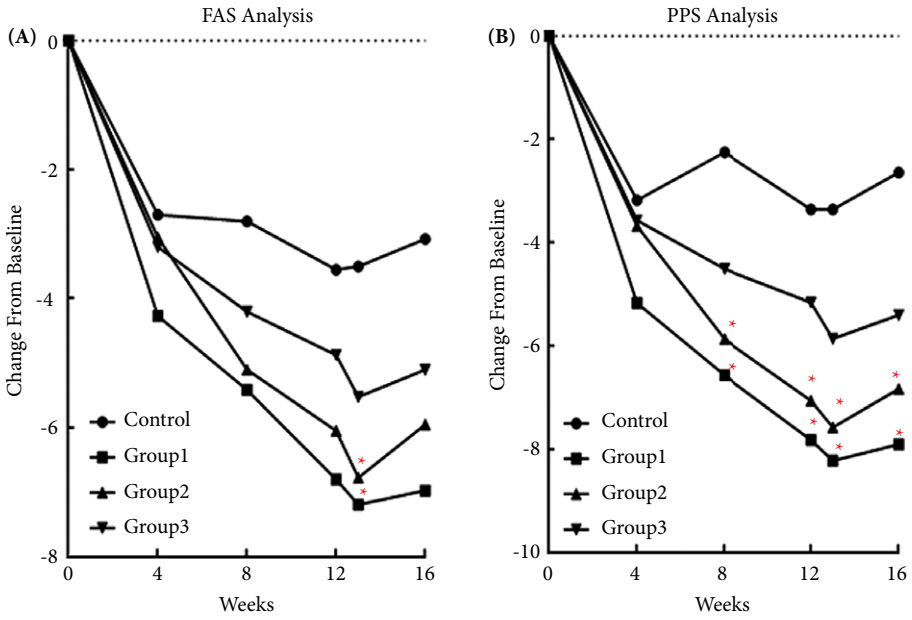
Fig. 2 IPSS CFB for all four groups: (A) FAS analysis, (B) PPS analysis. *$p < 0.05$ versus control group.



PVR

Data from weeks 4 to 16 revealed no statistically significant differences in mean CFB in PVR (Fig. 3C). However, a notable trend towards a decline was seen in all three treatment groups, particularly in Groups 2 and 3. At week 13, Group 2 showed a decline of 16.1 mL (nearly 40%) in mean PVR compared with the baseline level.

Erectile Function

The IIEF scores were slightly increased in all study groups from week 8 onwards (with the exception of Group 3 at 16 weeks), although these values did not reach statistical significance vs controls (Fig. 3D).

PSA Level

PSA levels at weeks 13 and 16 revealed no statistically significant mean CFB amongst the groups, although mean PSA levels were slightly increased in the control group and treatment Groups 2 and 3 at weeks 13 and 16 compared with baseline levels (Fig. 4A).

Testosterone and DHT

There were no significant differences in mean CFB in testosterone and DHT levels amongst the groups from weeks 4 to 16 (Fig. 4B and C).

Safety

Most patients (88.8%) received all planned study doses. The incidence of TEAEs in all patients is summarised in Table 3, showing no significant differences amongst the four groups. Most TEAEs were severity Grade 1 (20.5% of patients) and Grade 2 (5.0% of patients). Two patients had Grade 3 TEAEs, a clavicle fracture in treatment Group 2 and a dry eye in the control group, both of which were considered to not be treatment-related. No Grade 4 events were reported. None of the TEAEs were considered to be definitely or probably related to the study drug. The System Organ Classes (SOCs) with the most patients experiencing TEAEs were gastrointestinal disorders (12 patients, 7.5%), infections and infestations (12, 7.5%), and skin and subcutaneous tissue disorders (10, 6.2%). The most frequently reported TEAE by preferred term was nasopharyngitis (six patients, 3.7%), followed by toothache, urticaria, and headache (three for each, 1.9%).

With the exception of haematocrit percentage and leucocytes, haematology data showed no significant changes in any of the four study groups. For haematocrit percentage, significant changes were seen after study drug administration in four patients, but the observed fluctuations were all within the normal range. For leucocytes, a significant change was observed after study drug administration in one patient, but the fluctuations were all within the normal range. No clinically significant abnormalities were seen in blood chemistry parameters in any of the three treatment groups, whilst clinically significant abnormalities were seen in the

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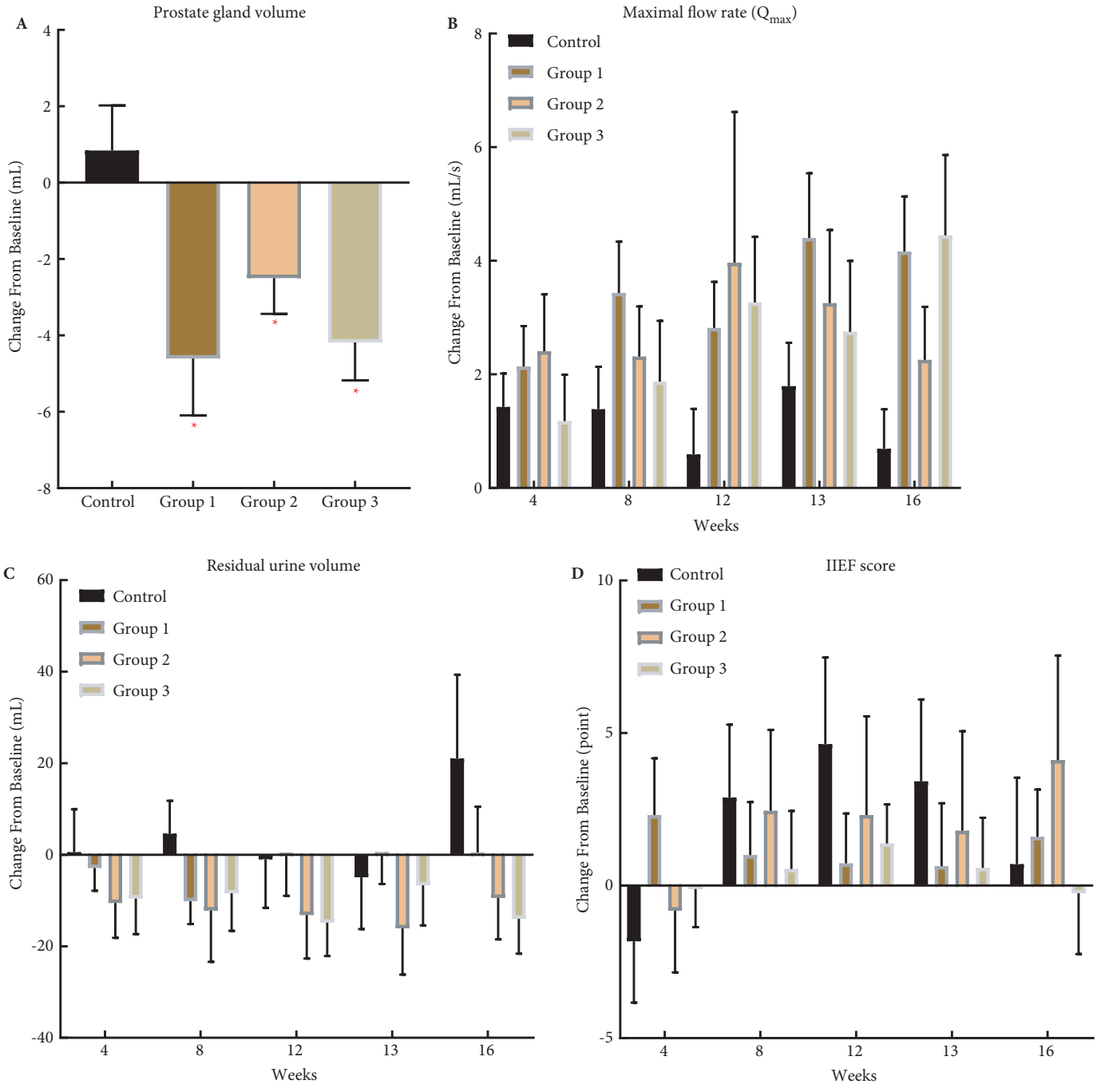
Fig. 3 CFB in all four groups for prostate gland volume (A), Q_{max} (B), PVR (C) and IIEF score (D). *$p < 0.05$ versus control group.



control group in two patients. One patient in the control group had clinically significant abnormal blood urea nitrogen and creatinine levels at week 16, and another patient in the control group had persistent clinically significant abnormal aspartate aminotransferase (AST) values from weeks 8 to 16. These two TEAEs were mild in severity and considered to definitely not be related to the study drug; patients were therefore not withdrawn from the study.

Clinically significant abnormalities in urine analysis results were seen in one patient in the control group and one patient in treatment Group 3. The one patient in the control group had a clinically significant abnormal urine glucose level at week 4. The patient had an ongoing medical history of diabetes mellitus since October 2013. This TEAE was not considered to be related to the study drug. One patient in treatment Group 3 had persistent clinically significant

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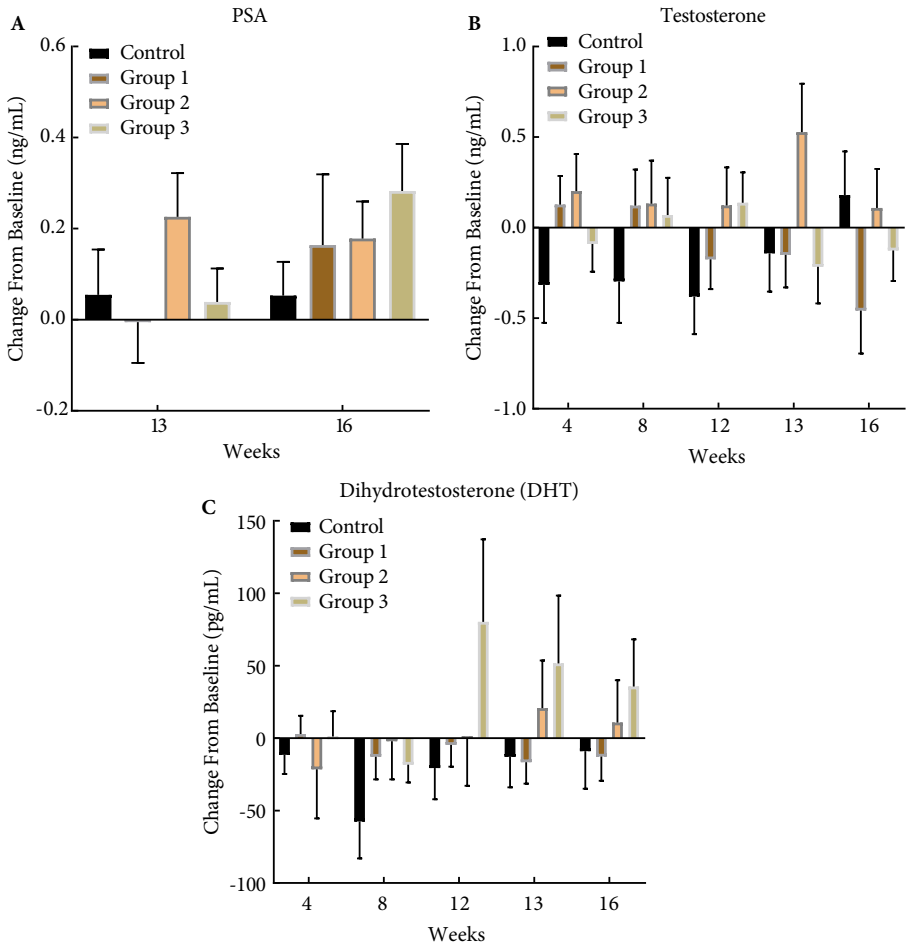
Fig. 4 CFB in all four groups for PSA level (A), testosterone level (B) and DHT level (C).



abnormal urine blood levels from weeks 8 to 16. This abnormality was reported as a mild TEAE of haematuria with an onset date of study day 57. The patient underwent a CT to identify the cause of the haematuria, and a small (3 mm) renal stone was found and considered to probably not be related to the study drug; this patient was, therefore, not withdrawn from the study.

There were no clinically significant abnormalities relating to vital signs and ECG. Clinically significant abnormal physical examination results were seen in three patients. One patient in the treatment Group 2 had mild poison ivy rash at week 12, constituting a clinically significant finding of allergy. This was also reported as a mild TEAE of contact dermatitis, which was considered to be definitely not related to the study drug. One patient in the treatment Group 3 had mild dermatitis at week 2, constituting a clinically significant finding of allergy. This was also reported as a mild TEAE, which was considered to be definitely not related to study drug. One patient in the control group had a clinically significant abnormal finding in his physical examination with regard to the abdomen; the patient was observed to have right inguinal hernia. This was reported as a moderate TEAE of hernia, which was considered to be probably not related to the study drug. The patient underwent inguinal herniorrhaphy. These three TEAEs were mild-to-moderate in severity and considered to be definitely not related to the study drug, and patients were, therefore, not withdrawn from the study.

Discussion

GV1001 was developed as an active immunotherapy for the treatment of cancer and has received marketing approval for the treatment of pancreatic cancer in South Korea. Here, we report the first clinical study of GV1001 in patients with BPH, the objective being to evaluate the efficacy and safety of different dosing regimens and schedules. At the evaluation visit (week 13), GV1001 treatment Groups 1 and 2 (doses of 0.4 or 0.56 mg at 2-week intervals) showed a statistically significant CFB in IPSS compared with the control group for the FAS population. From weeks 8 to 16, statistically

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Table 3 Incidence of TEAEs occurring in >1 patient overall: safety set population.

Systemic Organ Class Preferred term	*N* (%)				
	Group 1 (*n* = 41)	Group 2 (*n* = 40)	Group 3 (*n* = 42)	Control (*n* = 38)	Overall (*n* = 161)
Any TEAE	11 (26.8)	14 (35.0)	7 (16.7)	11 (28.9)	43 (26.7)
Gastrointestinal disorders	5 (12.2)	4 (10.0)	1 (2.4)	2 (5.3)	12 (7.5)
Toothache	2 (4.9)	1 (2.5)	0	0	3 (1.9)
Infections and infestations	4 (9.8)	4 (10.0)	2 (4.8)	2 (5.3)	12 (7.5)
Nasopharyngitis	1 (2.4)	3 (7.5)	1 (2.4)	1 (2.6)	6 (3.7)
Skin and subcutaneous tissue disorders	2 (4.9)	4 (10.0)	2 (4.8)	2 (5.3)	10 (6.2)
Urticaria	1 (2.4)	1 (2.5)	0	1 (2.6)	3 (1.9)
Nervous system disorders	0	2 (5.0)	1 (2.4)	3 (7.9)	6 (3.7)
Headache	0	1 (2.5)	0	2 (5.3)	3 (1.9)
Musculoskeletal and connective tissue disorders	1 (2.4)	3 (7.5)	1 (2.4)	0	5 (3.1)
General disorders and administration site conditions	2 (4.9)	0	0	2 (5.3)	4 (2.5)
Renal and urinary disorders	1 (2.4)	0	2 (4.8)	1 (2.6)	4 (2.5)
Haematuria	0	0	2 (4.8)	0	2 (1.2)
Respiratory, thoracic, and mediastinal disorders	0	2 (5.0)	0	1 (2.6)	3 (1.9)
Rhinorrhoea	0	2 (5.0)	0	0	2 (1.2)
Ear and labyrinth disorders	0	1 (2.5)	0	1 (2.6)	2 (1.2)
Injury, poisoning, and procedural complications	0	1 (2.5)	0	1 (2.6)	2 (1.2)

significant differences were also seen in Groups 1 and 2 vs the control Group for the PPS population. Whilst improvements in IPSS were also seen in treatment Group 3 (0.56 mg at 4-week intervals) these changes did not reach statistical significance. GV1001 treatment appeared to be well tolerated, with no significant differences in the rate of AEs between the treatment groups and controls.

Currently, α-adrenergic receptor blockers and 5α-reductase inhibitors are the conventional therapy for the treatment of BPH and are, therefore, widely used in clinical practice. There are several studies of mono- and combined therapy with α-adrenergic receptor blockers and 5α-reductase inhibitors for the treatment of BPH [18–22]. The Medical Therapy of Prostatic Symptoms (MTOPS) study evaluated mono- and combined therapy regimens with doxazosin and finasteride for BPH [21]. At 1-year follow-up, the median CFBs in IPSSs were −4.0, −6.0, and −6.0 in the finasteride monotherapy group, doxazosin monotherapy group, and combined therapy group, respectively. The Combination of Avodart and Tamsulosin (CombAT) study evaluated the clinical outcomes of dutasteride and tamsulosin for BPH [22]. In that study, the mean CFBs in IPSSs at the 3-month follow-up were −2.8, −4.5, and −4.8 with dutasteride monotherapy, tamsulosin monotherapy, and combined therapy, respectively. At 1-year follow-up, the mean CFBs in IPSSs were −4.2, −4.5, and −5.6, respectively. In the present study, improvements in IPSSs were ~30% compared with baseline in all the GV1001 treatment groups after 12 weeks, with a mean CFB in IPSSs at week 16 of −7.9, −6.8, and −5.4 in Groups 1, 2, and 3, respectively. The reduction rates in IPSS after GV1001 intradermal injection in the present study were, therefore, comparable with those in previous studies of α-adrenergic receptor blocker and 5α-reductase inhibitor combined therapy.

Most studies of 5α-reductase inhibitors demonstrated a reduction in prostate volume of ~20–30% with long-term use [18–22]. However, 5α-reductase inhibition can also suppress serum DHT, resulting in sexual side-effects that include erectile dysfunction, decreased libido, and ejaculatory disorders [19,23,24]. The results of the secondary efficacy objectives in the present study showed an overall trend towards improvement in prostate volume, Q_{max}, and PVR in all of the three GV1001 treatment groups. A reduction in the volume of the prostate gland was particularly marked, with statistically significant changes seen in each of the three GV1001 treatment groups vs controls. Regarding other secondary endpoints (IIEF, PSA level, and hormone levels) definite trends were not seen during the study period.

At week 16, a slight increase in PSA level was seen in all treatment groups, as well as in the control group, but the differences between increases in the treatment groups and the control group were not statistically significant. There was no correlation in PSA levels between the treatment groups; Group 2 and 3 showed a small increase after treatment at week 13, but Group 1 showed a decrease. There were no patients with significantly high PSA level (≥4 ng/mL or increases over baseline of >0.75 ng/mL). Elevated PSA levels are very important for BPH treatment; thus, long-term follow-up should be planned in future clinical trials and more relevant research should be conducted.

GV1001 has been proposed to act through its dual activity as a GnRH inhibitor and as a 5α-reductase inhibitor. The human GnRH receptor is a G protein-coupled receptor that

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couples exclusively with the Gq/11 family of G proteins [25]. However, the GnRH receptor also couples with the Gs family of G proteins. Gs proteins activate adenylate cyclase, leading to the production of cAMP and activation of protein kinase A [26,27]. In one study, GV1001 preferentially deactivated Gs-adenylate cyclase-cAMP signalling [15]. Therefore, it can be assumed that GV1001 can lead to a slight deterioration in function without affecting the important axis of the GnRH receptor. In addition, GV1001 may not significantly affect the hypothalamus–pituitary–gonad axis. GnRH receptors are found in prostate specimens of men with BPH [28], and GV1001 directly binds to GnRH receptors and induces apoptosis in prostate tissues. Recently, GV1001 was shown to act on prostate GnRH receptors directly and induce apoptosis in prostate tissues (internal report; Manuscript in preparation). GV1001 may also directly act on prostate GnRH receptors and increase apoptosis, resulting in the inhibition of proliferation and increases in the length of G0/1 phase through inhibition of epidermal growth factor receptor (EGFR) transduction and activation of the c-jun N-terminal kinase (JNK)/activator protein 1 (AP-1) pathway [29]. Due to these mechanisms, it would be expected that GV1001 would not significantly change the serum testosterone concentration, but would act on the prostate to mediate the BPH treatment effect.

In the BPH rat model, the mRNA level of 5α-reductase in prostate tissue was decreased after administration of GV1001, whereas its mRNA levels were increased in untreated rats. The upregulation was effectively attenuated by the addition of GV1001 in a dose-dependent manner [16]. However, in the present study, GV1001 did not decrease the serum DHT level. Based on these results, we suggest that GV1001 may decrease 5α-reductase mRNA levels in prostate tissue, but not at other sites that contain 5α-reductase. However, this hypothesis is insufficient to explain why there was no decrease in the DHT level after GV1001 administration in the present study.

GV1001 is a peptide fragment from the catalytic site of the enzyme telomerase. Telomerase has a variety of extra-telomeric functions, such as anti-inflammation, anti-oxidative, DNA damage repair, and anti-ageing functions, in addition to its inherent ability to increase telomere length [30]. There has also been much research in to the role of inflammation in BPH [31]. In the MTOPS study, 46% of 1056 patients who underwent prostate biopsy at baseline had chronic inflammation. A combination of finasteride and rofecoxib (cyclooxygenase 2 inhibitor) also leads to a rapid change in IPSS within 4 weeks [32]. GV1001 is a telomerase-mimicking small peptide derived from telomerase, and GV1001 also had been shown to have extra-telomeric functions such as anti-inflammation and anti-oxidative function [33–36]. Thus, the functions of telomerase might explain the rapid improvement in IPSS and prostate volume after administration of GV1001. Nevertheless, how GV1001 exerts its positive effect on BPH is still unclear. More basic science and clinical studies, including studies into the association between GV1001, hormone levels, and prostate tissue, will be required to resolve this issue.

The safety evaluation showed that GV1001 treatment was not associated with any safety concerns vs the control group. Most TEAEs were mild or moderate (Grade 1 and 2) in severity, and none were considered to be associated with the study treatment. There were no significant differences between the four study groups at all time-points in haematology, blood chemistry parameters, or the results of the physical examination. Likewise, there were no clinically significant abnormalities with regards to urine analysis parameters in the three treatment groups.

Conclusions

The results obtained in this Phase 2 clinical study indicate that GV1001 was effective and well-tolerated, and may provide potential beneficial effects in patients with BPH. Compared with medical therapies that require daily dosing, the convenient dosing regimen of GV1001 may provide greater patient adherence. Further evaluation of these observations will be required in large-scale clinical trials.

Conflict of Interest

None.

References

1 **Welch G, Weinger K, Barry MJ**. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. *Urology* 2002; 59: 245–50

2 **Roberts RO, Rhodes T, Panser LA et al**. Natural history of prostatism: worry and embarrassment from urinary symptoms and health care-seeking behavior. *Urology* 1994; 43: 621–8

3 **Homma Y, Kawabe K, Tsukamoto T et al**. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. *Int J Urol* 1997; 4: 40–6

4 **Andersson SO, Rashidkhani B, Karlberg L, Wolk A, Johansson JE**. Prevalence of lower urinary tract symptoms in men aged 45–79 years: a population-based study of 40 000 Swedish men. *BJU Int* 2004; 94: 327–31

5 **Shrivastava A, Gupta VB**. Various treatment options for benign prostatic hyperplasia: a current update. *J Mid-life Health* 2012; 3: 10

6 **Van Asseldonk B**. Medical therapy for benign prostatic hyperplasia: a review. *Can J Urol* 2015; 22(Suppl. 1): 7–17

7 **Nickel JC, Méndez-Probst CE, Whelan TF, Paterson RF, Razvi H**. 2010 update: guidelines for the management of benign prostatic hyperplasia. *Can Urol Assoc J* 2010; 4: 310–6

8 **Rocco B, Albo G, Ferreira RC et al**. Recent advances in the surgical treatment of benign prostatic hyperplasia. *Ther Adv Urol* 2011; 3: 263–72

9 **Ahyai SA, Gilling P, Kaplan SA et al**. Meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic enlargement. *Eur Urol* 2010; 58: 384–97

10 **Gratzke C, Schlenker B, Seitz M et al**. Complications and early postoperative outcome after open prostatectomy in patients with benign

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prostatic enlargement: results of a prospective multicenter study. *J Urol* 2007; 177: 1419–22

11 **Pokorny M**, **Novara G**, **Geurts N et al**. Robot-assisted simple prostatectomy for treatment of lower urinary tract symptoms secondary to benign prostatic enlargement: surgical technique and outcomes in a high-volume robotic centre. *Eur Urol* 2015; 68: 451–7

12 **Bernhardt S**, **Gjertsen M**, **Trachsel S et al**. Telomerase peptide vaccination of patients with non-resectable pancreatic cancer: a dose escalating phase I/II study. *Br J Cancer* 2006; 95: 1474–82

13 **Buanes T**, **Maurel J**, **Liauw W**, **Hebbar M**, **Nemunaitis J**. A randomized phase III study of gemcitabine (G) versus GV1001 in sequential combination with G in patients with unresectable and metastatic pancreatic cancer (PC). *J Clin Oncol* 2009; 27: 4601

14 **Middleton G**, **Silcocks P**, **Cox T et al**. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2014; 15: 829–40

15 **Kim JW**, **Lee MY**, **Kang KW**. Anti-prostate cancer effect of GV-1001, a novel gonadotropin-releasing hormone receptor ligand. *Int J Med Health Sci* 2015; 2: 493. https://doi.org/10.1999/1307-6892/22012

16 **Cheon JH**, **Kim HS**. Role of GV1001 on benign prostatic hyperplasia in Sprauge-Dawley rats. *Toxicol Lett* 2015; 238(Suppl.): S244. https://doi.org/10.1016/j.toxlet.2015.08.718

17 **Terris MK**, **Stamey TA**. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991; 145: 984–7

18 **Stoner E**. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. *Urology* 1994; 43: 284–94

19 **McConnell JD**, **Bruskewitz R**, **Walsh P et al**. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. *N Engl J Med* 1998; 338: 557–63

20 **Kirby RS**, **Roehrborn C**, **Boyle P et al**. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003; 61: 119–26

21 **McConnell JD**, **Roehrborn CG**, **Bautista OM et al**. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N Engl J Med* 2003; 349: 2387–98

22 **Roehrborn CG**, **Siami P**, **Barkin J et al**. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010; 57: 123–31

23 **Clark RV**, **Hermann DJ**, **Cunningham GR**, **Wilson TH**, **Morrill BB**, **Hobbs S**. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5α-reductase inhibitor. *J Clin Endocrinol Metab* 2004; 89: 2179–84

24 **Roehrborn CG**, **Boyle P**, **Nickel JC**, **Hoefner K**, **Andriole G**. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002; 60: 434–41

25 **Grosse R**, **Schmid A**, **Schoneberg T et al**. Gonadotropin-releasing hormone receptor initiates multiple signaling pathways by exclusively coupling to G(q/11) proteins. *J Biol Chem* 2000; 275: 9193–200

26 **Han XB**, **Conn PM**. The role of protein kinases A and C pathways in the regulation of mitogen-activated protein kinase activation in response to gonadotropin-releasing hormone receptor activation. *Endocrinology* 1999; 140: 2241–51

27 **Lin X**, **Conn PM**. Transcriptional activation of gonadotropin-releasing hormone (GnRH) receptor gene by GnRH and cyclic adenosine monophosphate. *Endocrinology* 1998; 139: 3896–902

28 **Bono AV**, **Salvadore M**, **Celato N**. Gonadotropin-releasing hormone receptors in prostate tissue. *Anal Quant Cytol Histol* 2002; 24: 221–7

29 **Gründker C**, **Emons G**. The role of gonadotropin-releasing hormone in cancer cell proliferation and metastasis. *Front Endocrinol (Lausanne)* 2017; 8: 187. https://doi.org/10.3389/fendo.2017.00187

30 **Ghosh A**, **Tergaonkar V**. Extra-Telomeric Roles of Telomeric Proteins. In: Bibo Li ed., *Reviews on Selected Topics of Telomere Biology*. InTech, 2012. Available at: https://www.intechopen.com/books/reviews-on-selected-topics-of-telomere-biology/extra-telomeric-roles-of-telomeric-proteins. Accessed April 2018

31 **Chughtai B**, **Lee R**, **Te A**, **Kaplan S**. Role of inflammation in benign prostatic hyperplasia. *Rev Urol* 2011; 13: 147–50

32 **Nickel JC**. Role of prostatic inflammation in the clinical presentation of benign prostatic hyperplasia. *Eur Urol Suppl* 2015; 14: e1459–63

33 **Choi J**, **Kim H**, **Kim Y et al**. The anti-inflammatory effect of GV1001 mediated by the downregulation of ENO1-induced pro-inflammatory cytokine production. *Immune Netw* 2015; 15: 291–303

34 **Ko YJ**, **Kwon KY**, **Kum KY et al**. The anti-inflammatory effect of human telomerase-derived peptide on *P. gingivalis* lipopolysaccharide-induced inflammatory cytokine production and its mechanism in human dental pulp cells. *Mediators Inflamm* 2015; 2015: 385127. https://doi.org/10.1155/2015/385127

35 **Park HH**, **Lee KY**, **Kim S et al**. Novel vaccine peptide GV1001 effectively blocks beta-amyloid toxicity by mimicking the extra-telomeric functions of human telomerase reverse transcriptase. *Neurobiol Aging* 2014; 35: 1255–74

36 **Park HH**, **Yu HJ**, **Kim S et al**. Neural stem cells injured by oxidative stress can be rejuvenated by GV1001, a novel peptide, through scavenging free radicals and enhancing survival signals. *Neurotoxicology* 2016; 55: 131–41

Correspondence: Kyung Seop Lee, Department of Urology, Dongguk University Gyeongju Hospital, Dongguk University College of Medicine, 87 Dongdae-ro, Gyeongju 780-350, Korea.

e-mail: ksleemd@dongguk.ac.kr

Abbreviations: (TE)AE, (treatment-emergent) adverse event; CFB, change from baseline; DHT, dihydrotestosterone; ECG, electrocardiogram; FAS, full analysis set; IIEF, International Index of Erectile Function; MTOPS, Medical Therapy of Prostatic Symptoms (study); PPS, per-protocol set; PVR, post-void residual urine volume; Q_{max}, maximum urinary flow rate.

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