

# A double-blind, randomized, placebo- and positive-controlled phase III trial of 1% benvitimod cream in mild-to-moderate plaque psoriasis

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## Abstract

**Background:** Benvitimod cream, a novel synthetic small molecule, was effective in treating mild-to-moderate plaque psoriasis. We conducted a phase III clinical trial to assess the efficacy and safety of benvitimod cream in patients with mild-to-moderate plaque psoriasis.

**Methods:** We randomly assigned 686 patients (2:1:1) to receive 1% benvitimod cream, 0.005% calcipotriol ointment or placebo twice a day for 12 weeks. The primary efficacy end points were the percentage of patients with a 75% or greater reduction from baseline in the psoriasis area and severity index (PASI 75) score and with a score of 0 or 1 in static physician's global assessment (sPGA) at week 12.

**Results:** The results showed that 50.4% of patients in the benvitimod group achieved PASI 75, which was significantly higher than that in the calcipotriol (38.5%,  $P < 0.05$ ) and placebo (13.9%,  $P < 0.05$ ) groups. The proportion of patients achieving an sPGA score 0 or 1 was 66.3% in the benvitimod group and 63.9% in the calcipotriol group, which were both significantly higher than that in the placebo group (34%,  $P < 0.05$ ). In the long-term follow-up study, 50.8% of patients experienced recurrence. After retreatment with 1% benvitimod, 73.3% of patients achieved an sPGA score of 0 or 1 again at week 52.

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Adverse events included application site irritation, follicular papules, and contact dermatitis. No systemic adverse reactions were reported.

**Conclusion:** During this 12-week study, benvitimod cream was demonstrated with high effectiveness and safety in patients with mild-to-moderate plaque psoriasis.

**Trial Registration:** Chinese Clinical Trial Registry (ChiCTR), ChiCTR-TRC-13003259; <http://www.chictr.org.cn/showprojen.aspx?proj=6300>.

**Keywords:** Psoriasis; Benvitimod; Immune modulator; Drug discovery; 3,5-dihydroxy-4-isopropylstilbene

## Introduction

Psoriasis is a chronic inflammatory skin disease, and more than eighty percent of patients have plaque psoriasis.<sup>[1-3]</sup> The prevalence of psoriasis in different countries ranges from 0.51% to 11.43%.<sup>[4]</sup> Topical treatments, including corticosteroids and vitamin D analogs, are mostly used in patients with mild-to-moderate psoriasis.<sup>[5,6]</sup> Considering the side effects of the long-term use of vitamin D and steroids,<sup>[7-10]</sup> additional topical treatments could be useful.

Benvitimod (3,5-dihydroxy-4-isopropylstilbene, also known as tapinarof and GSK2894512, previously known as WBI-1001) is a novel synthetic small molecule originally derived from metabolites of *Photobacterium luminescens*.<sup>[11]</sup> Preliminary evidence of the efficacy of benvitimod on psoriasis has been shown in preclinical studies and in phase I and II clinical trials.<sup>[12-14]</sup> We conducted a phase III clinical trial to assess the efficacy and safety of benvitimod cream in patients with mild-to-moderate plaque psoriasis.

## Methods

### Ethical approval

The trial was approved by the Ethics Committee of People's Hospital of Peking University and was conducted in compliance with the principles of the *Declaration of Helsinki*, the standards of Good Clinical Practice (as defined by the International Conference on Harmonization), and Chinese regulatory requirements (registration number: ChiCTR-TRC-13003259). Before enrollment, written informed consent was obtained from each participant.

### Study design

This double-blind, randomized, placebo- and positive-controlled trial was conducted in 23 centers in China from February 2013 to June 2014. The study protocols are provided in the Supplementary Appendix, <http://links.lww.com/CM9/A384>.

### Patients

Eligible patients were 18 to 65 years of age with mild-to-moderate plaque psoriasis with psoriasis lesions that were less than 10% of the body surface area and a static physician's global assessment (sPGA) score of 2 or higher (on a scale of 0 to 5, with higher scores indicating more severe disease).<sup>[15]</sup> Patients were randomized in a 2:1:1 ratio to receive topical 1% benvitimod cream, 0.005% calcipotriol ointment or placebo (vehicle of benvitimod

cream) twice a day for 12 weeks. Lesions on the face, scalp, groin or genital area were not treated with the study drugs. After 12 weeks of treatment with benvitimod and an 8-week follow-up, patients who achieved an sPGA score of 0 or 1 (clear or minimal, respectively) without recurrence before week 20 were screened for a long-term follow-up study until week 52 at the discretion of the investigators and patients. In the follow-up period, patients with recurrence received 1% benvitimod retreatment until an sPGA score of 0 or 1 was achieved again or until week 52. Details of the inclusion, exclusion, exit, and recurrence criteria are provided in the Supplementary Appendix, <http://links.lww.com/CM9/A384>.

### End points and assessments

The primary efficacy end points were the percentage of patients with a 75% or greater reduction from baseline in the psoriasis area and severity index (PASI 75) score and with an sPGA score of 0 or 1 at week 12. The secondary efficacy end points were PASI score reductions from baseline of 50% or more (PASI 50) and 90% or more (PASI 90) at week 12 (details are provided in the Supplementary Appendix, <http://links.lww.com/CM9/A384>).

Safety was evaluated by monitoring adverse events (AEs), including severity of events and the relationship between AEs and study drugs or placebo, and by obtaining clinical laboratory measurements through 12 weeks.

### Statistical analysis

Details of the statistical analysis (including sample size calculation) are summarized in the Supplementary Appendix, <http://links.lww.com/CM9/A384>. Briefly, a prerequisite of significance for the statistical demonstration of superiority of benvitimod cream *vs.* placebo and non-inferiority of benvitimod cream *vs.* calcipotriol ointment had to be attained for both primary endpoints (PASI 75 and sPGA response rates).

All analyses for efficacy were performed based on the full analysis set. For the primary end points of the PASI 75 and sPGA scores, a last observation carried forward approach was applied to post baseline visits for the missing value. Per-protocol analyses were also performed for the primary efficacy end point analyses. The analysis of AEs was carried out using the safety data.

For both primary efficacy end point analyses (superiority and non-inferiority), two-sided 95% confidence intervals

**Table 1: Demographic and clinical characteristics of the 686 patients with mild-to-moderate plaque psoriasis at baseline.\***

Characteristics	Placebo (n = 173)	Benvitimod (n = 344)	Calcipotriol (n = 169)
Age (years), mean ± SD (range)	41.4 ± 12.0 (18.0–65.0)	41.8 ± 12.6 (17.0–65.0)	41.2 ± 12.5 (17.0–64.0)
Male, n (%)	110 (63.6)	215 (62.5)	104 (61.5)
Duration of psoriasis (months), median (range)	118.4 (35.5–215.3)	96.0 (27.6–197.2)	96.0 (26.2–180.0)
Percent of body surface area involved, mean ± SD	5.30 ± 2.67	5.32 ± 2.55	5.68 ± 2.70
PASI score <sup>†</sup> , mean ± SD	6.43 ± 3.29	6.34 ± 2.89	6.50 ± 2.77
sPGA score, median (range) <sup>‡</sup>	3.13 (3–5)	3.13 (2–5)	3.12 (2–5)

\* No significant differences between the placebo, benvitimod and calcipotriol groups were found in any of the listed categories. <sup>†</sup> The PASI score ranged from 0 to 72, with higher scores indicating greater severity. <sup>‡</sup> The sPGA score ranged from 0 to 5, with higher scores indicating greater severity. PASI: Psoriasis area and severity index; sPGA: Static physician's global assessment; SD: Standard deviation.

(CIs) were calculated. The two-sided 95% CIs for the difference between benvitimod cream and placebo were to exceed zero to show superiority versus placebo ( $P < 0.05$ ). Statistical significance for non-inferiority was inferred if the lower limits of the two-sided 95% CIs for the difference between benvitimod cream and calcipotriol ointment was less than the given non-inferiority margin of 15% points ( $P < 0.05$ ). The secondary efficacy variables and safety variables were analyzed using the Chi-square test. All statistical tests were two-sided with a significance ( $P$ ) level of 0.05. All statistical analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

## Results

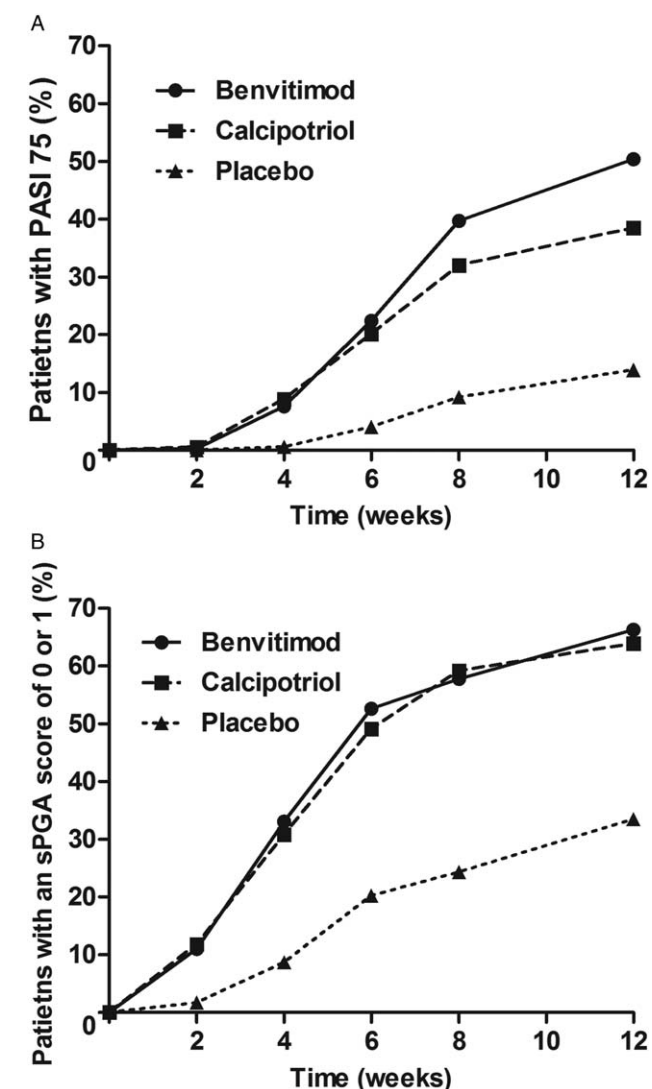
### Patient characteristics

A total of 732 patients with mild-to-moderate plaque psoriasis were screened, and 686 were randomly assigned to the 1% benvitimod cream group (344 patients), 0.005% calcipotriol ointment group (169 patients), and placebo group (173 patients) [Supplementary Figure 1, <http://links.lww.com/CM9/A384>]. The patient baseline demographic and clinical characteristics were generally similar among the three groups. The mean PASI scores were 6.43 in the benvitimod group, 6.50 in the calcipotriol group, and 6.34 in the placebo group. The mean sPGA scores were 3.13 (2–5) in the benvitimod group, 3.12 (2–5) in the calcipotriol group, and 3.13 (3–5) in the placebo group [Table 1].

### Efficacy

#### Primary efficacy end points

As shown in Figure 1, 50.4% of patients achieved PASI 75 at week 12 in the benvitimod group, which was significantly higher than that in either the calcipotriol group (38.5%,  $P < 0.05$ , 95% CI: 29.2%–43.9%) or the placebo group (13.9%,  $P < 0.05$ , 95% CI: 2.9%–21.0%). An sPGA score of 0 or 1 was achieved in 66.3% of the benvitimod group and 63.9% of the calcipotriol group, both of which were significantly higher than that in the placebo group (33.5%,  $P < 0.05$ , respectively). 95% CI of



**Figure 1:** Efficacy of benvitimod cream after 12 weeks of treatment in 686 patients with mild-to-moderate plaque psoriasis. The treatment period lasted for 12 weeks. The patients received 1% benvitimod cream (344 patients) or 0.005% calcipotriol ointment (169 patients) twice a day; a total of 173 patients received placebo. (A) The percentage of patients with a 75% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI 75). (B) The percentage of patients with a static Physician's Global Assessment (sPGA) score of 0 or 1.

**Table 2: Adverse events during the 12-week treatment period in 686 patients with mild-to-moderate plaque psoriasis, *n* (%).**

Events	Placebo ( <i>n</i> = 173)	Benvitimod ( <i>n</i> = 344)	Calcipotriol ( <i>n</i> = 169)
Adverse events	54 (31.2)	197 (57.3)	61 (36.1)
Serious adverse events*	2 (1.2)	4 (1.2)	2 (1.2)
Adverse drug reactions	35 (20.2)	153 (44.5)	33 (19.5)
Serious adverse events related to study drugs	0	2 (0.6)	1 (0.6)
Discontinuation of study regimen because of an adverse event	4 (2.3)	29 (8.4)	5 (2.9)
Selected adverse events of special interest			
Skin adverse events	36 (20.8)	166 (48.3)	35 (20.7)
Infectious adverse events	5 (2.9)	23 (6.7)	14 (8.3)
Abnormality of test	6 (3.5)	15 (4.4)	6 (3.5)
Gastrointestinal diseases	3 (1.7)	14 (4.1)	4 (2.4)
Systemic diseases	3 (1.7)	8 (2.3)	0
Nervous system diseases	2 (1.2)	6 (1.7)	2 (1.2)

\* Serious adverse events were reported in eight patients, three of which were considered to be related to the study drugs: two patients in the benvitimod group (contact dermatitis) and one patient in the calcipotriol group (deterioration of psoriasis).

the sPGA difference between benvitimod and calcipotriol groups was 24.1% to 41.4%.

### Secondary efficacy end points

PASI 50 was achieved in 67.3% of the benvitimod group and 69.8% of the calcipotriol group, both significantly higher than that in the placebo group (40.5%,  $P < 0.05$ , respectively) [Supplementary Figure 2, <http://links.lww.com/CM9/A384>]. PASI 90 was achieved in 32.6% of patients in the benvitimod group, which was significantly higher than that in the calcipotriol group (20.1%,  $P < 0.05$ ) and the placebo group (3.5%,  $P < 0.05$ ) [Supplementary Figure 3, <http://links.lww.com/CM9/A384>].

### Safety

As shown in Table 2, patients who received benvitimod had a higher rate of AEs during the treatment period than those who received calcipotriol or placebo. A total of 312 AEs were reported, of which 57.3% (197 patients) were in the benvitimod group, most of which were due to the treatment of benvitimod (153 patients). No significant differences were observed between the placebo group (31.2%) and calcipotriol group (36.1%) with respect to AEs and adverse drug reactions [Table 2].

The most common AEs were skin and subcutaneous diseases, which were found in 48.3% of patients in the benvitimod group, 20.7% in the calcipotriol group, and 20.8% in the placebo group [Supplementary Appendix, <http://links.lww.com/CM9/A384>]. Among the most common AEs, pruritus was found in 21.2% of patients in the benvitimod group, 10.1% of patients in the calcipotriol group, and 12.1% of patients in the placebo group. Contact dermatitis and folliculitis were also included as common AEs. During the follow-up period, drug-related AEs occurred in five patients (16.7%) [Supplementary Appendix, <http://links.lww.com/CM9/A384>]. In most cases, the symptoms were transient and mild. Serious AEs were found in eight patients: 4 (1.2%) in the

benvitimod group, 2 (1.2%) in the calcipotriol group, and 2 (1.2%) in the placebo group ( $P > 0.05$ ). Of these eight patients, three were considered to be related to the study drugs (two patients in the benvitimod group had contact dermatitis, and one patient in the calcipotriol group had deterioration of psoriasis). No treatment-emergent systemic AEs were found.

### Discussion

In this phase III trial, we demonstrated that benvitimod was superior to placebo with respect to all primary and major secondary end points. The results showed that the percentage of patients who achieved PASI 75 in the benvitimod group was significantly higher than that in either the calcipotriol group or placebo group. The percentage of patients who achieved an sPGA score of 0 or 1 was comparable in the benvitimod and calcipotriol groups, and both were significantly higher than that in the placebo group. In addition, 33.8% of patients who received benvitimod achieved PASI 90 at week 12, which was higher than that in the calcipotriol group (19.5%) [Supplementary Appendix, <http://links.lww.com/CM9/A384>], and calcipotriol is the standard therapeutic drug against plaque psoriasis in the clinic. After 12 weeks of treatment with benvitimod and 8 weeks of follow-up, 59 patients were screened for the long-term follow-up study [Supplementary Figure 4, <http://links.lww.com/CM9/A384>]. Among them, 29 patients had maintained resolution of psoriasis plaques until week 52. The median recurrence time was 36 weeks. Patient with recurrence gradually achieved PASI 75 and an sPGA score of 0 or 1 after retreatment with benvitimod [Supplementary Figure 5, <http://links.lww.com/CM9/A384>].

A higher frequency of irritation and itching at application sites occurred within the first 2 weeks of treatment in benvitimod-treated patients. After that, the percentage of patients with side effects decreased to less than 3% in both treatment periods. Of all reported AEs, most were mild-to-moderate and subsided spontaneously without treatment. No systemic side effects were reported.



After the development of corticosteroids in the mid-1950s and vitamin D analogs in the mid-1980s,<sup>[16]</sup> the apparent great effect of benvitimod as a new non-steroid topical treatment for patients with psoriasis is encouraging. Preliminary evidence has shown that benvitimod is a therapeutic aryl hydrocarbon receptor (AhR) modulating agent that can protect skin from pathologic processes of psoriasis by influencing cytokine production.<sup>[17-20]</sup> We first indicated the good efficacy profile in psoriasis by targeting AhR, which seems to be an attractive therapeutic target that deserves more attention.

As with any treatment, the benefits need to be weighed against the AEs, and the safety profile of longer-term treatment with benvitimod should be examined.

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### Conflicts of interest

None.

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