Supplementary Appendix

1. Inclusion criteria

Patients aged 18–65 years and older with stable psoriasis vulgaris and lesion area no more than 10% of body surface area were eligible for enrollment. Patients had mild-to-moderate disease, with an static Physician's Global Assessment (sPGA) score from 2 to 3 (the patient's psoriasis is determined as clear [0], minimal [1], mild [2], moderate [3], severe [4], or very severe [5]), and the diameter of lesions no less than 2 cm. All the participants in this trail have signed the informed consent.

2. Exclusion criteria

The criteria for patient exclusion are as follows:

A. Severe diseases of central nervous system, cardiovascular system, kidney liver digestive tract, respiratory system, metabolism, skeletal and muscular system.

B. The level of ALT or AST in serum more than 2 times than the upper limit of normal value, or the level of creatinine higher than the upper limit of normal value.

C. Diagnosed as erythroderma, pustular psoriasis, articular psoriasis or advanced psoriasis vulgaris, or psoriasis caused by drugs.

D. Pregnancy or planned pregnancy, lactation.

E. Allergic to ingredients of research drugs.

F. Participated in any clinical studies within 12 weeks before baseline visit.

G. Alcohol addicts or frequent use of herbal medicine, sedatives, hypnotics, tranquilizers and other addictive drugs.

H. History of other serious skin diseases other than psoriasis.

I. Systemic non-biologic psoriasis therapy or phototherapy (within 4 weeks of baseline), certain classes of topical psoriasis treatment (within two weeks of baseline), previous biologic therapies (within 36 weeks).

J. Patients who were not able to complete this study for other reasons, or the researchers did not consider it appropriate to participate in this study.

K. Psoriasis vulgaris with lesion area greater than 10% of body surface area.

L. Psoriasis vulgaris of face, scalp, groin, genital, palms or soles.

3. Exit criteria

The criteria for patient exit included voluntary exit, failure to use test drugs on time or in quantity, failure to follow up, new diseases or more severe psoriasis, use of prohibited drugs or therapies, pregnancy, or the researchers considered it appropriate to terminated. Results were recorded when patients terminated this trail for the above reasons. Patients who exit due to adverse events were followed up until the symptoms returned to the state before the start of this trail or reached a stable state.

4. Recurrence criteria

The recurrence of psoriasis was defined as described in the Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis (EMEA, 2005), being when the achieved maximal improvement from baseline is reduced by >50%. A more subjective definition would be a recurrence of psoriasis necessitating the re-initiation of treatment. i.e.

A. New nidus (previous application site or other site) or aggravating psoriasis (such as erythema, scale, immersion) after discontinuation of benvitimod, the patient

needs to start a new treatment (topical or systemic) for psoriasis at the sponsor's judgement.

B. Compared with the first visit in this long-term follow-up study, the decrease rate of PASI score was less than 37.5% (37.5% = 75% × 50%).

5. Restricted medications

During the course of the study, patients could only use drugs for treatment of adverse events. All concomitant treatments were recorded in the electronic case report form. The medications (or classes of medication) must not be taken before randomization and for the whole duration of the study including the follow-up period are as follows:

A. Drugs prohibited before the trial: Chinese herbal medicine or sedatives, sleeping pills, tranquilizers and other addictive drugs; systemic biological agents known to affect psoriasis (e.g. alefacept), UV phototherapy, photochemical therapy or systemic psoriasis drugs (such as systemic corticosteroids, methotrexate, tretinoin or cyclosporine); local anti psoriasis drugs (including local use of corticosteroids and vitamin D analogues).

B. Drugs prohibited during the trial: any drug known to interfere with or to aggravate psoriasis including but not limited to lithium, or phototherapy; oral or injectable psoriasis medications (not biologicals), immunosuppressive drugs (cyclosporine, methylphenytoin, etc.), any other drugs known to possibly benefit psoriasis; topical psoriasis treatments such as glucocorticoids (if necessary, desonide and hydrocortisone can be topical used for facial and groin areas) or other external treatments such as retinoids, vitamin D derivatives, vitamin A derivatives.

6. Details of Efficacy Endpoints

The primary and major secondary endpoints were collected at week 0, 1, 2, 4, 8, and 12. The severity of psoriasis is defined in part by the static Physician's Global Assessment (sPGA) by evaluation of overall lesions for induration, erythema, and scaling. The severity of psoriasis is also defined by the Psoriasis Area and Severity Index (PASI) which is a combination of the involvement of body-surface area and the intensity of redness, scaling, and plaque thickness, ultimately producing a score from 0 (for no disease) to 72 (for maximal disease).

7. Method of Random Allocation

In week 0, patients who were screened and signed the informed consent form (ICF) were randomly divided into treatment groups by using an interactive web response system (IWRS). Researchers entered the random number in the case report form of each patient.

8. Details of Statistical Analysis

A prerequisite significance of statistical demonstration of superiority of benvitimod cream versus placebo and non-inferiority of benvitimod cream versus calcipotriol ointment had to be attained for the two primary endpoints (PASI 75 response rate and PGA response rate).

We assumed a PASI 75 response rate of 50% for benvitimod cream and calcipotriol ointment, 4.8% for placebo. A sample size of 524 with a ratio of 2:1:1 for benvitimod cream, calcipotriol ointment and placebo had a power of 80% based on a two-sided significance level of 5% to detect a difference in PASI 75 response rates

between the benvitimod cream and placebo groups and test non-inferiority (non-inferiority margin of 15%) between the benvitimod cream and calcipotriol ointment groups.

A requirement of 480 subjects with a ratio of 2:1:1 for benvitimod cream, calcipotriol ointment and placebo was calculated based on 80% power and a two-sided significance level of 5% to detect a difference in PGA response rates between the benvitimod cream and placebo groups and test non-inferiority (non-inferiority margin of 15%) between the benvitimod cream and calcipotriol ointment groups, assuming a PGA response rate of 65% for benvitimod cream and calcipotriol ointment, 4.8% for placebo.

In addition, considering the minimum sample size of 300 cases that is required by official regulatory for safety observation for new drug registration in China and assuming a 20% drop-out rate, 720 patients were to be randomized in a 2:1:1 scheme (n=360 for benvitimod cream, n=180 for calcipotriol ointment and n=180 for placebo).

All analyses of efficacy were performed on the basis of the full analysis set (FAS), i.e., the intent-to-treat population restricted to the patients who had received at least one dose of treatment in each group and had at least one observation after dosing. For the primary end point of PASI 75 and PGA response, a last observation carried forward (LOCF) approach was applied to post-baseline visits for missing data. Per-protocol analyses were also performed for the primary efficacy end points analyses. Patients were assigned to the per-protocol set if they had no major protocol

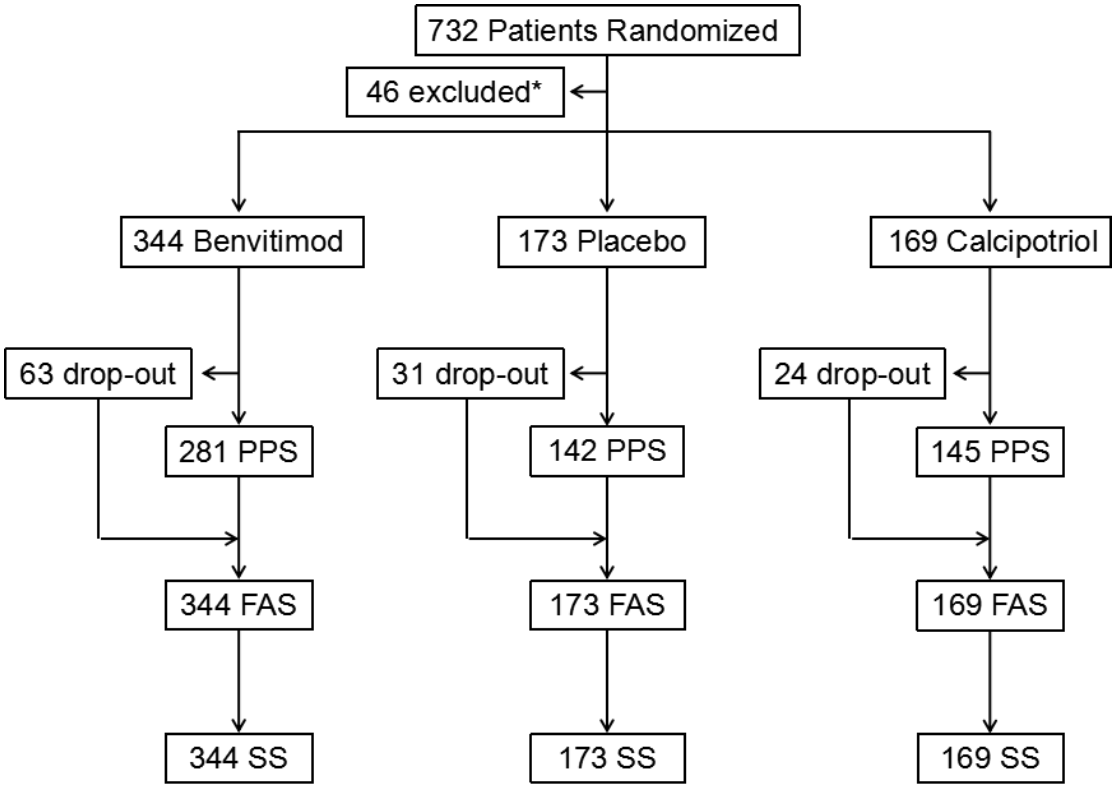
deviation affecting the primary analysis. The analysis of adverse events was carried out on the safety population, which included all patients who received at least one application of treatment in each group.

For both primary efficacy end points analyses (superiority and non-inferiority), the two sided 95% confidence intervals (CIs) were calculated. The two-sided 95% confidence limits 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 lower limits of the two-sided 95% confidence for the difference between benvitimod cream and calcipotriol ointment less than the given non-inferiority margin of 15% points (P<0.05).

The secondary efficacy variables and the safety variables were analyzed using chi-square test.

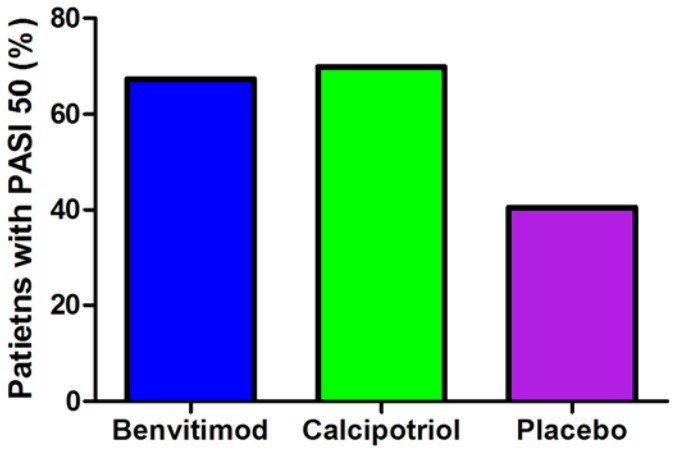
All statistical tests were two-sided with a significance (a) level of 0.05. All statistical analyses were performed with the use of SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

9.



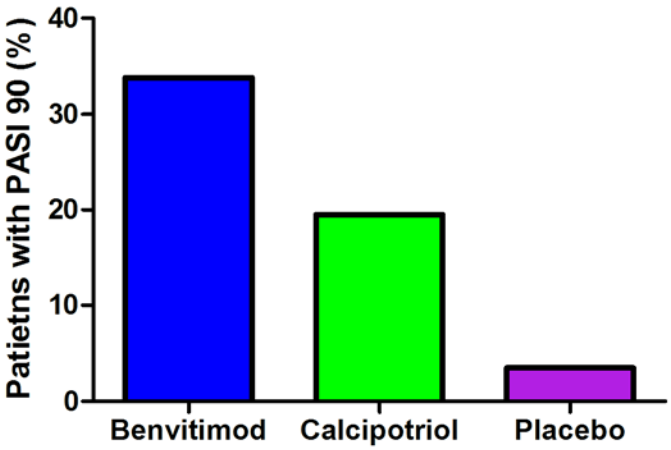
Supplementary Figure 1: Distribution of Patients in Phase 3. *Ninety-four percent of patients in one of the centers used restricted drugs, so the whole center (40 patients) was excluded and not analyzed. Six patients used benvitimod on face, were excluded and not analyzed. PPS: Per protocol set; FAS: Full analysis set; SS: Safety set.

10.



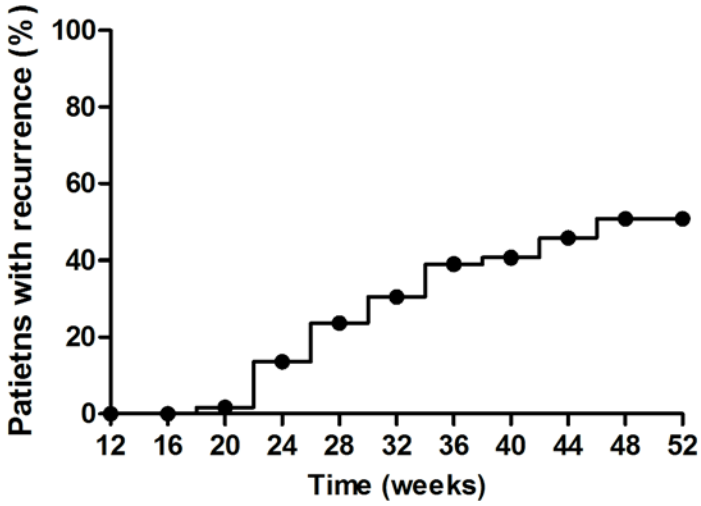
Supplementary Figure 2: PASI 50 response during weeks 0–12. Percentage of patients who achieved PASI 50 (50% reduction from baseline) at week 12. Both benvitimod and calcipotriol were significantly greater than placebo; for all comparisons, $P<0.05$.

11.



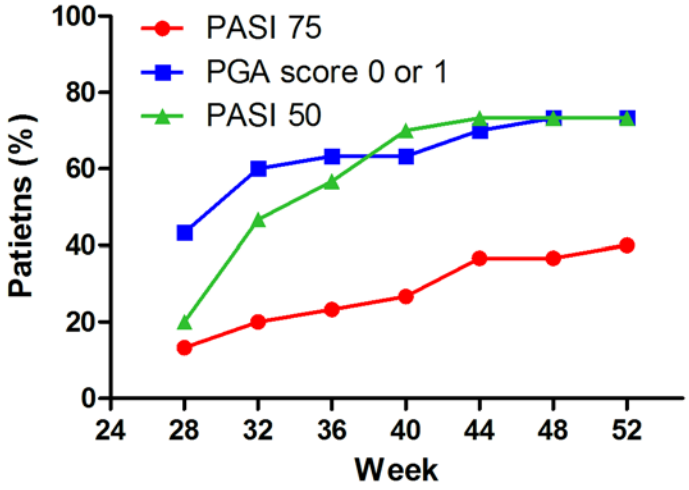
Supplementary Figure 3: PASI 90 response during week 0–12. Percentage of patients who achieved PASI 90 (90% reduction from baseline) at week 12. Benvitimod was significantly greater than calcipotriol; calcipotriol was significantly greater than placebo; for all comparisons, P <0.05.

12.



Supplementary Figure 4: Maintenance of response to benvitimod cream in a long-term follow-up study. After 12 weeks of treatment with benvitimod, 59 patients who achieved an sPGA score of 0 or 1 without recurrence before week 20 were screened for a long-term follow-up study until week 52.

13.



Supplementary Figure 5: Efficacy of benvitimod cream in patients with recurrence. Percentage of patients who achieved PASI 75, sPGA 0-1 or PASI 50. The first recurrence was found in week 24 and benvitimod was retreated in patients with recurrence.

14.

Supplementary Table 1: Details of the most common adverse events during 12 week treatment period, *n* (%).

Events	**Placebo** (*n*=173)	**Benvitimod** (*n*=344)	**Calcipotriol** (*n*=169)
Skin adeverse events			
Pruritus	21 (12.1)	73 (21.2)	17 (10.1)
Contact dermatitis	7 (4.0)	30 (8.7)	9 (5.3)
Folliculitis	2 (1.2)	35 (10.2)	1 (0.6)
Allergic dermatitis	3 (1.7)	27 (7.8)	1 (0.6)
Erythema	1 (0.6)	8 (2.3)	3 (1.8)
Skin pain	1 (0.6)	9 (2.6)	2 (1.2)
Rash	3 (1.7)	6 (1.7)	1 (0.6)
Dermatitis	2 (1.2)	5 (1.5)	2 (1.2)
Papule	1 (0.6)	7 (2.0)	0
Papuloid rash	1 (0.6)	6 (1.7)	0
Pruritus	0	6 (1.7)	0
Skin irritation	0	4 (1.2)	1 (0.6)
Pigment abnormality	0	5 (1.5)	0
Eczema	1 (0.6)	3 (0.9)	0
Drying of external parts	1 (0.6)	3 (0.9)	0
Xerosis cutis	0	3 (0.9)	0
Infectious adverse events			
Upper respiratory infections	3 (1.7)	13 (3.8)	8 (4.7)
Urinary tract infection	0	3 (0.9)	4 (2.4)
Upper respiratory tract infection	0	3 (0.9)	2 (1.2)
Others			
Leukocyte count rise	0	4 (1.2)	1 (0.6)
Diarrhea	0	4 (1.2)	1 (0.6)
Oropharyngeal pain	0	3 (0.9)	2 (1.2)
Abdominal pain	1 (0.6)	3 (0.9)	0
Dizziness	2 (1.2)	4 (1.2)	0
Supraventricular premature beats	0	3 (0.9)	0

* The most common adverse events were defined as those reported by three or more patients in any group.

15. Supplementary Table 2: Details of Adverse Events during the long-term follow-up study.

Events	Benvitimod (*n*=30)
Adverse events	5 (16.7)
Serious adverse events	0
Adverse drug reactions	3 (10.0)
Skin adverse events	3 (10.0)
Presence of urinary protei	2 (6.7)
Decrease in leukocyte count	1 (3.3)
Liver and gallbladder adverse events	1 (3.3)
Increased RBC count	1 (3.3)
Urinary leukocyte positive	1 (3.3)
Presence of urine glucose	1 (3.3)
Hemoglobin rise	1 (3.3)
Infectious adverse events	1 (3.3)