

Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial

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Summary

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Conflicts of interest

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Background There is a need for the development of novel nonsteroidal topical drugs for the treatment of atopic dermatitis (AD).

Objectives The primary objective was to evaluate the efficacy of WBI-1001 over 6 weeks of treatment of mild to severe AD.

Methods Patients with AD affecting 3–20% of their body surface area and with an Investigator's Global Assessment (IGA) of 2–4 were randomized (1 : 1 : 1) to receive placebo, WBI-1001 0.5% or WBI-1001 1.0% in a cream formulation applied twice daily for 6 weeks. At the end of this phase, patients receiving WBI-1001 continued the same treatment for an additional 6 weeks. Patients receiving placebo entered into a 6-week double-blind phase with re-randomization (1 : 1) to WBI-1001 0.5% or 1.0% cream. The primary objective was to evaluate the efficacy of WBI-1001 over 6 weeks of treatment of mild to severe AD. The primary endpoint was the mean change from baseline in IGA at day 42 (week 6).

Results In total, 148 patients were randomized and analysed in the placebo (51), WBI-1001 0.5% (50) and WBI-1001 1.0% (47) groups. There was a decrease of 1.3 [43%; $P < 0.001$; 95% confidence interval (CI) -1.2 to -0.5] and 1.8 (56.3%; $P < 0.001$; 95% CI -1.6 to -0.9) in IGA at day 42 in the WBI-1001 0.5% and 1.0% groups, respectively, as compared with a decrease of 0.5 (14.7%) in the placebo group. Adverse drug reactions included a few cases of folliculitis and contact dermatitis.

Conclusions WBI-1001 is an efficacious novel topical anti-inflammatory molecule for the treatment of AD.

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Atopic dermatitis (AD) is an increasingly prevalent chronic and relapsing inflammatory skin disease affecting up to 20% of children and 3% of adults.^{1–3} AD is a multifactorial disease and its pathophysiology has been linked to genetic modifica-

tions in barrier properties of the skin and to immunological mechanisms.^{4,5}

Most patients with AD are currently treated with topical therapeutics such as corticosteroids and calcineurin inhibitors.

However, there can be safety concerns with long-term use of these topical agents.^{6,7} WBI-1001 [2-isopropyl-5-((E)-2-phenylethenyl) benzene-1,3-diol: IPBD] is a novel small molecule that has been shown to decrease the production of proinflammatory cytokines and migration of T cells. Originally derived from metabolites of a unique group of bacterial symbionts of entomopathogenic nematodes, IPBD has been demonstrated to inhibit inflammatory cytokine secretion by activated T cells, including tumour necrosis factor- α and interferon- γ *in vitro* (data on file at Welichem Biotech Inc., Burnaby, BC, Canada). Furthermore, it has been demonstrated to inhibit allergic contact dermatitis in a mouse oedema model (data on file at Welichem Biotech Inc.). A previous 36-patient study suggested that WBI-1001 could improve mild to moderate AD.⁸ The objective of the current study was to evaluate the safety and efficacy of topically applied WBI-1001 (at 0.5% and 1.0%) in patients with AD.

Materials and methods

Patients

This multicentre, phase IIB, randomized, parallel group, double-blinded, placebo-controlled trial was undertaken in five centres in Canada. Patients eligible for the study were men or women aged between 18 and 65 years, with a clinical diagnosis of chronic AD for ≥ 6 months based on Hanifin's criteria.^{9,10} Patients had to have a minimum of 3% and a maximum of 20% of their total body surface area (BSA) affected with AD and an Investigator's Global Assessment (IGA) of mild (2) to severe (4) on a scale ranging from 0 (clear) to 5 (very severe). Patients were excluded if they had spontaneously improving or rapidly deteriorating AD, presence of AD lesions on only hands and/or feet, active allergic contact dermatitis or other nonatopic forms of dermatitis. Patients were required to stop all topical AD therapy (including topical corticosteroids and calcineurin inhibitors) and any phototherapy (including laser), photochemotherapy, or systemic AD therapy (systemic corticosteroids, tacrolimus, methotrexate, ciclosporin etc.) within 2 weeks prior to the baseline visit. Prolonged exposure to natural or artificial sources of ultraviolet radiation and systemic immunomodulatory therapies for other conditions were prohibited for a period of 4 weeks prior to the baseline visit.

Procedures

The study was approved by an Institutional Review Board and informed consent was obtained from each patient before beginning any study-related procedure. Patients were randomized (1 : 1 : 1) to receive WBI-1001 0.5%, WBI-1001 1.0% or the vehicle. A randomization code list was generated (ClinPro/LBL version 8.0; Clinical Systems, Inc., Garden City, NY, U.S.A.) and a unique randomization number was assigned to each patient at the day 0 visit according to the order of entry into the study. Randomization occurred in the order that patients met selection criteria at each centre. Neither patients nor study personnel (with

the exception of the unblinded pharmacist at the site) knew the nature of study cream being applied by each patient. The principal investigator was not involved in the distribution or assignment of the study creams and did not come in contact with the study cream. After 6 weeks, patients receiving WBI-1001 0.5% or WBI-1001 1.0% continued to receive double-blind treatment with the same cream for an additional 6 weeks. Patients initially randomized to placebo entered into a 6-week double-blind, nonplacebo-controlled phase and were randomly assigned (1 : 1) to WBI-1001 0.5% or 1.0%.

Efficacy and safety evaluations

The primary efficacy variable was the IGA score as evaluated by the physician using the following definitions: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe; 5, very severe. The secondary efficacy variables included Eczema Area and Severity Index (EASI) score^{11,12} and SCORAD,^{12,13} which includes BSA and pruritus severity score.

The primary efficacy endpoint was the mean change from baseline in IGA at day 42 (week 6) in patients randomized to WBI-1001 (0.5% and 1.0%) as compared with patients randomized to placebo. Secondary efficacy endpoints included the mean percentage change from baseline in IGA at day 42, the rate of treatment success at day 42 [defined as the proportion of patients who achieved 'clear' (IGA = 0) or 'almost clear' (IGA = 1) or a minimum of a 2-point improvement over the baseline in IGA score], mean change and mean percentage change from baseline at day 42 in EASI, SCORAD, pruritus severity score and BSA in patients randomized to WBI-1001 (0.5% and 1.0%) as compared with patients randomized to placebo. Also, mean change and mean percentage change from baseline at day 84 in IGA, EASI, SCORAD, pruritus severity score and BSA were evaluated in patients randomized to WBI-1001 (0.5% and 1.0%).

Safety and tolerability were evaluated by adverse event reporting, clinical laboratory testing, electrocardiogram recordings, vital signs and physical examinations.

Statistical analysis

A total of 50 patients per treatment group would provide a power of at least 95% to detect a change of two points from baseline in mean IGA at day 42 between the two groups, assuming an α level of 0.01 and a noncompleter rate of 20%.

The intent-to-treat (ITT) population was used for all efficacy analyses. Missing data were not imputed in this study. For the primary efficacy endpoint (change from baseline in IGA at day 42), repeated-measures analysis with fixed effects for treatment group as well as baseline value as a covariate was performed to compare the treatment group means over time for change from baseline scores. An unstructured variance-covariance matrix was assumed. Least square (LS) means, associated standard errors (SEs), confidence intervals (CIs), differences in LS means (SEs), CIs for the differences in LS means and P-values were calculated for day 42 and day 84. Similar analysis was performed for percentage change from

baseline in IGA over time and for the change from baseline and percentage change from baseline in EASI, SCORAD, pruritus and BSA scores. The rate of 'treatment success' based on IGA was analysed using generalized estimating equations analysis assuming a binomial distribution and exchangeable correlation for the successful treatment rate between groups. The safety population consisted of all patients who received at least one application of study cream.

This trial was registered with ClinicalTrials.gov, number NCT01098734.

Results

Demographics and patient disposition

Of 148 patients recruited between November 2009 and July 2010, aged from 18 to 65 years (mean 33.3), 124 completed the study. Patient disposition and reasons for discontinuations are presented in Figure 1. Demographics and baseline values for all efficacy assessments by treatment group are presented in Table 1. All patients were included in the safety and ITT populations.

Efficacy data analyses

Of the 148 patients included in the study, 51 were randomized and analysed in the placebo group, 50 in the WBI-1001 0.5% group and 47 in the WBI-1001 1.0% group. All the analyses were performed according to the original assigned groups. All patients completed day 42 in the WBI-1001 0.5%

Table 1 Demographics and baseline values of efficacy measures

	Placebo (n = 51)	WBI-1001 0.5% (n = 50)	WBI-1001 1.0% (n = 47)
Male, n (%)	24 (47)	20 (40)	16 (34)
Age (years), mean $\pm$ SD	35.4 $\pm$ 13.1	32.2 $\pm$ 12.4	30.9 $\pm$ 11.6
Baseline scores, mean $\pm$ SD			
IGA	3.1 $\pm$ 0.6	2.9 $\pm$ 0.6	3.0 $\pm$ 0.6
EASI	9.8 $\pm$ 5.5	8.5 $\pm$ 4.5	7.4 $\pm$ 3.9
Pruritus	5.9 $\pm$ 2.4	6.5 $\pm$ 2.4	5.5 $\pm$ 2.3
SCORAD	45.0 $\pm$ 12.0	47.6 $\pm$ 11.9	42.1 $\pm$ 10.5
BSA	9.3 $\pm$ 4.6	8.9 $\pm$ 4.7	7.7 $\pm$ 4.5

IGA, Investigator's Global Assessment; EASI, Eczema Area and Severity Index; BSA, affected body surface area.

group whereas 41 and 38 patients completed day 42 in the WBI-1001 1.0% and placebo groups, respectively.

Investigator's global assessment

There was a gradual improvement in IGA over time for patients randomized to WBI-1001 (Fig. 2). There was a 43.0% ($P < 0.001$) and 56.3% ($P < 0.001$) decrease in IGA at day 42 for patients randomized to WBI-1001 0.5% and 1.0%, respectively, as compared with a decrease of 14.7% for patients randomized to placebo. The mean change from baseline in IGA at day 42 was -1.3 ± 0.97 (95% CI -1.2 to

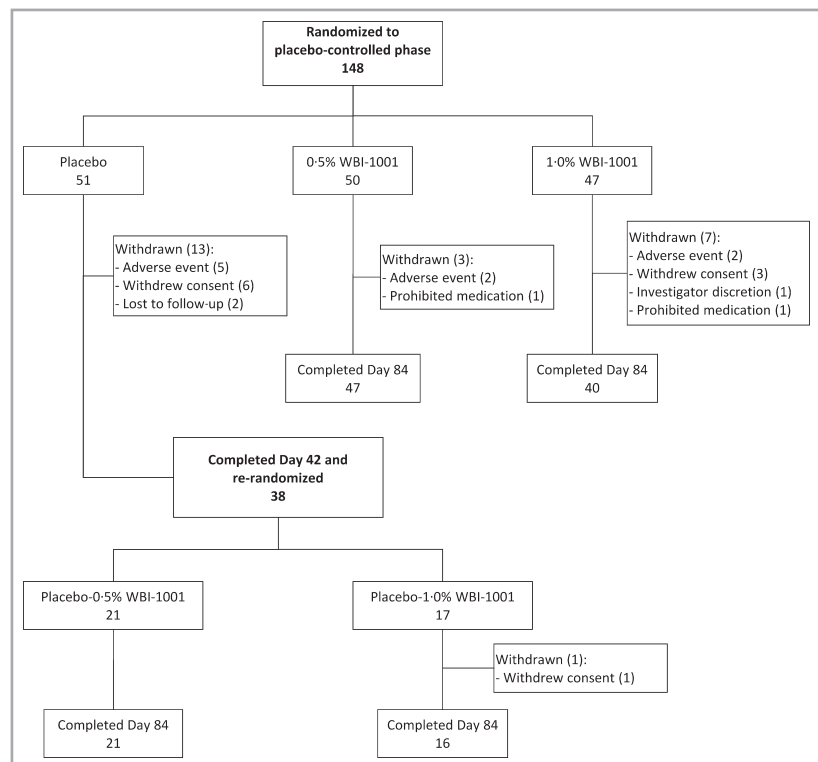


Fig 1. Patient disposition.

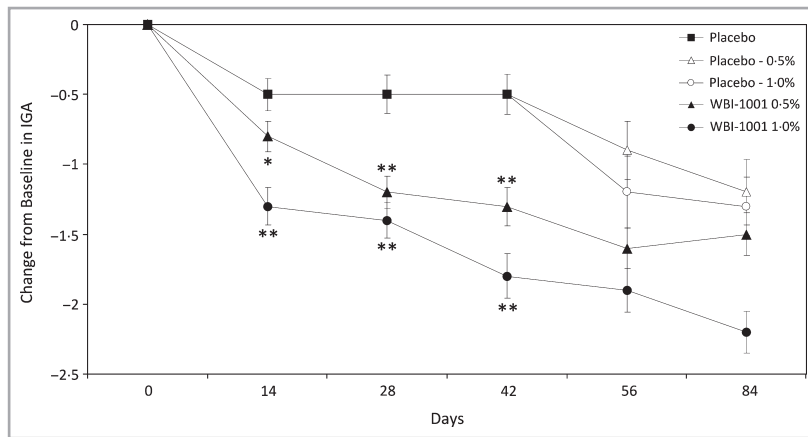


Fig 2. Change from baseline in Investigator's Global Assessment (IGA) up to day 84. Note: baseline for the placebo - 0.5% and placebo - 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. *P = 0.002 vs. placebo for WBI-1001 0.5% group. **P < 0.001 vs. placebo for WBI-1001 0.5% and WBI-1001 1.0% groups.

-0.5) for the WBI-1001 0.5% group and -1.8 ± 1.02 (95% CI -1.6 to -0.9) for the WBI-1001 1.0% group as compared with -0.5 ± 0.89 for the placebo group ($P < 0.001$ for both WBI-1001 creams) (Fig. 2). The mean change from baseline in IGA at day 42 and day 84 was significantly higher ($P = 0.032$ and $P < 0.001$, respectively) for the WBI-1001 1.0% group as compared with the WBI-1001 0.5% group.

The proportion of patients achieving an IGA of 0 or 1 or a minimum of a 2-point improvement in IGA over the baseline (treatment success) at each visit is presented in Figure 3. The proportion of patients achieving treatment success at day 42 was significantly higher for both the WBI-1001 0.5% group (50.0%, $P = 0.001$) and WBI-1001 1.0% group (63.4%, $P < 0.001$) compared with placebo (15.8%). There was no significant difference ($P = 0.146$) between the WBI-1001 1.0% group and the WBI-1001 0.5% group in proportion of patients achieving treatment success at day 42. However, at day 84 the proportion was significantly higher ($P = 0.017$) for the WBI-1001 1.0% group (85.0%) as compared with the WBI-1001 0.5% group (61.7%).

Eczema Area and Severity Index and SCORAD

Gradual improvement in EASI and SCORAD for patients randomized to WBI-1001 was observed (Figs 4 and 5, respectively). At

day 42, improvement in EASI was 68.9% ($P < 0.001$) and 76.3% ($P < 0.001$) for WBI-1001 0.5% and WBI-1001 1.0%, respectively, compared with 23.3% for placebo. There was no significant difference in mean change from baseline in EASI at day 42 and day 84 ($P = 0.718$ and $P = 0.144$, respectively) between the WBI-1001 1.0% and WBI-1001 0.5% groups.

Improvement in SCORAD at day 42 amounted to 57.5% ($P < 0.001$) and 63.4% ($P < 0.001$) for WBI-1001 0.5% and WBI-1001 1.0%, respectively, compared with 13.9% for placebo. There was no significant difference in mean change from baseline in SCORAD at day 42 and day 84 ($P = 0.520$ and $P = 0.074$, respectively) between the WBI-1001 1.0% and WBI-1001 0.5% groups.

Pruritus severity score

There was a rapid improvement in pruritus for patients randomized to WBI-1001 (Fig. 6). Improvement in pruritus severity score at day 42 was 29.8% ($P < 0.001$) and 66.9% ($P < 0.001$) for WBI-1001 0.5% and WBI-1001 1.0%, respectively, compared with 9.5% for placebo. There was no significant difference in mean change from baseline in pruritus severity score at day 42 and day 84 ($P = 0.120$ and $P = 0.561$, respectively) between the WBI-1001 1.0% and WBI-1001 0.5% groups.

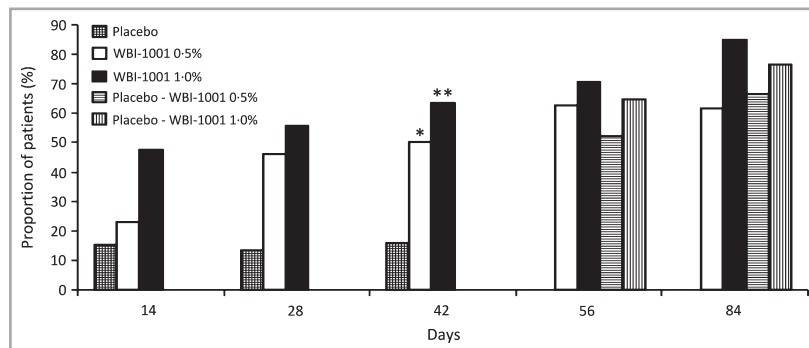


Fig 3. Summary of treatment success based on Investigator's Global Assessment (IGA). Treatment success was defined as the proportion of patients reaching an IGA of 0 (clear) or 1 (almost clear) or a minimum of a 2-point improvement in IGA at day 42. Note: baseline for the placebo - 0.5% and placebo - 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. *P = 0.001 vs. placebo for WBI-1001 0.5% group. **P < 0.001 vs. placebo for WBI-1001 1.0% group.

Fig 4. Change from baseline in Eczema Area and Severity Index (EASI) up to day 84. Note: baseline for the placebo – 0.5% and placebo – 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. ** $P < 0.001$ vs. placebo for WBI-1001 0.5% and WBI-1001 1.0% groups.

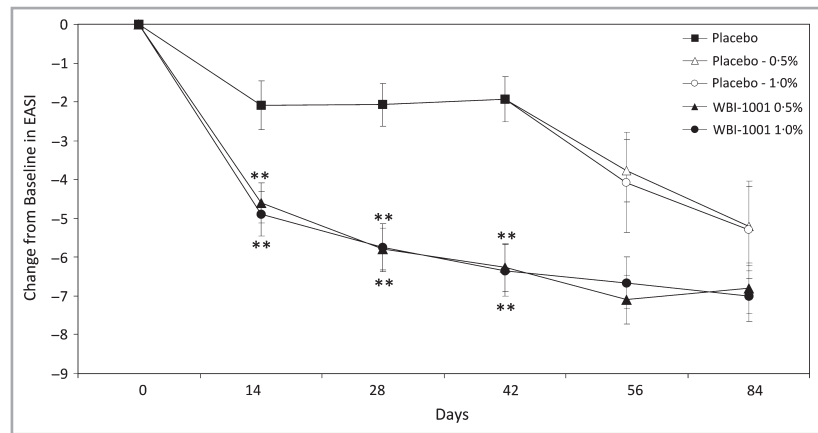


Fig 5. Change from baseline in SCORAD up to day 84. Note: baseline for the placebo – 0.5% and placebo – 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. ** $P < 0.001$ vs. placebo for WBI-1001 0.5% and WBI-1001 1.0% groups.

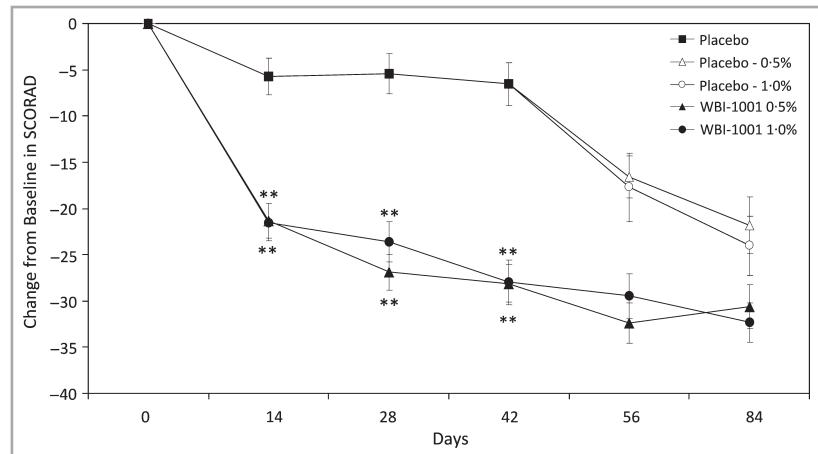
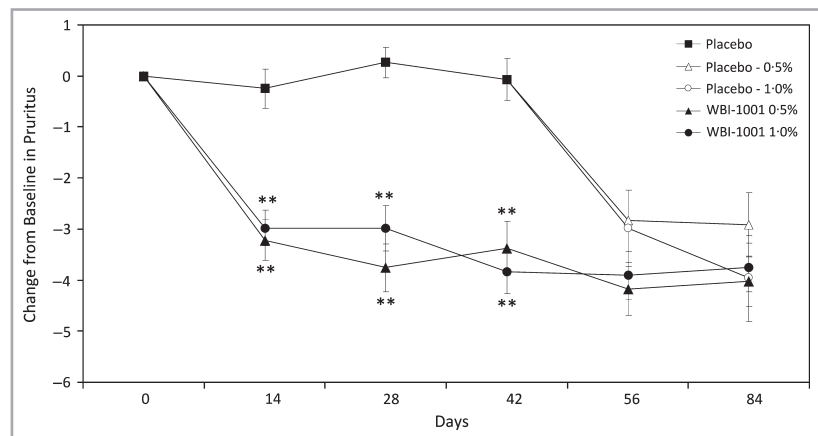


Fig 6. Change from baseline in pruritus severity score up to day 84. Note: baseline for the placebo – 0.5% and placebo – 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. ** $P < 0.001$ vs. placebo for WBI-1001 0.5% and WBI-1001 1.0% groups.



Body surface area

There was a gradual improvement in BSA for patients randomized to WBI-1001 (Fig. 7). Improvement in BSA at day 42 was 65.5% ($P < 0.001$) and 71.5% ($P < 0.001$) for WBI-1001 0.5% and WBI-1001 1.0%, respectively, compared with 12.1% for placebo. There was no significant difference in mean change from baseline in BSA at day 42 and day 84

($P = 0.993$ and $P = 0.319$, respectively) between the WBI-1001 1.0% and WBI-1001 0.5% groups.

Safety analyses

Treatment-emergent adverse events, regardless of relationship to study treatment and occurring in at least 2% of patients receiving WBI-1001 (0.5% and 1.0%), are summarized in

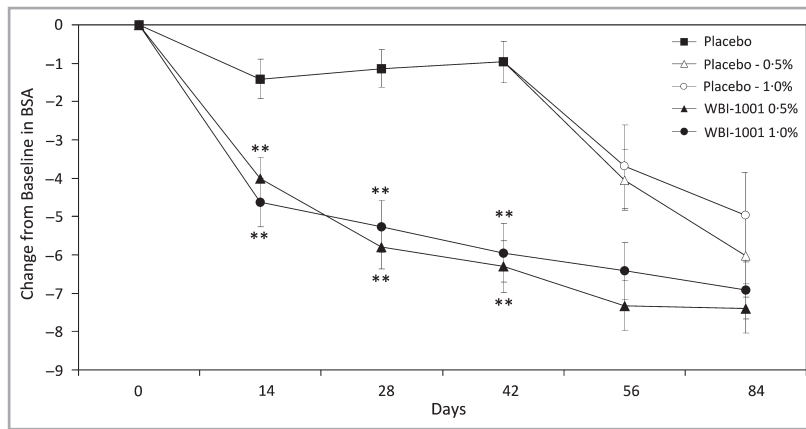


Fig 7. Change from baseline in affected body surface area (BSA) up to day 84. Note: baseline for the placebo – 0.5% and placebo – 1.0% (nonplacebo-controlled phase) groups was considered the day 42 (week 6) assessment. ** $p < 0.001$ vs. placebo for WBI-1001 0.5% and WBI-1001 1.0% groups.

Table 2. The most frequently reported adverse events related to study treatment were folliculitis, contact dermatitis and headache. Most skin-related adverse events were mild to moderate in intensity. Nine patients discontinued the study due to adverse events: five in the placebo group (four adverse events of eczema and one of worsening of AD), two in the WBI-1001 0.5% group (one adverse event of eczema and one of contact dermatitis) and two in the WBI-1001 1.0% group (two adverse events of contact dermatitis). Two serious adverse events, cellulitis and acute cholecystitis, were reported by two patients receiving WBI-1001 0.5% and WBI-1001

1.0%, respectively. Both were deemed not related to study treatment by the investigator. There were no notable differences between groups in vital signs, laboratory values, physical assessment or electrocardiogram findings in this study.

Discussion

This study demonstrated that topical WBI-1001 at 0.5% and 1.0% is efficacious for the treatment of AD. There was a significant difference between placebo and both concentrations of WBI-1001 in change from baseline in IGA at week 6,

Table 2 Treatment-emergent adverse events occurring in $\geq 2\%$ of WBI-1001 patients by body system and preferred term

	WBI-1001			
	Placebo (n = 51)	0.5% (n = 71)	1.0% (n = 64)	All (n = 135)
One or more adverse events, n (%)	22 (43)	41 (58)	41 (64)	82 (60.7)
Gastrointestinal disorders	1 (2)	3 (4)	5 (8)	8 (5.9)
Abdominal pain	0	1 (1)	2 (3)	3 (2.2)
General disorders and administration site conditions	3 (6)	5 (7)	5 (8)	10 (7.4)
Application site irritation	1 (2)	2 (3)	1 (2)	3 (2.2)
Infections and infestations	11 (22)	22 (31)	25 (39)	47 (34.8)
Application site folliculitis	2 (4)	2 (3)	1 (2)	3 (2.2)
Folliculitis	0	4 (6)	5 (8)	9 (6.7)
Gastroenteritis	0	1 (1)	2 (3)	3 (2.2)
Nasopharyngitis	5 (10)	10 (14)	10 (16)	20 (14.8)
Upper respiratory tract infection	0	1 (1)	2 (3)	3 (2.2)
Musculoskeletal and connective tissue disorders	1 (2)	5 (7)	4 (6)	9 (6.7)
Back pain	0	3 (4)	1 (2)	4 (3.0)
Neck pain	1 (2)	1 (1)	2 (3)	3 (2.2)
Nervous system disorders	1 (2)	10 (14)	11 (17)	21 (15.6)
Headache	1 (2)	6 (8)	9 (14)	15 (11.1)
Migraine	0	3 (4)	2 (3)	5 (3.7)
Respiratory, thoracic and mediastinal disorders	0	3 (4)	5 (8)	8 (5.9)
Cough	0	2 (3)	2 (3)	4 (3.0)
Skin and subcutaneous tissue disorders	6 (12)	6 (8)	10 (16)	16 (11.9)
Contact dermatitis	0	2 (3)	3 (5)	5 (3.7)
Papular rash	0	1 (1)	2 (3)	3 (2.2)

Patients randomized in the placebo-controlled phase who continued in the nonplacebo-controlled phase were summarized in the placebo column if the adverse event started during the placebo-controlled phase. They were summarized in the 0.5% or 1.0% column if the adverse event started during the nonplacebo-controlled phase.

which was the primary endpoint of the study. Furthermore, the proportion of patients achieving an IGA of 0 (clear) or 1 (almost clear) or a minimum of a 2-point improvement at week 6 (day 42) was 50.0% and 63.4% for patients randomized to WBI-1001 0.5% and 1.0%, respectively, compared with 15.8% for patients randomized to placebo. Improvements in all efficacy parameters were significantly higher in patients randomized to WBI-1001 as compared with patients randomized to placebo as early as day 14 for all endpoints, indicating a rapid onset of action of WBI-1001. Improvement in AD was not limited to improvement in lesion severity but also included significant improvements in BSA affected by AD as shown by a decrease of 65.5% and 71.5% in BSA at week 6 for patients randomized to WBI-1001 0.5% and 1.0%, respectively, as compared with a decrease of 12.1% for patients randomized to placebo.

Based on BSA at baseline (3–20%), the current study included patients with mild-moderate AD and severe AD. WBI-1001 has been studied in a previous single-centre, parallel group, randomized, double-blinded, placebo-controlled, phase II study in 37 patients with milder AD involving 1–10% of BSA.⁸ WBI-1001 was well tolerated and no systemic accumulation was observed after topical application for 4 weeks. After 4 weeks (28 days) of treatment, the mean percentage change from baseline in IGA was –38.9% and –45.8% (WBI-1001 0.5% and 1.0%, respectively) which is very similar to the mean percentage change in IGA of –39.8% and –47.5% (WBI-1001 0.5% and 1.0%, respectively) observed at week 4 in the current study. Similarly, all other efficacy parameters (treatment success, EASI, SCORAD, BSA and pruritus) showed comparable results between the two studies. The results presented herein show that WBI-1001 is efficacious for the treatment of patients with AD including patients with severe disease. Moreover, this study demonstrated that there was additional improvement in most efficacy parameters between week 4 and week 12.

WBI-1001 was generally well tolerated in the current study. Cases of contact dermatitis, folliculitis and papular rash were seen more frequently in patients randomized to WBI-1001. As patch testing was not performed in this study, it is not possible to know if the cases of contact dermatitis had an allergic or irritant aetiology. The appearance of papules with a different morphology from AD has been reported before with WBI-1001⁸ and it is possible that this is a milder expression of the contact dermatitis reported by some patients. The incidence and nature of adverse events in the two WBI-1001 groups was fairly similar (Table 2).

Although this study did not evaluate WBI-1001 vs. an active comparator, the rates of treatment success observed (Fig. 3) and the improvements in efficacy parameters appear to be similar or superior to what has been previously reported for tacrolimus.^{14,15} In a previous trial comparing tacrolimus ointment 0.03% and pimecrolimus cream 1% in 281 patients, an IGA of 0 or 1 was achieved at week 6 by only 40.4% of patients randomized to tacrolimus. Also, EASI was improved by 56.9% and BSA was improved by 48.8% in patients randomized to tacrolimus.¹⁴

Limitations of the current study include a limited number of study sites and the sample size. Also, the study was performed in a single country. Future studies including treatment over a longer period and comparison with either tacrolimus or a topical corticosteroid are required, better to characterize the safety and efficacy of WBI-1001 in patients with AD. These studies should also include the possibility of patch testing, better to evaluate the irritation and sensitization potential of WBI-1001.

What's already known about this topic?

- There is a need for the development of topical drugs for the treatment of atopic dermatitis (AD) as there are safety concerns with long-term use of currently available topical agents.
- WBI-1001 is a novel nonsteroidal topical agent that has previously been shown to be safe and effective for the treatment of mild to moderate AD in a small single-centre 4-week trial.

What does this study add?

- This study provides information on the safety and efficacy of topical WBI-1001 for AD in a multicentre trial over a longer evaluation time and involving a larger study population than the previous study.

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