

ORIGINAL ARTICLE

Efficacy and safety of topical WBI-1001 in patients with mild to moderate psoriasis: results from a randomized double-blind placebo-controlled, phase II trial

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Abstract

Background There is a need for the development of novel non-steroidal topical drugs for the treatment of psoriasis.

Objective To assess the efficacy and safety of topical 1.0% WBI-1001 in patients with mild to moderate plaque psoriasis.

Methods A total of 61 patients with 1–10% body surface area (BSA) covered with plaque psoriasis and a physician's global assessment score (PGA) of 2–4 were randomized (2 : 1) to receive either 1% WBI-1001 in a cream formulation or placebo, applied twice daily for 12 weeks. Efficacy was evaluated using PGA, BSA and Psoriasis Area and Severity Index (PASI). The primary endpoint was the change from baseline (Day 0) in PGA at week 12.

Results The improvement in PGA at week 12 was 62.8% for patients randomized to WBI-1001 when compared with 13.0% for patients randomized to placebo ($P < 0.0001$). At week 12, the proportion of patients who achieved a PGA of clear or almost clear and the mean improvement in BSA were 67.5% and 79.1%, respectively, for patients randomized to WBI-1001, when compared with 4.8% ($P < 0.0001$) and an increase of 9.4% ($P < 0.0001$), respectively, for patients randomized to placebo. More application site adverse drug reactions were observed in patients randomized to WBI-1001 than in those randomized to placebo. These adverse drug reactions were all mild or moderate in intensity.

Conclusion Topical WBI-1001 induces rapid and significant improvement in patients with plaque psoriasis.

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Conflicts of interest

Robert Bissonnette has been a speaker, consultant, advisory board member and/or investigator and/or has received honoraria and grants from Abbott laboratories, Amgen, Astellas Pharma, Centocor, Janssen-Ortho, Novartis, Celgene, Boehringer, Leo Pharma, Merck, Galderma, Isotechnika, Pfizer and Welichem Biotech Inc. Chantal Bolduc has been a speaker, consultant, advisory board member and/or investigator and/or has received honoraria and grants from Abbott laboratories, Amgen, Astellas Pharma, Celgene, Centocor, Isotechnika, Janssen-Ortho, Leo Pharma, Merck, Merck-Serono, Novartis, Pfizer, Boehringer and Welichem Biotech Inc. Catherine Maari has been a speaker, consultant, advisory board member and/or investigator and/or has received honoraria and grants from Abbott laboratories, Amgen, Astellas Pharma, Centocor, Janssen-Ortho, Novartis, Celgene, Boehringer, Leo Pharma, Merck, Merck-Serono, Isotechnika, Pfizer and Welichem Biotech Inc. Simon Nigen has been a speaker, consultant, advisory board member and/or investigator and/or has received honoraria and grants from Abbott laboratories, Amgen, Astellas Pharma, Centocor, Janssen-Ortho, Novartis, Celgene, Boehringer, Leo Pharma, Merck, Merck-Serono, Isotechnika, Pfizer and Welichem Biotech Inc. Dr John M. Webster, Dr Liren Tang and Dr Michael Lyle are full time employees of Welichem Biotech Inc.

Introduction

Psoriasis is a chronic inflammatory skin disorder with a prevalence of up to 3%.¹ Despite major advances in the treatment of severe psoriasis, such as the development of biological therapies, the treatment of patients with milder disease has not changed signifi-

cantly over the past 10 years. The most frequently used topical treatments for mild to moderate psoriasis are topical corticosteroids, vitamin D analogues and tar.^{2–4} There is a need for the development of novel non-steroidal topical treatments for psoriasis. WBI-1001 (2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol) is a non-steroidal, anti-inflammatory, new chemical entity (NCE) that was originally derived from the metabolites of a group of

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bacterial symbionts of entomopathogenic nematodes. WBI-1001 has been shown to affect T-cells through the inhibition of multiple pro-inflammatory cytokines including tumour necrosis factor α and interferon γ and by inhibiting both T-cell viability and infiltration processes.⁵

A recent study showed that a 4-week treatment with WBI-1001 was safe and effective in patients with atopic dermatitis.⁶ The objectives of the current study were to evaluate the safety and efficacy of topical WBI-1001 at 1% in a cream formulation for the treatment of psoriasis.

Methods

Study design

This was a randomized, double-blinded, placebo-controlled, phase IIa study conducted at a single centre. Research ethics board approval was obtained, and patients signed an informed consent. Sixty-one men and women with plaque psoriasis were randomized (2 : 1) to apply either 1.0% WBI-1001 cream or placebo cream twice daily for 12 weeks. The ingredients in the vehicle cream (placebo) and the study cream were identical with the exception that the latter contained WBI-1001. A randomization code list was generated using statistical analysis software (ClinPro/LBL version 8.0, Clinical Systems Inc, Garden City, NY, USA). The randomization took place strictly in the order that patients were found to be eligible at Day 0. An un-blinded pharmacist at the investigator's site had access to the randomization list and was the only person knowing which cream was provided to patients. Patients were assessed at seven visits: screening, Day 0 (baseline), Day 14, Day 28, Day 42, Day 56 and Day 84. Patients were followed for safety (adverse events), 28 days after the last treatment (phone call at Day 112). Care was taken to have the same patient assessed by the same investigator throughout the study.

Study population

To be eligible, patients had to be between 18 and 65 years of age, diagnosed with stable, mild to moderate plaque psoriasis for at least 6 months. Patients had to have between 1% and 10% of body surface area (BSA) covered with psoriasis (excluding the face, groin, scalp and genital regions) and a Physician's Global Assessment (PGA) of two (mild) to four (severe) at Day 0. Patients were excluded if they had pustular, erythrodermic or other non-plaque forms of psoriasis.

Efficacy evaluations

A PGA score corresponding to the degree of overall lesion severity using a 5-point scale ranging from 0 to 5 (clear to very severe) was performed for the entire body excluding face, scalp, groin and genitals.⁷ Psoriasis severity was also assessed using the Psoriasis Area and Severity Index (PASI).⁸ In addition, the BSA affected by psoriasis was evaluated at each visit. The primary efficacy parameter was the change from baseline in PGA at Day 84. Secondary efficacy parameters included the proportion of patients who

achieved a PGA of 0 (clear) or 1 (almost clear) at Day 84, the proportion of patients who achieved a 50% and a 75% improvement in PASI at Day 84 (PASI 50 and PASI 75 respectively) and the change from baseline in BSA and PASI at Day 84.

Safety evaluations

Safety and tolerability were evaluated at each visit by adverse event reporting, clinical laboratory testing and vital signs measurement. Physical assessments and 12-lead electrocardiograms were performed at screening and at the last visit (Day 84).

Statistical analysis

A sample size of 60 (40 patients on WBI-1001 and 20 patients on placebo) had a power of 80% to detect a difference in PGA of 0.738 at Day 84 between the two groups, assuming a mean PGA of 3.3 at baseline, an improvement in PGA of 0.7 in the placebo group at Day 84 and a drop-out rate of 20%.

All efficacy analyses were conducted, and are presented, on the Intent-To-Treat (ITT) population, which consisted of all patients enrolled in the study that received at least one application of study medication. Efficacy analyses were performed on the per-protocol (PP) population for the following endpoints: the change from baseline in PGA at Day 84, the proportion of patients that achieved a PGA of 0 or 1 at Day 84, PASI 50 and PASI 75 at Day 84. The PP population consisted of patients who completed at least 80% of planned applications during the study, who completed the study with no more than one missing visit and who did not use prohibited medication during the study. The safety population consisted of all those patients who received at least one application of study cream. For the ITT population, the last observation carried forward imputation (LOCF) or the non-responder imputation (NRI) was used to handle missing data for continuous and dichotomous variables respectively. For the PP population, no imputation technique was used.

The evolution of change from baseline for both groups was studied using a repeated-measures ANOVA with one within-patient factor, time and one between-patient factor, treatment group. The analysis was performed using a mixed model. A Student's *t*-test (two tailed) was performed for each visit to compare changes from baseline of patients randomized to placebo and patients randomized to WBI-1001. The proportions for each group were compared using the Fisher's exact test. Statistical analysis was performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) and the significance level was 0.05.

This trial was registered under clinical trial number NCT 01098721.

Results

Demographics and patients' disposition

A total of 61 patients aged from 22 to 65 years (mean 50.6 years) were included in this study between February and August 2010.

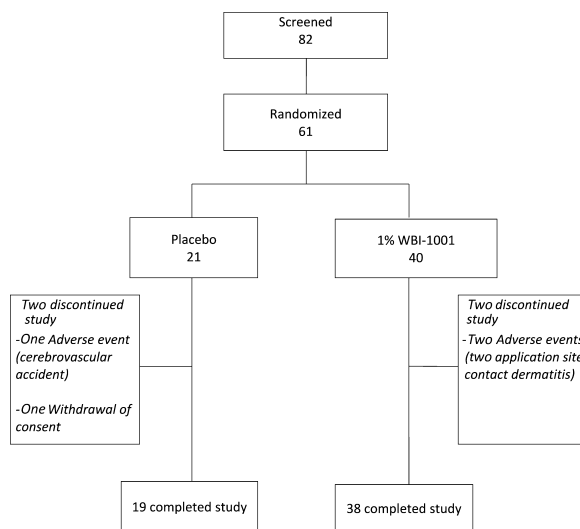


Figure 1 Patients' disposition.

Table 1 Demographics and baseline values of efficacy assessments

Characteristic	1% WBI-1001 (N = 40)	placebo (N = 21)	All (N = 61)
Age mean $\pm$ SD	50.4 $\pm$ 8.8	51.1 $\pm$ 13.0	50.6 $\pm$ 10.3
Male N (%)	33 (82.5)	18 (85.7)	51 (83.6)
Mean PGA $\pm$ SD	3.2 $\pm$ 0.6	3.4 $\pm$ 0.5	3.3 $\pm$ 0.6
Mean PASI $\pm$ SD	5.9 $\pm$ 2.7	6.2 $\pm$ 2.0	6 $\pm$ 2.5
Mean BSA $\pm$ SD	3.3 $\pm$ 2.1	3 $\pm$ 1.6	3.2 $\pm$ 2.0

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment.

Patients' disposition and reasons for discontinuations are presented in Fig. 1. Demographics and baseline values for all efficacy assessments by treatment group are presented in Table 1. Main protocol deviations included prohibited medication intake by two patients and non compliance to study treatment by one patient (application of study product on <80% of psoriasis plaques). In addition, on Day 56, one patient randomized to placebo inadvertently received 1.0% WBI-1001 and the other patient, who was randomized to WBI-1001 group, inadvertently received placebo. Finally, the centre enrolled 61 patients instead of 60 as planned in the protocol. All patients were included in the safety and ITT populations. Nine patients were excluded from the PP efficacy analyses due to protocol deviations or early termination.

Efficacy data analyses

Physician's global assessment (PGA) The mean change from baseline in PGA at Day 84 for the ITT and the PP population (Fig. 2) was -62.5% and -62.8% , respectively, for the WBI-1001

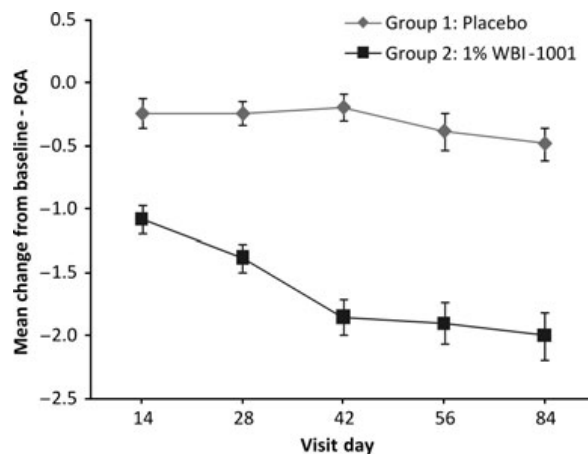


Figure 2 Change from baseline in PGA at each visit; ITT population (mean $\pm$ SEM).

Table 2 Proportion of patients with PGA 0 or 1 at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)
Day 0	0 (0)	0 (0)
Day 14	5 (12.5)	0 (0)
Day 28	11 (27.5)	0 (0)
Day 42	23 (57.5)	0 (0)
Day 56	22 (55.0)	1 (4.8)
Day 84	27 (67.5)	1 (4.8)

PGA, physician's global assessment.

group when compared with -14.2% and -13.2% , respectively, for the placebo group ($P < 0.0001$ for both).

The proportion of patients who achieved a PGA score of clear (0) or almost clear (1) at Day 84 for the ITT population (Table 2) was 67.5% for the WBI-1001 group when compared with 4.8% for the placebo group ($P < 0.0001$).

Psoriasis area and severity index (PASI) Change from baseline in PASI is presented in Table 3. At Day 84, there was a 71.0% decrease in PASI for the WBI-1001 group when compared with a decrease of 11.1% for the placebo group ($P < 0.0001$).

The proportion of patients who achieved PASI 50 or PASI 75 at Day 84 for the ITT population was significantly higher ($P < 0.0001$ and $P = 0.0004$ respectively) for the WBI-1001 group (72.5% and 50.0% , respectively) when compared with the placebo group (9.5% and 4.8% respectively).

Body surface area (BSA) Change from baseline in BSA is presented in Table 3. There was a decrease of 79.1% in BSA at Day 84 for patients randomized to WBI-1001 when compared with an increase of 9.4% for patients randomized to placebo ($P < 0.0001$).

Table 3 Change from baseline in PASI and BSA at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)	P-value
PASI			
Day 14	-1.9 (-31.9)	-0.8 (-12.4)	0.0010
Day 28	-2.8 (-47.5)	-0.8 (-13.1)	<0.0001
Day 42	-3.6 (-60.7)	-0.8 (-12.7)	<0.0001
Day 56	-3.9 (-65.9)	-0.8 (-12.4)	<0.0001
Day 84	-4.2 (-71.0)	-0.7 (-11.1)	<0.0001
BSA			
Day 14	-0.5 (-16.3)	-0.1 (-2.7)	0.0273
Day 28	-1.3 (-40.8)	0.1 (+2.4)	0.0004
Day 42	-2.1 (-63.4)	0.01 (+0.3)	<0.0001
Day 56	-2.4 (-71.6)	0.3 (+9.4)	<0.0001
Day 84	-2.6 (-79.1)	0.3 (+9.4)	<0.0001

PASI, Psoriasis Area Severity Index; BSA, body surface area.

There was a significant difference between the two groups in the mean change from baseline in PGA, PASI and BSA as early as Day 14.

Safety analyses Adverse events experienced during the study with an incidence of 5% or higher in WBI-1001-treated or placebo-treated patients are presented in Table 4. The only serious

Table 4 Adverse events with incidence of 5% or higher in patients treated with WBI-1001 or placebo

	1% WBI-1001 (N = 40)	Placebo (N = 21)
Number of patients with ≥ 1 AE (%)	32 (80.0)	11 (52.4)
Adverse event with an incidence of 5% or higher	Number of patients (%)	Number of patients (%)
Nasopharyngitis	15 (37.5)	6 (28.6)
Application site discolouration*	11 (27.5)	0 (0.0)
Application site folliculitis*	4 (10.0)	0 (0.0)
Application site dermatitis*	6 (15.0)	0 (0.0)
Abdominal pain	3 (7.5)	0 (0.0)
Application site papules*	3 (7.5)	0 (0.0)
Application site pain*	2 (5.0)	1 (4.8)
Application site pruritus*	2 (5.0)	0 (0.0)
Pruritus†	2 (5.0)	0 (0.0)
Contact dermatitis	2 (5.0)	0 (0.0)
Dry skin	2 (5.0)	0 (0.0)
Back pain	2 (5.0)	2 (9.5)
Headache	2 (5.0)	1 (4.8)

*Treatment-related AEs.

†Treatment-related AE for only one of the two patients.
AE, adverse event.

adverse event during the study was a cerebrovascular accident that occurred in a patient randomized to placebo. All the non-dermatological adverse events were not suspected to be related to the study medication and were minor medical problems such as nasopharyngitis, headache and gastrointestinal disorders. The main adverse events suspected to be related to the study drug were application site discolouration (hyperpigmentation), application site dermatitis, application site folliculitis, application site papules, application site pain and application site pruritus. All dermatological adverse events observed in patients randomized to WBI-1001 were either mild (34) or moderate (two) in intensity. A total of three patients discontinued from the study due to adverse events: two patients randomized to WBI-1001 discontinued because of application site dermatitis and a third patient, randomized to placebo, due to a cerebrovascular accident. Finally, there were no clinically significant abnormal laboratory values or ECG results during the study.

Discussion

This study demonstrated that topical WBI-1001 at 1% is effective for the treatment of mild to moderate plaque psoriasis. There was a statistically significant difference between placebo and WBI-1001 in change from baseline in PGA at Day 84 (primary endpoint). Furthermore, the proportion of patients that achieved a PGA of 0 (clear) or 1 (almost clear) at Day 84 was 67.5% for patients randomized to WBI-1001 when compared with 4.8% for patients randomized to placebo. Interestingly, the only patient randomized to placebo who achieved a PGA of 0 or 1 started a prohibited medication (ustekinumab) at week 56. A statistical difference between WBI-1001 and placebo was observed as early as Day 14, indicating the rapid action of WBI-1001. Improvement in plaque psoriasis was not only limited to plaque severity but also included a decrease in BSA affected by psoriasis (Fig. 3). BSA decreased by 79.1% at week 12 for patients randomized to WBI-1001 when compared with an increase in 9.4% for patients randomized to placebo.

Although this study did not evaluate WBI-1001 vs. an active comparator, the improvements observed are in the same order of magnitude or better than what has been previously published for potent topical corticosteroids such as betamethasone dipropionate and combination of calcipotriol and betamethasone dipropionate. For example, a PGA of 0 or 1 with at least a 2 grade PGA improvement by 19.1% (betamethasone dipropionate) and 31.7% (calcipotriol/betamethasone dipropionate) of patients was achieved at week 8 with mild to moderate disease using a 6-point scale PGA.⁹

The only adverse events that were suspected to be related to WBI-1001 were application site reactions such as hyperpigmentation, dermatitis, folliculitis and papules. Local hyperpigmentation after resolution of psoriasis plaques is a frequent phenomenon. The hyperpigmentation observed in the current trial faded gradually over time and was generally not a significant concern for

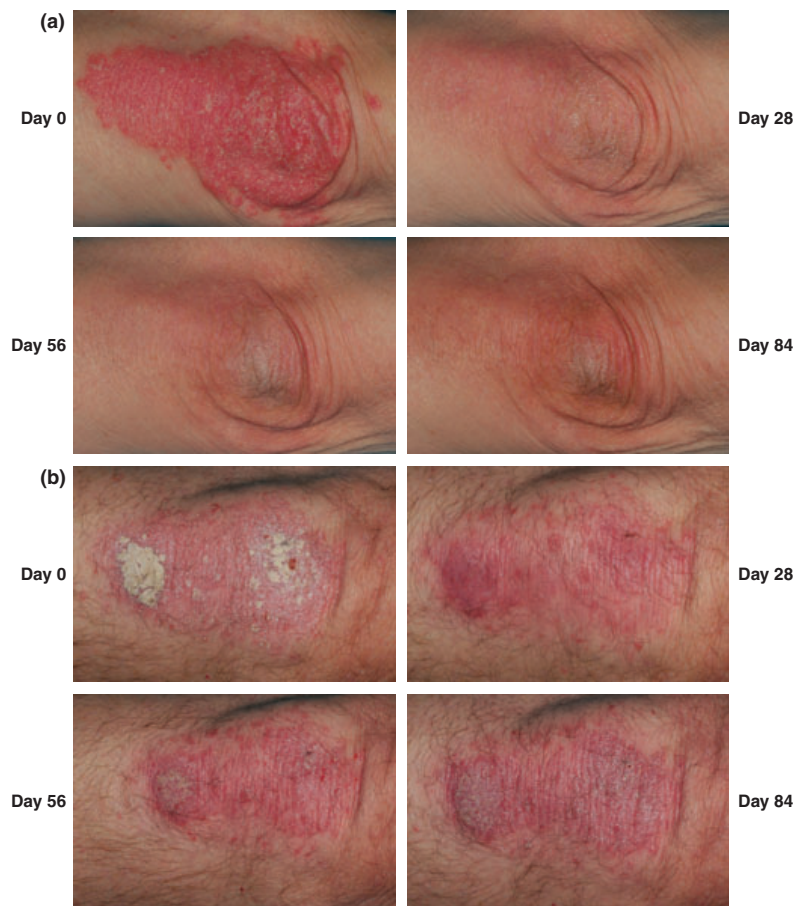


Figure 3 Photographs of representative psoriasis plaques at baseline, Day 28, Day 56 and Day 84 showing improvements in a patient randomized to WBI-1001 (a) and no significant improvement in a patient randomized to placebo (b).

patients. All drug-related dermatological adverse events observed in the WBI-1001 group were mild or moderate in intensity, and only two patients discontinued the study due to such adverse events. WBI-1001 at 0.5% has been shown to be effective in treatment of atopic dermatitis,⁶ and this lower concentration may have decreased the incidence of application site adverse drug reactions observed in the current study. Further studies with WBI-1001 should include skin biopsies and patch testing to better evaluate and understand these adverse events and quality of life questionnaires to assess changes in physical and psychological components of quality of life in patients treated with WBI-1001.

In conclusion, this study showed that WBI-1001 is effective for the treatment of mild to moderate psoriasis. Further studies are required to better assess the long-term safety and efficacy of WBI-1001 for the treatment of mild to moderate psoriasis.

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