Concise Report

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Efficacy and safety of HAT1 compared with calcipotriol in the treatment of patients with mild to moderate chronic plaque psoriasis: results from an open-label randomized comparative pilot clinical study

P. Alex,[1] S. Williams,[1] L. Sutton,[1] T. Yesudas,[1] C. Sutton,[1] S. Thomas[1] and M. Centola[1]

[1]*Haus Clinical Research Program, Haus Bioceuticals, Oklahoma City, OK, USA*

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Summary

Psoriasis is commonly treated with topical corticosteroids, oral cytotoxic drugs and biologic agents, which can be associated with significant adverse effects (AEs), high cost and response attenuation. Additionally, patients often use alternative therapies *ad hoc*, which can be challenging to integrate into a treatment regimen, owing to a lack of adequately powered controlled trials assessing efficacy and safety. We developed a novel topical botanical complex, herbal anti-inflammatory treatment (HAT1), through extensive preclinical *in vitro* and *in vivo* modelling to define key mechanisms of action and clinical potential. To assess the efficacy and safety of HAT1 in psoriasis, we performed a 10-week, open-label, pilot clinical trial comparing topical treatment of HAT1 with calcipotriol 0.005% in adult patients with mild to moderate psoriasis. Primary and secondary endpoints included the percentage of patients obtaining improvement of $\geq 75\%$ in Psoriasis Area and Severity Index (PASI 75), Physician's Global Assessment (PGA) response, and evaluation of tolerability and safety of HAT1. In the HAT1 arm, 85.7% of study patients reached PASI 75 compared with 21.4% in the calcipotriol comparator group. Additionally, 78.6% of patients in the HAT1 arm achieved a 'clear' or 'minimal' PGA response. HAT1 was well tolerated, with no AEs observed throughout the trial. These results suggest that HAT1 reduces psoriasis disease activity in a clinically relevant manner. Ongoing studies, including well-powered, double-blind, randomized controlled trials will be required to assess the potential of HAT1 in psoriasis.

Psoriasis, the most prevalent autoimmune skin disease, is a multifactorial systemic disease, and is a significant cause of physical and psychosocial morbidity.[1] Topical treatments, such as vitamin D analogues and tar products, have various limitations including poor efficacy, tachyphylaxis, skin atrophy, irritation and difficulty with application.[2] Treatments such as biological drugs, methotrexate and ciclosporin provide an affordable long-term management option, but also have limited efficacy and potential adverse effects (AEs), such as liver toxicity, hyperlipidaemia and immune suppression.[3] Despite the plethora of treatment options, a large-scale survey of patients with psoriasis, which was sponsored by the National Psoriasis Foundation, suggested that inadequately controlled disease is common and many patients are undertreated.[4] To address this treatment gap, it is estimated that approximately half (46.7%) of patients with psoriasis use alternative therapies *ad hoc*.[5] These treatments can be challenging for a physician to integrate into an

**Correspondence:* Dr Philip Alex, Haus Clinical Research Program, Haus Bioceuticals, 755 Research Parkway, Suite 460, Oklahoma City, OK, USA
E-mail: palex@hausbio.com

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already complex therapeutic framework, owing, in large part, to a lack of adequately powered randomized controlled trials (RCTs) assessing the efficacy and safety of alternative psoriasis therapies.[6]

We developed a topical botanical complex, denoted herbal anti-inflammatory treatment (HAT1), using data from broad-based mechanism of action (MOA) studies, in which HAT1 demonstrated significant therapeutic effects and anti-inflammatory activity, including modulation of Toll-like receptor (TLR)-mediated thymic stromal lymphopoietin expression, in preclinical chronic inflammatory skin disease models, and was found to have a favourable safety profile in extensive clinical assessments of safety and sensitivity (manuscript in preparation). HAT1 is a US Food and Drug Administration (FDA)-compliant over-the-counter product comprising a unique combination of herbal extracts of the following botanical ingredients: *Achillea millefolium*, *Aesculus hippocastanum*, *Althaea officinalis*, *Avena sativa*, *Berberis vulgaris*, *Cochlearia officinalis*, *Conium maculatum*, *Ervum lens*, *Hamamelis virginiana*, *Hydrastis canadensis*, *Malva sylvestris*, *Matricaria chamomilla*, *Nasturtium officinale*, *Phytolacca decandra*, *Pimpinella saxifraga*, *Populus alba*, *Populus tremuloides*, *Rhus toxicodendron*, *Sambucus nigra*, *Sanguinaria canadensis*, *Scrophularia nodosa*, *Smilax medica*, *Tussilago farfara*, *Veronica officinalis* and *Vincetoxicum officinale*. HAT1 was prepared as a spray formulation (20% extract in a 5% ethanol solution) manufactured in an US FDA registered current Good Manufacturing Practices (cGMP) facility in the USA. The objective of the present open-label trial was to quantitate the relative safety and efficacy of topical HAT1 in comparison to calcipotriol in the treatment of patients with mild to moderate psoriasis.

Report

This study protocol was approved by an institutional review board and written informed consent was obtained from all participants prior to screening, and conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. The trial is registered on Clinicaltrials.gov (identifier: NCT03069144).

The study was designed as an exploratory, open-label, pilot clinical trial to assess the safety and efficacy of topical HAT1 relative to topical calcipotriol in adult patients with mild to moderate, active, chronic plaque psoriasis. It was an 11-week (77-day), open-label, pilot, in-home use study comprising a 1-week washout period and 10-week treatment phase.

The study population comprised 28 male and female participants aged 12–60 years old. Patient eligibility was evaluated during a screening visit prior to study entry. Inclusion criteria included a clinical diagnosis of psoriasis and Psoriasis Area and Severity Index (PASI) ≤ 12, while the exclusion criteria included receipt of systemic therapy or presence of specific comorbidities. Full inclusion and exclusion criteria and the methods used for the determination of sample size are available in Supporting Information (Data S1) online.

The study had an experimental arm and a comparator arm. In the experimental arm, each patient was instructed to administer twice-daily applications of HAT1 (20% formulated in a 5% ethanol solution, administered as a spray). The comparator arm included twice-daily applications of calcipotriol ointment 0.005%. For patients with mild to moderate psoriasis, vitamin D3 analogues (such as calcipotriol) and corticosteroids are the first choice.[7] The choice of calcipotriol fills the gap of effective steroid-free topical treatment, and was therefore used as the comparator in this study.

Patients were randomly assigned in a 1 : 1 ratio using a computer-generated schema. All patients who met the eligibility criteria were randomized to receive either topical HAT1 or calcipotriol. All allocations were completed by the study coordinator, and the randomization scheme was not provided to or shared with the treating physicians.

During the treatment phase, participants were provided one of the two products to use twice daily on all lesions and on nonlesional areas, including lesions on the face, as instructed (see Supporting Information Data S1). No additional creams or lotions, other than provided test products were allowed throughout the duration of the study. Patients were evaluated at baseline, 2, 4, 8 and 10 weeks throughout therapy.

The primary endpoint for this study, analysed on an intention-to-treat basis, was the percentage of patients obtaining an improvement in PASI of $\geq 75\%$ (PASI 75) from baseline to week 10.[8] Secondary endpoints of the study included a dynamic measure of the Physician's Global Assessment (PGA) response, which ranges from 1 (clear) to 6 (worse).[9] All assessments of PASI and PGA were conducted by the treating physicians, who were unaware of the allocation. Safety assessments were performed at each visit and assessed by evaluation of the incidence of treatment-emergent AEs, history and physical examination and assessment of AEs and vital signs.

Group assignments in the study were balanced by age and psoriasis severity, and participants who fulfilled inclusion and exclusion criteria were randomized into each arm (Table 1). During the study, three participants were lost to follow-up, of whom two had attended only for the baseline visit. All of participants enrolled in each arm composed the final trial population assessed in this study. The imputation strategy of the last observation carried forward method was used to handle missing data. A flowchart of the study design and patient distribution is shown in Fig. 1.

Standard statistical methodology, using *t*-test, was used to assess the results for HAT1 compared with calcipotriol for all of the endpoints. The analysis was used to identify significant differences between the visits compared with baseline, and between the test and comparator product at each visit and compared with baseline. $P < 0.05$ was considered significant. All statistical analyses were performed using SAS software (SAS Institute, Cary, NC, USA).

The results demonstrated a statistically significant improvement in PASI at each evaluation for the patients treated with HAT1 compared with those treated with calcipotriol. A sustained improvement in PASI was observed in the HAT1 arm, with 85.71% of study patients obtaining PASI 75 at 10 weeks compared with 21.43% in the comparator calcipotriol 0.005% arm ($P < 0.01$; Fig. 2a). Improvement in both severity and extent of psoriasis was observed for HAT1. Significant reduction in desquamation and erythema was observed within 4 weeks compared with baseline ($P < 0.01$), which was followed by improvements in induration within 8 weeks following treatment with HAT1. Clearing of psoriatic plaques was noted as early as week 2, and maximal benefit appeared with 10 weeks of treatment for the majority of patients.

Table 1 Demographic and clinical characteristics of the patients at baseline.

Characteristic	Calcipotriol	HAT1
Age, years	39.4 ± 6.3	41.1 ± 8.8
Duration of psoriasis, years	11.2 ± 10.7	15.4 ± 11.0
Previous treatments, *n* (%)		
Topical agents	11 (78.6)	12 (85.7)
Phototherapy	5 (35.7)	6 (42.8)
Systemic	0 (0)	0 (0)
Clinical characteristics		
PASI*	7.9 ± 2.2	8.6 ± 1.5
PGA†	3.0 ± 0.9	2.9 ± 1.0

PASI, Psoriasis Area and Severity Index; PGA, Physicians Global Index. Data are mean ± SD unless stated otherwise. *Scores range from 0 to 72, with higher scores indicating greater severity of psoriasis. †Scores range from 0 to 5, with higher scores indicating greater severity of psoriasis.

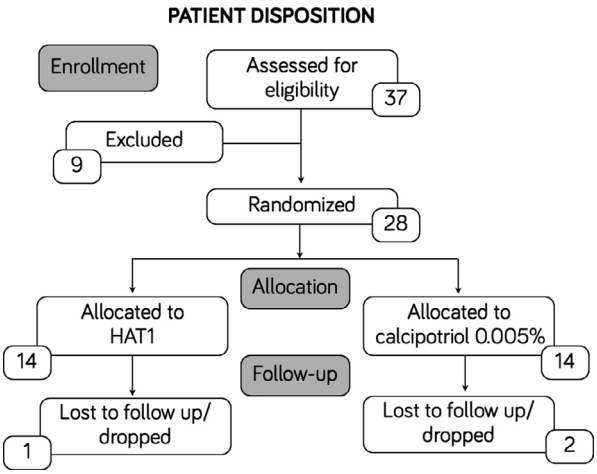

Figure 1 Distribution of patients.

Similar results were also observed in the secondary outcomes assessed in this trial. Significant reductions in PGA to a score of 1 (minimal) at 10 weeks relative to baseline was observed in 11 of 14 participants (78.57%) in the HAT1 arm ($P < 0.01$; Fig. 2b), whereas treatment with calcipotriol had a significantly lower number of participants (3 of 14; 21.43%) with reductions in PGA values at 10 weeks of treatment relative to baseline (Fig. 2b).

In the calcipotriol arm, three participants reported AEs of burning and skin irritation, leading to cessation of treatment for two of these. By contrast, HAT1 treatment was found to be well tolerated, with no treatment-related AEs observed in this arm throughout the 10-week trial. These findings suggest that HAT1 is a safe and potent topical therapeutic that significantly reduced the disease activity of psoriasis in a clinically relevant manner.

The therapeutic uses of medicines with botanical ingredients, the most commonly used treatments in the field of complementary and alternative medicine, are a rapidly growing area of medical and public interest, with over 38 million consumers in the USA alone.[10] However, alternative psoriasis therapies have a number of issues, including standardization of botanical preparations, potential toxicity concerns, related lack of information on MOA, and inadequacy, or complete lack, of quality clinical trials. These issues can lead to confusion and misuse among patients and difficulty for healthcare professionals when called upon to guide use of such therapies,

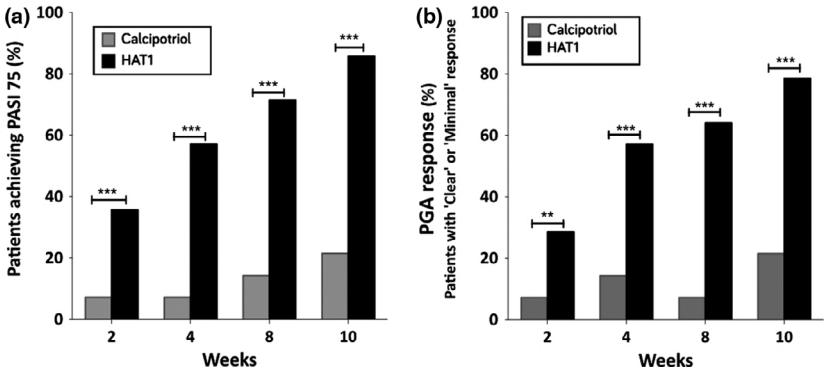

Figure 2 (a,b) Response as measured by (a) ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) and (b) Physician's Global Assessment (PGA) at each evaluation for the patients treated with herbal anti-inflammatory treatment (HAT1) compared with those treated with calcipotriol.

particularly in diseases such as psoriasis, for which alternative therapy usage is so widespread.[6,10] To address these informational gaps, a Botanical Drug Development Guidance for Industry has recently been issued by the FDA outlining safety and efficacy evaluation criteria for botanical drugs.[11] These criteria parallel those required for chemical agents, including the need to demonstrate efficacy and safety in adequately powered RCTs. In addition, the National Center for Complementary and Alternative Medicine, part of the National Institutes of Health, is supporting evidenced-based MOA and clinical studies of alternative therapies.[12]

The limitations of this study include its short duration and the lack of a regression phase, which limited our ability to determine if the effects persisted for a period of time following the final treatment. Another limitation in this study is the inclusion of patients with facial lesions. Calcipotriol is not recommended on the face, as it is known to cause irritation in some patients (the three patients in our study who experienced irritation did not have facial psoriasis). Future studies of HAT1 in facial psoriasis should be compared against a topical steroid or a calcineurin inhibitor in order to avoid any possibility of bias.

The present open-label study was designed to test the feasibility and potential of the study protocol for a full RCT to test the efficacy and safety of topical HAT1 in psoriasis. We have developed a therapeutic botanical complex, denoted HAT1, based on an evidenced-based process, including extensive preclinical *in vitro* and *in vivo* modelling, to define key mechanisms of action and clinical potential. The composition of HAT1 comprises a unique complex preparation of botanicals that have long been used to treat inflammatory conditions.[13] The results from this pilot study suggest that HAT1 is an effective and safe psoriasis treatment, controlling signs and symptoms in the majority of patients. Ongoing studies into well-powered, double-blind RCTs will be required to assess the potential of HAT1 in psoriasis.

Learning points

- Psoriasis is commonly treated with topical corticosteroids, cytotoxic drugs and biological agents, which can be associated with significant AEs, high cost and response attenuation.
- Patients often use alternative therapies *ad hoc*, which can be challenging for dermatologists to recommend as a treatment regimen, owing to a lack of adequately powered clinical trials assessing the efficacy and safety of such therapies.
- We conducted a randomized pilot study to investigate the feasibility of a protocol to test the relative safety and efficacy of topical HAT1, a novel topical botanical complex, in the treatment of patients with mild to moderate psoriasis.
- The findings from this pilot study show that HAT1 is effective in controlling signs and symptoms in the majority of patients with psoriasis.
- HAT1 was well-tolerated, with no AEs observed throughout the trial.
- These findings suggest that HAT1 is a safe and effective topical therapeutic that significantly reduced the disease activity of psoriasis in a clinically relevant manner.

References

1 Vanderpuye-Orgle J, Zhao Y, Lu J *et al*. Evaluating the economic burden of psoriasis in the United States. *J Am Acad Dermatol* 2015; **72**: 961–7.e5.

2 Wu JJ, Lynde CW, Kleyn CE *et al*. Identification of key research needs for topical therapy treatment of psoriasis – a consensus paper by the International Psoriasis Council. *J Eur Acad Dermatol Venereol* 2016; **30**: 1115–19.

3 Carey W, Glazer S, Gottlieb A *et al*. Relapse, rebound, and psoriasis adverse events: an advisory group report. *J Am Acad Dermatol* 2006; **54**(Suppl): S171–81.

4 Armstrong AW, Robertson AD, Wu J *et al*. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003–11. *JAMA Dermatol* 2013; **149**: 1180–5.

5 Damevska K, Neloska L, Nikolovska S *et al*. Complementary and alternative medicine use among patients with psoriasis. *Dermatol Ther* 2014; **27**: 281–3.

6 Smith N, Weymann A, Tausk FA, Gelfand JM. Complementary and alternative medicine for psoriasis: a qualitative review of the clinical trial literature. *J Am Acad Dermatol* 2009; **61**: 841–56.

7 Segaert S, Duvold LB. Calcipotriol cream: a review of its use in the management of psoriasis. *J Dermatolog Treat* 2006; **17**: 327–37.

8 Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *Br J Dermatol* 1999; **141**: 185–91.

9 Langley RG, Feldman SR, Nyirady J *et al*. The 5-point Investigator's Global Assessment (IGA) Scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat* 2015; **26**: 23–31.

10 Farahnik B, Sharma D, Alban J, Sivamani RK. Topical botanical agents for the treatment of psoriasis: a systematic review. *Am J Clin Dermatol* 2017; **18**: 451–68.

11 Food and Drug Administration. Botanical drug development: guidance for industry. 2016; Available at: https://www.fda.gov/media/93113/download.

12 Parkman CA. NCCAM herbal supplement studies underway in the United States. *Case Manager* 2005; **16**: 41–3.

13 Tan HY, Zhang AL, Chen D *et al*. Chinese herbal medicine for atopic dermatitis: a systematic review. *J Am Acad Dermatol* 2013; **69**: 295–304.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Study inclusion and exclusion criteria, determination of sample size, and product usage details are further described in the Supporting Information.

