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Research Article

A randomized, active-controlled, multicenter, phase 3 clinical trial to evaluate the efficacy and safety of GV1001 in patients with benign prostatic hyperplasia

Teak Jun Shin [a,1], Ji Yong Ha [a,1], Se Yun Kwon [b], Dong Jin Park [b], Jang Hwan Kim [c], Sung Won Lee [d], In Gab Jeong [e], Ji Youl Lee [f], Tag Keun Yoo [g], Tae Hyoung Kim [h], Du Geon Moon [i], Sung Kyu Hong [j], Jin Seon Cho [k], Hong Sang Moon [l], Jeong Woo Lee [m], Seok Joong Yun [n], Youn Soo Jeon [o], Jong Gwan Park [p], Taek Won Kang [q], Ki Hak Moon [r], Jae Shin Park [s], Yoon Soo Hah [s], Tae Gyun Kwon [t], Jae Wook Chung [t], Jae Il Chung [u], Dong Soo Ryu [v], Sung Woo Park [w], Kyung Seop Lee [a,*]

[a] *Keimyung University Dongsan Hospital, Korea*
[b] *Dongguk University Gyeongju Hospital, Korea*
[c] *Severance Hospital, Korea*
[d] *Seoul Samsung Medical Center, Korea*
[e] *Seoul Asan Medical Center, Korea*
[f] *The Catholic University of Korea, Seoul ST. Mary's Hospital, Korea*
[g] *Nowon Eulji Medical Center, Eulji University, Korea*
[h] *Chung-Ang University Hospital, Korea*
[i] *Korea University Guro Hospital, Korea*
[j] *Seoul National University Bundang Hospital, Korea*
[k] *Hallym University Medical Center, Korea*
[l] *Hanyang University Medical Center, Korea*
[m] *Dongguk University Medical Center, Korea*
[n] *Chungbuk National University Hospital, Korea*
[o] *Soonchunhyang University Hospital, Korea*
[p] *Jeonbuk National University Hospital, Korea*
[q] *Chonnam National University Hospital, Korea*
[r] *Yeungnam University Medical Center, Korea*
[s] *Daegu Catholic University Medical Center, Korea*
[t] *Kyungpook National University Chilgok Hospital, Korea*
[u] *Inje University Busan Paik Hospital, Korea*
[v] *Changwon Samsung Medical Center, Korea*
[w] *Pusan National University Yangsan Hospital, Korea*

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ABSTRACT

Objectives: To determine and compare the efficacy and safety of GV1001 and 5 mg finasteride for benign prostatic hyperplasia (BPH) patients.
Patients and methods: This randomized, active-controlled, multicenter, phase 3 clinical trial enrolled 423 patients aged ≥50 years with a prostate volume (PV) >30 mL. Patients were randomized into Group 1 (GV1001 0.56 mg + finasteride placebo), Group 2 (GV1001 1.12 mg + finasteride placebo), or Group 3 (GV1001 placebo +5 mg finasteride). The patients received the study drug during clinic visits every 2 weeks at weeks 0–22. Changes in the international prostate symptom score (IPSS), PV, maximum urinary flow rate (Qmax), prostate-specific antigen (PSA) level, residual urine volume, testosterone and dihydrotestosterone (DHT) levels, and international index of erectile function (IIEF) were assessed.
Results: We included 408 (96.45%) patients (Group 1, $n = 138$; Group 2, $n = 134$; Group 3, $n = 136$) in full analysis set for primary efficacy evaluations. All groups showed significant decreases and increases in the

* Corresponding author. Department of Urology, Keimyung University School of Medicine, Dongsan hospital, 1035 Dalgubeoldae-ro, Dalseo-gu, Daegu (42601), Korea.
E-mail address: ksleemd@dsmc.or.kr (K.S. Lee).
[1] These authors contributed equally to this study and should be considered co-first authors.

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Prostate volume
Randomized controlled trial

IPSS and Qmax, respectively (Groups 1, 2, and 3, IPSS: −4.78 ± 6.50, −4.99 ± 6.66, and −5.51 ± 6.42, respectively; $P < 0.0001$; Qmax: $P = 0.0005$, $P = 0.0039$, and $P < 0.0001$, respectively). PV reductions were observed in Groups 2 and 3 (−0.75 ± 8.21 mL [$P = 0.3280$] and −2.47 ± 7.92 mL [$P = 0.0010$], respectively). The PSA and testosterone levels of Group 3 significantly decreased and changed, respectively (−0.90 ± 1.25 ng/mL, $P < 0.0001$ and $P < 0.0001$, respectively). No significant differences were observed in the residual urine volume. DHT significantly decreased in all groups (Groups 1, 2, and 3: −71.41 ± 244.06 ng/mL [$P = 0.0025$], −73.84 ± 249.26 ng/mL [$P = 0.0019$], and −106.60 ± 178.29 ng/mL [$P < 0.0001$], respectively). Only Group 3 exhibited a significantly decreased IIEF (−3.06 ± 15.34; $P = 0.0323$). Acute urinary retention occurred in one patient in Group 2. No patients underwent prostate surgery or minimally invasive procedures during the study.

Conclusions: GV1001 exhibited corresponding efficacy and tolerability, providing evidence of amelioration in urinary symptoms among patients with BPH in comparison to the use of 5 mg finasteride.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a common condition experienced by male individuals that is characterized by prostate gland enlargement and leads to lower urinary tract symptoms (LUTS).[1] The pathology of BPH involves prostate enlargement, prostatic hypertrophy, lower urinary tract irritative symptoms, and urethral obstruction.[2] Additionally, various factors contribute to the development of BPH, including the transition from smooth muscle to collagen fibers within the prostatic stroma during normal aging, muscle tissue weakening and fibrosis caused by misrepaired processes, chronic inflammation, immune inflammation, and oxidative stress. However, the specific underlying mechanisms remain not fully understood, and investigations on the multiple factors influencing the occurrence and progression of BPH are ongoing.[3–5]

The two main treatment modalities for BPH are medical therapy and surgical intervention. For cases of severe or impaired renal function, surgical procedures such as transurethral resection or holmium laser enucleation of the prostate or simple prostatectomy may be performed. Although these surgical interventions are highly effective for improving urinary symptoms, they can lead to surgical complications such as postoperative bleeding, urethral stricture, retrograde ejaculation, and urinary incontinence.[6–8]

Medical therapy, such as antiandrogens, alpha-blockers, and 5-alpha-reductase inhibitors (5-ARIs), is primarily used for patients with mild-to-moderate symptoms.[9] Alpha-blockers block the alpha-adrenergic receptors, which relax the bladder outlet by maintaining tension in the sympathetic nervous system, thereby preventing urine leakage. 5-ARIs inhibit the conversion of testosterone to dihydrotestosterone (DHT) within the prostate tissue, leading to reduced prostate size.[10] Nevertheless, both medication and surgical treatments have various side effects and functional limitations.[11] Therefore, developing therapeutic agents that act rapidly and have minimal side effects is necessary.

GV1001 was initially developed as an active immunotherapy vaccine for cancers that express telomerase, such as pancreatic and prostate cancers.[12,13] However, *in vivo* studies have demonstrated its effects in reducing prostate size and alleviating BPH symptoms.[14] The mechanism of action of GV1001 has been proposed to be the dual activity of a gonadotropin-releasing hormone (GnRH) inhibitor and 5-ARI. GnRH antagonistic activity was established through the interaction between GV1001 and GnRH receptors, as demonstrated by coimmunoprecipitation assays.[12] GV1001 also inhibits the expression of 5-alpha-reductase.[14] In a BPH model using Dawley rats, GV1001 administration resulted in decreased 5-alpha-reductase mRNA levels, whereas untreated rats showed upregulated mRNA levels. Additionally, GV1001 reduced oxidative stress and chronic inflammation, which are closely associated with BPH.[15]

During a preliminary phase 2 clinical trial of GV1001 for BPH patients, the group administered GV1001 showed significantly decreased international prostate symptom scores (IPSS) compared with the control group. Furthermore, significantly reduced prostate volumes (PVs) were observed at the end of the study.[16] Considering its various functions and safety profile in previous clinical trials, GV1001 may be a novel therapeutic option for BPH. Therefore, in this study, we aim to compare the efficacy and safety of GV1001 with those of existing 5-ARI agents.

2. Patients and methods

2.1. Study design

This was a multicenter, randomized, active-controlled, phase 3 clinical study involving BPH patients. During the screening visit, the study participants voluntarily provided written consent to participate in the clinical trial. If deemed eligible for the study, then they participated in a 4-week run-in period during which they received a GV1001 placebo (administered twice at 2-week intervals) and finasteride tablets (once daily). After completion of the run-in period, the final eligibility criteria were evaluated, and eligible participants were randomly assigned to Group 1 (GV1001 0.56 mg + finasteride placebo), Group 2 (GV1001 1.12 mg + finasteride placebo), or Group 3 (GV1001 placebo + finasteride).

Group 1 participants received GV1001 0.56 mg via subcutaneous injection every 2 weeks for a total of 12 doses and finasteride placebo tablets once daily for 24 weeks. Group 2 participants received GV1001 1.12 mg via subcutaneous injection every 2 weeks for a total of 12 doses and finasteride placebo tablets once daily for 24 weeks. Group 3 participants received a GV1001 placebo via subcutaneous injection every 2 weeks for a total of 12 doses and finasteride tablets once daily for 24 weeks.

During the 24-week treatment period, the participants visited the clinic at weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 to receive the investigational drug (GV1001 or GV1001 placebo).

2.2. Patient inclusion and exclusion criteria

The study enrolled men aged 50 years or older with a PV >30 mL, IPSS of 13 or more, and maximum urinary flow rate of 5–15 mL/s when the urine volume was at least 125 mL. Participants had a prostate-specific antigen (PSA) level <10 ng/mL (except when the PSA level was 4–10 ng/mL, and prostate cancer was ruled out

through biopsy) and residual urine volume ≤200 mL and did not use any medication that could affect BPH symptoms during the study period.

The exclusion criteria were patients with hypersensitivity to GV1001, a history of receiving luteinizing hormone-releasing hormone analogs within the past 6 months, coexisting conditions that could affect the LUTS evaluation (such as neurogenic bladder, urethral stricture, acute/chronic prostatitis, urinary tract infection, and bladder cancer), who received alpha-blockers within 2 weeks before screening or 5-ARI and antiandrogen therapy within the past 6 months, who underwent surgery or radiation therapy for the prostate, bladder, or pelvic area, or who underwent surgical treatment for BPH. Patients with serious medical conditions such as chronic heart failure, uncontrolled diabetes, mental disorders, substance or alcohol abuse, or severe liver or renal dysfunction were also excluded.

2.3. Outcome assessment

Efficacy assessments were performed during visits at 0, 4, 8, 12, 16, 20, and 24 weeks. The primary efficacy variable was the change in IPSS at 24 weeks compared with that at baseline. The secondary efficacy variables included changes in IPSS at 4, 8, 12, 16, and 20 weeks and PV, maximum urinary flow rate (Qmax), PSA levels, and residual urine volume at 12 and 24 weeks compared with those at baseline. Additionally, changes in testosterone and DHT levels at 4, 8, 12, 16, 20, and 24 weeks and changes in the international index of erectile function (IIEF) were included as secondary efficacy variables.

Safety variables included adverse events, changes in laboratory test results (hematology, blood chemistry, and urinalysis), changes in physical measurements and vital signs, electrocardiogram evaluation results, and physical examination results. The severity of adverse events was determined according to the Common Terminology Criteria for Adverse Events version 4.03. Safety was evaluated over the 24-week study period.

2.4. Statistical analysis

An efficacy analysis of the full analysis set and per-protocol set was performed, and a safety analysis of the safety set was performed. The primary efficacy evaluation focused on changes in the IPSS. Paired t tests or Wilcoxon signed-rank tests were conducted to assess within-group changes of each treatment group. Two-sample t tests or Wilcoxon rank-sum tests were performed to compare the different dosages of the investigational and control groups.

For the secondary efficacy evaluations, we used paired t tests to examine changes in the evaluation variables within each treatment group. Similarly, two-sample t tests were conducted to compare each dose of the investigational and control groups. All safety analyses included participants randomly assigned to receive the investigational medicinal product at least once during the clinical trial.

3. Results

3.1. Baseline patient characteristics

Patient enrollment is shown in Fig. 1. In total, 704 participants from 23 clinical trial centers underwent screening after providing written consent. Of these, 281 were excluded during the screening process for the following reasons: inappropriate selection/exclusion criteria (230 men); withdrawal of consent by the participant (45 men); failed tracking observation (1 man); and other reasons (5 men). Finally, 423 participants we included, and 143, 140, and 140 were assigned to Groups 1 (test group), 2 (test group), and 3 (control group), respectively. The numbers of participants who completed the study were 126, 127, and 129 in Groups 1, 2, and 3, respectively. Three men and one man in groups 1 and 3, respectively, had to discontinue the study because of significant adverse reactions.

The average age (±standard deviation [SD]) of the study participants was 66.50 years (±7.23 years). The average body mass index (±SD) was 24.81 kg/m^2 (±2.79 kg/m^2). The mean duration of BPH (duration of disease, ±SD) was 50.40 months (±54.83 months). No significant differences were observed among the groups regarding basic characteristics related to BPH (Table 1).

3.2. Primary endpoint

During the study of the full analysis set, the average change in IPSS over 24 weeks significantly reduced compared with that at baseline in all groups. The mean changes were −4.78 (±6.50 points), −4.99 (±6.66 points), and −5.51 points (±6.42 points) in Groups 1, 2, and 3, respectively (Table 2). Additionally, there was no

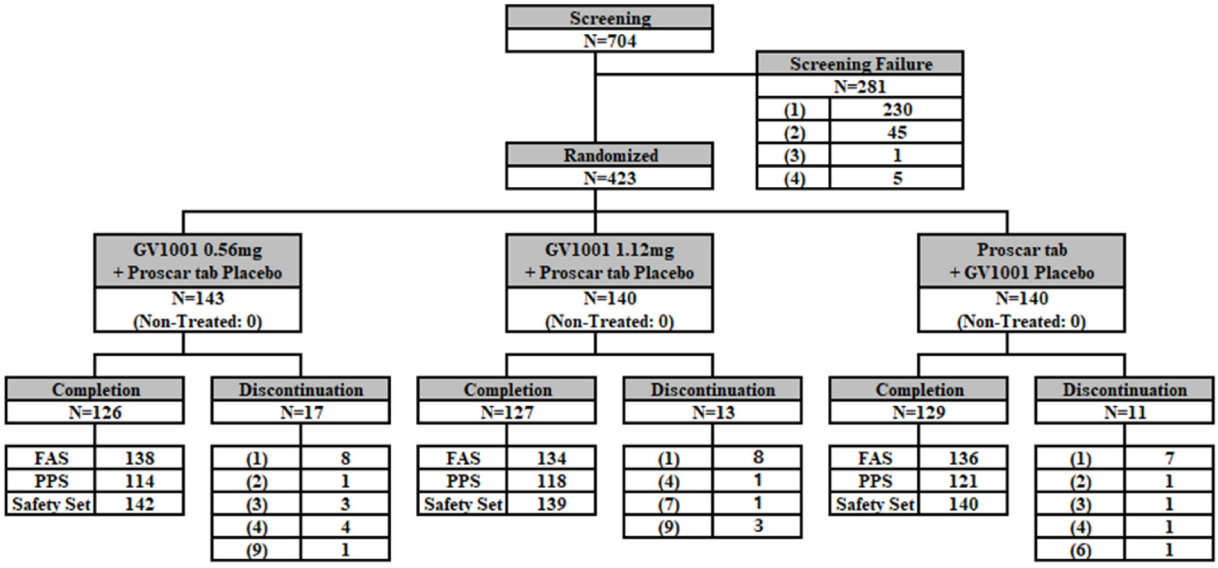

Figure 1. Flow chart of the study patients.

Table 1
Baseline characteristics of the full analysis set

Variable	GV1001 0.56 mg + Proscar tab placebo (n = 138)	GV1001 1.12 mg + Proscar tab placebo (n = 134)	Proscar tab + GV1001 placebo (n = 136)	Total (N = 408)
Mean (SD)				
Age, years	66.74 (7.37)	66.33 (7.24)	66.41 (7.12)	66.50 (7.23)
P*	0.7089‡	0.9240§		
Body mass index, kg/m^2	24.79 (2.75)	24.62 (2.77)	25.02 (2.86)	24.81 (2.79)
P*	0.4978‡	0.2443§		
Duration of disease, months	47.39 (56.71)	52.74 (53.23)	51.16 (54.69)	50.40 (54.83)
P-value*	0.5756‡	0.8099§		
IPSS	19.79 (5.05)	20.60 (5.38)	19.16 (4.98)	
Prostate volume, mL	44.15 (13.97)	44.38 (16.73)	44.48 (14.72)	
Qmax, mL/s	10.33 (2.41)	10.39 (2.42)	10.66 (2.55)	
PVR, mL	47.84 (48.47)	50.28 (46.10)	45.78 (47.73)	
Serum prostate-specific antigen level, ng/mL	2.17 (1.76)	2.20 (1.81)	2.12 (1.77)	
International index of erectile function	28.82 (18.94)	31.21 (19.02)	29.91 (18.38)	
Serum testosterone level, ng/mL	4.81 (1.50)	5.18 (1.78)	4.83 (1.74)	
Serum dihydrotestosterone level, pg/mL	472.38 (260.69)	440.71 (250.09)	374.77 (182.26)	

IPSS, international prostate symptom score, PVR, postvoid residual; Qmax, maximum urinary flow rate; SD, standard deviation.
Body mass index (kg/m^2) = weight (kg)/(height (cm)/100)^2.
Duration of disease (months) = (randomization date − diagnosis date + 1) × 12/365.25.
The denominator of the percentage is the number of participants with the result in each group.
Data source: Listing 16.2.5, 16.3.4, 16.3.5, 16.3.9, 16.3.14.
* Testing for differences between GV1001 and Proscar tab (two sample t-test).
‡ Proscar tab versus GV1001 0.56 mg.
§ Proscar tab versus GV1001 1.12 mg.

significant difference in IPSS reduction between Groups 1 and 2 compared to Group 3 (Fig. S1). Similarly, during the perprotocol set analysis, the mean change in the IPSS over 24 weeks was significantly reduced compared with that at baseline in all groups. The mean changes were −4.58 (±6.53 points), −5.26 (±6.77 points), and −5.64 points (±6.62 points) in Groups 1, 2, and 3, respectively (Table S1).

3.3. Secondary endpoint

3.3.1. IPSS

The IPSS significantly decreased in all groups at various time points, including 4, 8, 12, 16, and 20 weeks, compared with that at baseline (Fig. 2). However, no significant differences were observed between Groups 1 and 2 in comparison with Group 3.

3.3.2. Prostate volume

Compared with the baseline PV, the average changes in PV at 12 and 24 weeks were −1.32 mL (±6.92 mL), −0.55 mL (±9.11 mL), and −8.14 mL (±6.87 mL) in Groups 1, 2, and 3, respectively. Groups 1 and 3 exhibited significantly decreased PV (Group 1, $P = 0.0338$; Group 2, $P = 0.5095$; Group 3, $P < 0.0001$). Compared with the baseline PV, the PV decreased by −0.75 mL (±8.21 mL), −2.47 mL (±7.92 mL), and −9.55 mL (±8.20 mL) at 24 weeks in Groups 1, 2, and 3, respectively, with Groups 2 and 3 showing significant changes compared with the baseline PV ($P = 0.0010$ and $P < 0.0001$, respectively) (Fig. 3A).

3.3.3. Maximum urinary flow rate

A significant increase in the average Qmax compared with that at baseline was observed in all groups at 12 and 24 weeks, with mean changes of 1.48 mL/sec (±4.70 mL/s; $P = 0.0006$), 1.22 mL/s (±4.77 mL/sec, $P = 0.0053$), and 2.58 mL/sec (±5.71 mL/s, $P < 0.0001$) in Groups 1, 2, and 3, respectively. Compared with the flow rate at baseline, a significant increase was observed in Group 1 at 24 weeks (1.82 ± 5.43 mL/s; $P = 0.0005$). Similarly, Groups 2 and 3 also exhibited a significant increase (1.58 ± 5.76 mL/s; $P = 0.0039$ and 2.59 ± 5.61 mL/s; $P < 0.0001$, respectively; Fig. 3B).

3.3.4. Postvoid residual

Compared with the baseline values, average changes in the residual urinary volume (mean ± SD) of each group at 12 weeks were 6.55 ± 61.97 mL, −4.87 ± 53.15 mL, and −6.73 ± 48.31 mL for Groups 1, 2, and 3, respectively. At 24 weeks, compared with the baseline values, the changes were 9.46 ± 57.27 mL, −0.39 ± 51.46 mL, and 1.89 ± 60.59 mL for Groups 1, 2, and 3, respectively. At any time point, no significant differences were observed within each group, and Groups 1 and 2 showed no significant differences when compared with Group 3 (Fig. 3C).

3.3.5. PSA level

Compared with the baseline values, the average changes in the PSA levels of each group at 12 weeks were −0.03 ± 0.74 ng/mL, 0.03 ± 0.85 ng/mL, and −0.81 ± 1.18 ng/mL for Groups 1, 2, and 3, respectively; a significant decrease was only observed in Group 3 (Groups 1, 2, and 3: $P = 0.6853$, $P = 0.7095$, $P < 0.0001$, respectively). Compared with Group 3, the average changes significantly differed in both Groups 1 and 2 (0.78 ng/mL and 0.84 ng/mL, respectively; all $P < 0.0001$). Compared with the baseline values, the average changes in the PSA levels in each group at 24 weeks were 0.01 ng/mL±0.65 ng/mL, 0.15 ± 1.06 ng/mL, and −0.90 ± 1.25 ng/mL in Groups 1, 2, and 3, respectively. Significant decrease was only observed in Group 3 (Groups 1, 2, and 3: $P = 0.8491$, $P = 0.1208$, $P < 0.0001$, respectively). Compared with Group 3, both Groups 1 and 2 exhibited significant differences in the average PSA level changes (0.92 ng/mL and 1.06 ng/mL, respectively; all $P < 0.0001$) (Fig. 3D).

3.3.6. Erectile function

Compared with the baseline values, a significant decrease in IIEF of Group 3 was observed at all time points (4, 8, 12, 16, 20, and 24 weeks). After 8 weeks, a significant difference between the test groups and control group was observed (Fig. 4A).

3.3.7. Testosterone and DHT

Compared with the baseline values, the testosterone levels were significantly higher in Group 3 than in Groups 1 and 2 at all time

Table 2
Changes in the international prostate symptom scores at week 24 compared with those at baseline (full analysis set)

	GV1001 0.56 mg + Proscar tab placebo (n = 138)	GV1001 1.12 mg + Proscar tab placebo (n = 134)	Proscar tab + GV1001 placebo (n = 136)
Baseline			
n	138	134	136
Mean (SD)	19.79 (5.05)	20.60 (5.38)	19.16 (4.98)
Median	19.00	19.00	18.00
Min, max	13.00, 33.00	13.00, 34.00	13.00, 33.00
Week 24			
n	138	134	136
Mean (SD)	15.01 (7.41)	15.60 (7.97)	13.65 (6.97)
Median	14.00	16.00	12.50
Min, max	2.00, 33.00	0.00, 35.00	0.00, 31.00
Change at week 24 compared with baseline			
n	138	134	136
Mean (SD)	−4.78 (6.50)	−4.99 (6.66)	−5.51 (6.42)
Median	−5.00	−5.00	−6.00
Min, max	−21.00, 9.00	−23.00, 13.00	−33.00, 15.00
P*	<0.0001 (t)	<0.0001 (t)	<0.0001 (w)
Mean difference (SD)	0.74 (6.46)	0.52 (6.54)	
95% CI for the mean difference	[-0.80, 2.28]	[-1.05, 2.09]	
P†	0.3784 (w)	0.5563 (w)	
Superiority‡	No	No	

CI, confidence interval; Max, maximum; Min, minimum; SD, standard deviation.
Data source: Listing 16.2.10, 16.3.26, 16.3.27.
* Testing for changes within the treatment group (paired t-test [t] or Wilcoxon signed-rank test [w]).
† Testing for differences between GV1001 and Proscar tab (two-sample t test [t] or Wilcoxon rank-sum test [w]).
‡ Hochberg's step-up procedure. If $p(2) \leq 0.05$, then both treatment groups are superior to the placebo. However, if $p(2) > 0.05$ and $p(1) \leq 0.025$, then the treatment group associated with $p(1)$ is superior to the placebo, where $p(1) \leq p(2)$.

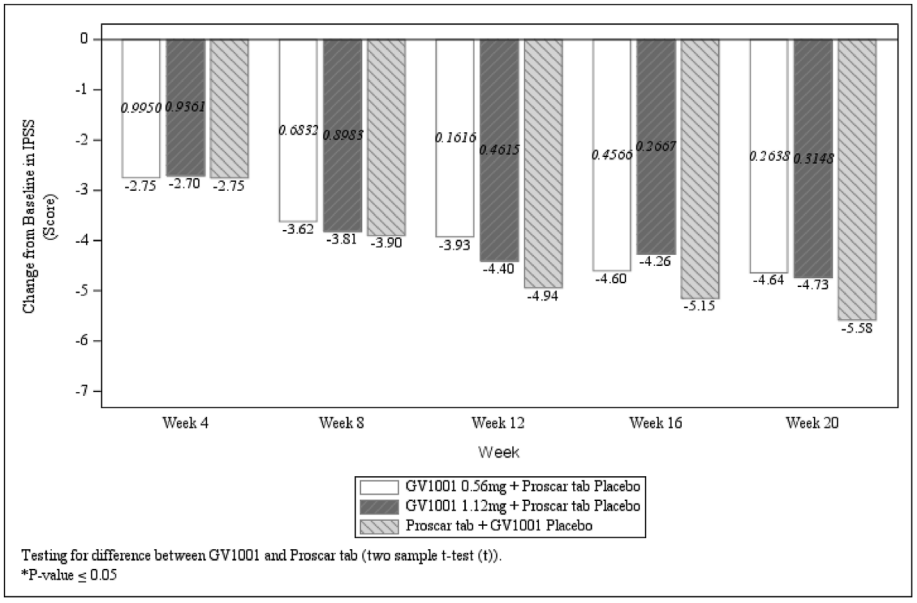

Figure 2. Changes in the international prostate symptom scores (IPSS) compared with those at baseline (full analysis set).

points (Fig. 4B). The DHT level significantly differed in Group 2 than in Group 3 at 4, 8, and 20 weeks; however, no significant differences were observed at 12, 16, and 24 weeks (Fig. 4C).

3.4. Safety

During the clinical trial period, 164 treatment-emergent adverse events (TEAEs) were reported in 102 of the 421 participants (24.23%). Among the TEAEs, 76 occurred in 37 of 142 participants (26.06%) in Group 1, 40 occurred in 26 of 139 participants (18.71%) in Group 2, and 48 occurred in 39 of 140 participants (27.86%) in Group 3. A total of 14 serious TEAEs were reported in 13 individuals (3.09%): 8 occurred in 8 participants (5.63%). In Group 1, 4 occurred in 3 participants (2.16%) in Group 2, and 2 occurred in 2 individuals (1.43%) in the Group 3. A total of six adverse events resulted in the discontinuation of the investigational drug in five participants (1.19%). Of the events, three (2.11%), two (0.72%), and one (0.71%) occurred in Groups 1, 2, and 3, respectively. No deaths were caused by these adverse events (Table 3).

Regarding TEAEs, based on the standard of care criteria, gastrointestinal disorders had the highest frequency, with 23 cases in 18 individuals (4.28%). The second most frequent was nervous

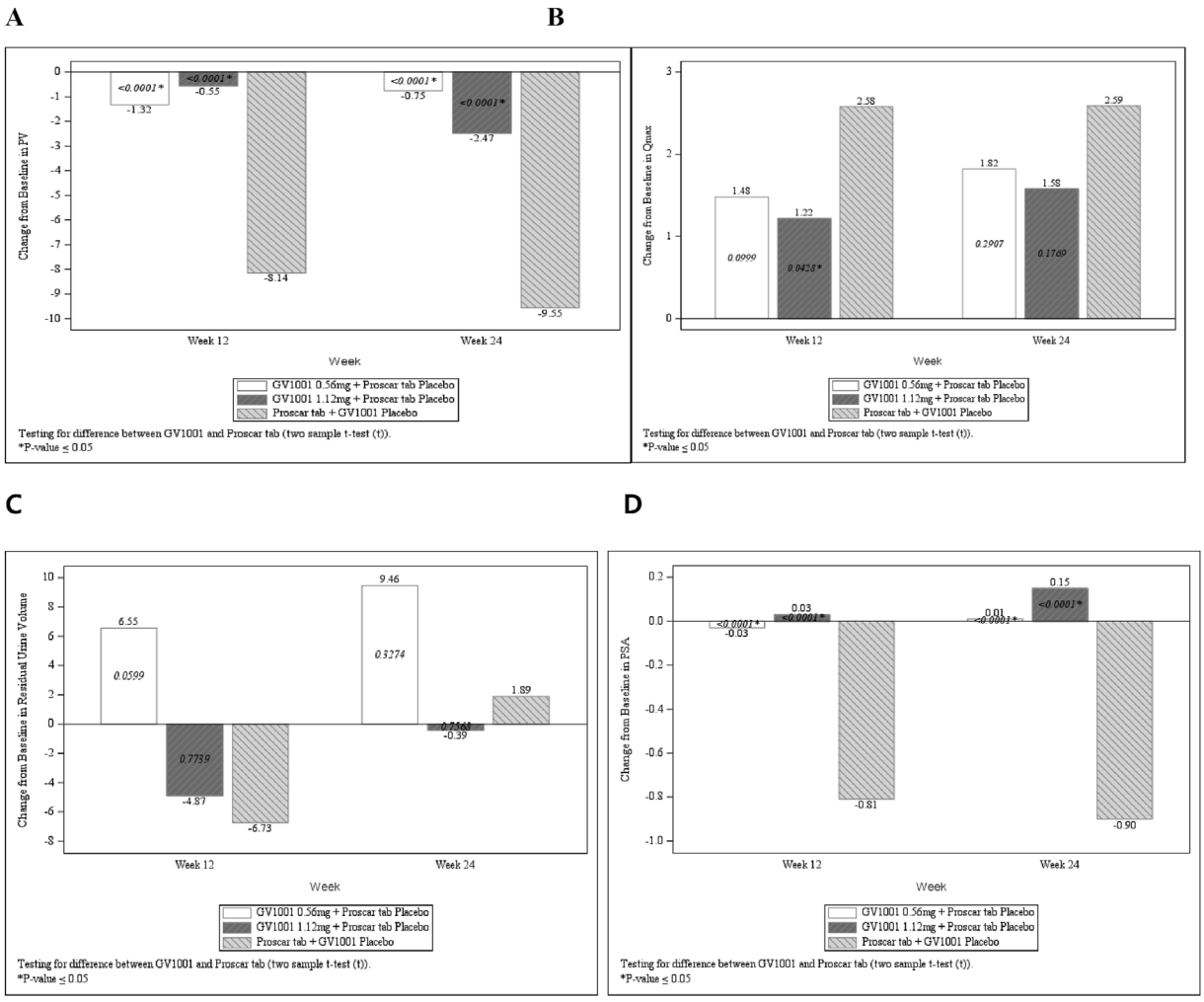

Figure 3. Changes from baseline in the prostate volume (PV) (A), maximum urinary flow rate (Qmax) (B), postvoid residual (PVR) (C), and prostate-specific antigen (PSA) (D) at week 12 and week 24 (full analysis set).

system disorders, with 20 cases occurring in 18 individuals (4.28%), followed by 14 cases of musculoskeletal and connective tissue disorders in 14 individuals (3.33%). In Group 1, the most prevalent adverse event category was nervous system disorders (7 cases in 7 individuals; 4.93%), followed by gastrointestinal disorders (11 cases in 6 individuals; 4.23%) and musculoskeletal and connective tissue disorders and infections and infestations (5 cases in 5 individuals; 3.52%; for each category). In Group 2, infections and infestations comprised the highest number of cases (six cases in five individuals; 3.60%), followed by gastrointestinal disorders (five cases in five individuals; 3.60%) and nervous system disorders (five cases in three individuals; 2.16%). In Group 3, nervous system disorders and musculoskeletal, and connective tissue disorders were the most common (eight cases in eight individuals; 5.71%; for each category), followed by gastrointestinal disorders (seven cases in seven individuals; 5.0%).

Regarding the incidence rate of severe TEAEs classified by the standard of care, three cases (2.11%) of benign, malignant, and unspecified neoplasms (including cysts and polyps) were observed in Group 1; when classified based on PT, one case (0.7%) of hepatocellular carcinoma was observed. In Group 2, the incidences of severe TEAEs according to the standard of care were one case (0.72%) of gastrointestinal disorders and one case (0.72%) of renal and urinary disorders. According to PT, the incidences were as follows: one case (0.72%) of inguinal hernia and one case (0.72%) of urinary retention. No severe TEAEs were observed in group 3.

4. Discussion

In this phase 3 randomized clinical trial, we found that GV1001 can improve LUTS in BPH patients. However, GV1001 did not result in a significant PV reduction. GV1001 is a peptide fragment derived from the catalytic site of telomerase. In addition to its inherent ability to increase telomere length, telomerase possesses antiinflammatory, antioxidant, DNA damage repair, and antiaging effects.[17] Furthermore, it has proven anticancer effects and has received approval to be marketed for the treatment of pancreatic cancer. Based on its documented antioxidant and antifibrotic effects, we hypothesized that GV1001 could be effective for the treatment of BPH.

During our preclinical study using a testosterone-induced BPH animal model, GV1001 significantly decreased the prostate weight and prostatic index through the inhibition of 5-alpha-reductase activity, which is a critical enzyme that converts some testosterone to DHT.[15] Additionally, following an antiproliferative effect on prostatic cells, GV1001 interacts with the androgen receptor in prostatic epithelial cells and stromal cells treated with DHT.[18,19] Recently, androgen/androgen receptor signals have been

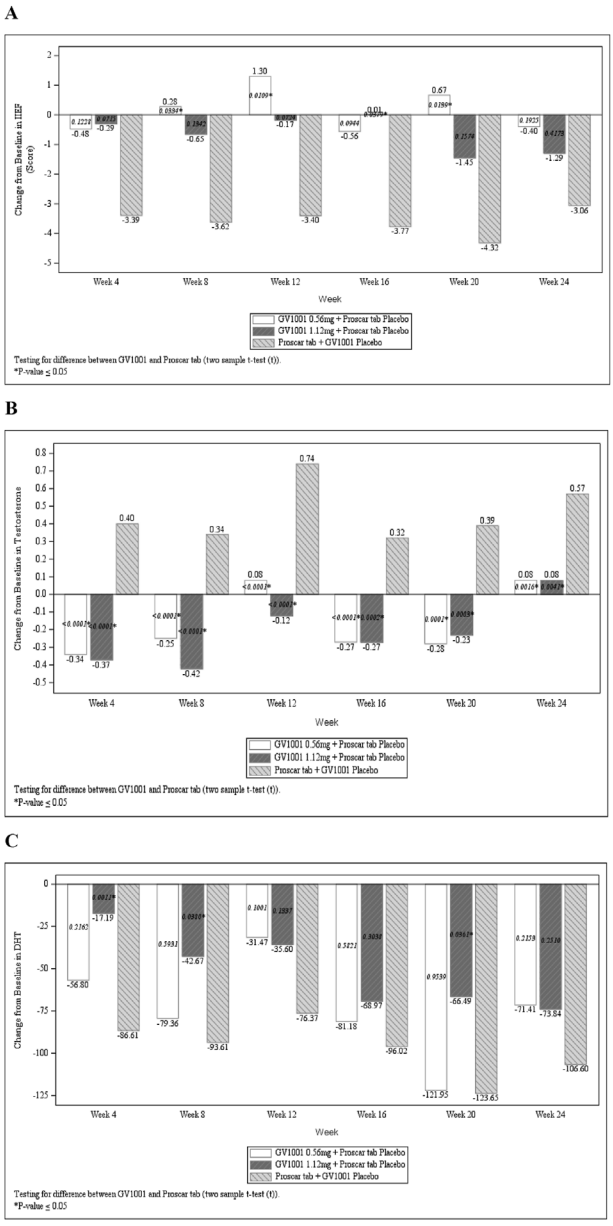

Figure 4. Changes in the international index of erectile function (IIEF) (A), testosterone level (B), and dihydrotestosterone (DHT) level (C) compared with those at baseline (full analysis set).

reported to affect the development and progression of BPH by altering the expression levels of protein markers involved in epithelial–mesenchymal transition, which has been observed clinically in BPH patients.[20,21] In general, transforming growth factor-β, produced by the androgen/androgen receptor signals, has an important role in epithelial–mesenchymal transition that accompanies fibrosis in the prostate.[22] We have found that GV1001 relieves BPH by multiple effects on prostate cells by preventing transforming growth factor-β-mediated epithelial–mesenchymal transition and fibrosis via interaction with the androgen receptor.[18] In addition to androgen receptor, GV1001 directly binds to GnRH receptors,[12,18,19] which are hypothalamic factors known to have a central role in the control of the hypothalamic–pituitary axis in mammals. Furthermore, the GnRH receptors have been found in extra-pituitary tissues, including the prostate, ovaries, placenta, and breast. GnRH antagonists inhibited cell growth by decreasing cell proliferation and increasing apoptosis in BPH animal models.[23]

Because the reported prevalence of chronic inflammation is 46% for with BPH patients,[24] GV1001, with its extra-telomeric functions such as antiinflammatory and antioxidant properties, may improve IPSS and PV.[25,26] GV1001 binds to the GnRH receptor located in the prostate tissue, demonstrating antiproliferative activity in the prostate. Coimmunoprecipitation assays confirmed the interaction between GV1001 and GnRH receptors, and animal experiments confirmed that the inhibitory effect of GV1001 binding to GnRH receptors on prostate growth is mediated by apoptosis.

Based on these findings, we planned a clinical study of GV1001 for the treatment of BPH. During a preliminary phase 2 clinical trial of GV1001 for BPH patients, a significant reduction in prostate size was observed;[16] therefore, similar results were expected during this phase 3 clinical trial. However, the degree of prostate size reduction with GV1001 was not as significant as initially anticipated, especially when compared with that resulted from 5 mg finasteride. However, IPSS improvements were observed, which was similar to that of finasteride treatment. The mean changes in the IPSS at 24 weeks compared with those at baseline were significant in all groups. Moreover, the Qmax increased at all time points compared with that at baseline value in both the test and control groups. This indicates that BPH symptoms improved significantly in all groups throughout the study period after GV1001 administration. These results inferred that although finasteride reduces prostate size and improves voiding symptoms, GV1001 improves voiding symptoms through a different mechanism.

Most studies have shown that 5-ARIs, including finasteride, reduce PV by 20%–30%.[27] However, as 5-ARIs inhibit serum DHT, it can cause sexual side effects such as erectile dysfunction and decreased libido.[28,29] In the present study, the control group exhibited a significant decrease in the IIEF, whereas the test groups did not. Therefore, GV1001 can be considered for patients concerned about the sexual function-associated side effects of finasteride. Additionally, GV1001 is advantageous because it has a similar effect on improving voiding symptoms to that of finasteride without affecting sexual function.

Similar to finasteride, 5-ARIs reduce serum PSA levels and can reduce prostate cancer risk by 24.8%. However, these patients are at higher risk for high-grade prostate cancer,[30] suggesting that finasteride may interfere with PSA levels and potentially mask prostate cancer. In contrast, GV1001 did not affect PSA levels, presenting its possibility as an alternative drug that can alleviate concerns regarding PSA changes in BPH patients with high PSA levels. Further studies on the relationship between GV1001 and prostate cancer are required to confirm this hypothesis.

During this study, adverse drug reactions occurred in 9 participants with 33 events in Group 1, 6 participants with 8 events in Group 2, and 9 participants with 12 events in Group 3. Because 14 cases of injection site erythema and injection site hypersensitivity were reported for only 1 participant in the test Group 1, it can be inferred that the test and control groups had similar adverse drug reaction profiles. Laboratory test results indicated that one participant in the test group experienced a mild increase in gamma-glutamyl transpeptidase level at 12 and 24 weeks compared with that at baseline; however, no causal relationship with GV1001 was observed.

This study had some limitations. First, because we anticipated that urinary symptom improvement would be achieved through a reduction in PV based on a preliminary phase 2 clinical trial, a finasteride treatment group was used as the control group, and no placebo group was included. Second, the study targeted patients with large PVs and moderate-to-severe voiding symptoms; therefore, a period of tolerance to urinary symptoms to establish a

Table 3
Overall summary of TEAEs (safety set)

	GV1001 0.56 mg + Proscar tab placebo ($n = 142$)	GV1001 1.12 mg + Proscar tab placebo ($n = 139$)	Proscar tab + GV1001 placebo ($n = 140$)	Total ($N = 421$)
Participants with TEAEs	37 (26.06) [76]	26 (18.71) [40]	39 (27.86) [48]	102 (24.23) [164]
95% CI	[18.84, 33.28]	[12.22, 25.19]	[20.43, 35.28]	[20.14, 28.32]
P*				0.1676 (c)
Participants with serious TEAEs	8 (5.63) [8]	3 (2.16) [4]	2 (1.43) [2]	13 (3.09) [14]
Exact 95% CI	[2.46, 10.80]	[0.45, 6.18]	[0.17, 5.07]	[1.65, 5.22]
P*				0.1545 (f)
Participants with TEAEs leading to permanent drug discontinuation	3 (2.11) [3]	1 (0.72) [2]	1 (0.71) [1]	5 (1.19) [6]
Exact 95% CI	[0.44, 6.05]	[0.02, 3.94]	[0.02, 3.92]	[0.39, 2.75]
P*				0.6261 (f)
Participants with TEAEs leading to death	0	0	0	0
Exact 95% CI	[0.00, 2.56]	[0.00, 2.62]	[0.00, 2.60]	[0.00, 0.87]
P*				-

CI, confidence interval; TEAEs, treatment-emergent adverse events.
The denominator of the percentage is the number of participants in each group.
TEAEs are displayed as the number of participants (percentage of participants) [number of events].
Data source: Listing 16.2.21, 16.3.49, 16.3.50.
* Testing among treatment groups (chi-square test [c] or Fisher's exact test [f]).

window period was required. This limitation arose from the nature of the clinical trial and may have contributed to the initially high dropout rates. Therefore, some differences between the study results and actual clinical practice are expected.

In conclusion, GV1001 demonstrated improvement in LUTS comparable to that achieved with 5 mg finasteride without causing sexual dysfunction or affecting PSA levels. However, GV1001 did not result in a significant reduction in PV. Additionally, no notable safety concerns were identified, indicating that GV1001 could provide safe and beneficial effects for BPH patients. Furthermore, because its administration is convenient, and daily intake is not required, GV1001 could be a promising treatment option for BPH.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2024.10.001.

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