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Original Research Paper

Pharma

CLINICAL DEVELOPMENT PLAN OF TAPINAROF 1% FOR PLAQUE PSORIASIS IN ADULTS.

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ABSTRACT Tapinarof 1% is under clinical development as a novel topical therapy for plaque psoriasis in adults. This document outlines the clinical development plan for tapinarof, focusing on its mechanism of action through the Aryl Hydrocarbon Receptor (AhR), and summarizing its efficacy and safety profiles observed in clinical studies. Tapinarof, an AhR agonist, has demonstrated promising results in improving psoriasis symptoms, as measured by the Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA). Clinical trials have evaluated its safety and efficacy over varying durations, including long-term studies.

KEYWORDS : Tapinarof, Plaque Psoriasis, Aryl Hydrocarbon Receptor, Topical Therapy, Clinical Development, Efficacy, Safety

INTRODUCTION

The skin, which constitutes approximately 15% of an adult's body weight, is the largest organ in the human body. Skin is as a protective barrier against physical, chemical and biological threats. Additionally, plays an important role in prevention of excessive water loss and maintenance of body temperature[1].

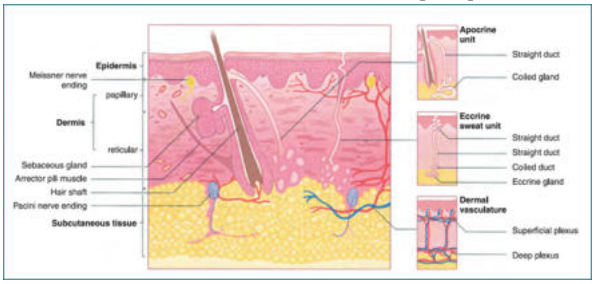

Figure 1 Anatomy of skin[1].

The integumentary system originates from the surface ectoderm and the underlying mesenchyme. It includes the skin and its related structures, such as hair follicles, nails, and sebaceous and sweat glands. The skin is made up of of three distinct layers: the epidermis, the dermis, and the hypodermis[2] (figure 1).

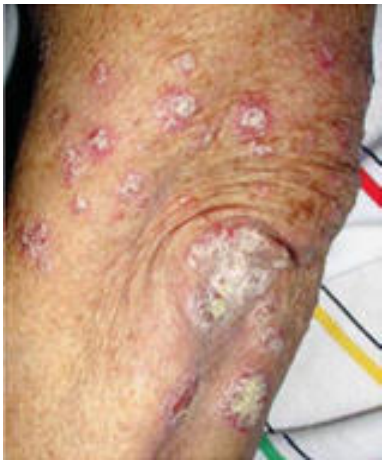

Figure 2 Plaque Psoriasis on elbow[10].

The epidermis mainly consists of keratinocytes, and other specialized cells like melanocytes, Langerhans cells, and Merkel cells. Melanocytes are dendritic in nature, distributing melanin pigment to keratinocytes, which contributes to skin pigmentation[3].

The skin adnexa consist of eccrine and apocrine glands, ducts, and pilosebaceous units. These structures perform various functions and can serve as a substitute epidermis by facilitating epithelialization after surface damage[3]. Below the epidermis lies the dermis, which is subdivided into the papillary layer and the reticular layer.

This layer houses the skin's neurovascular system. Beneath the dermis is the subcutaneous tissue, which includes subcutaneous fat, the superficial fascia and large blood vessels[2–4].

The dermis has excess blood flow, redistributed by arteriovenous shunts, ranging from 1 to 150 ml/100 g skin/min. Blood flow is controlled by neural, humoral, and local factors. Vasoconstriction uses alpha-adrenergic receptors, while beta-adrenergic receptors mediate vasodilation. Local factors like hypoxia, hypercapnia, and hyperthermia also influence flow[5, 6]. Psoriasis is a chronic and inflammatory disorder of skin that affects, which as almost three percntage prevalence in United States population and estimate affected to 125 million individuals worldwide[6]. It can affect both men and women equally in proportion, but it in more common in adults than children[7]. The typical signs of psoriasis include scaly skin plaques, often involving nails and joints.

The condition arises from abnormal epidermal proliferation due to T cell dysfunction. Triggered by environmental factors. It is considered an immune-mediated condition in genetically predisposed individuals[6–9].

There are several variants of psoriasis such as plaque psoriasis, guttate psoriasis, pustular psoriasis and inverse psoriasis[9]. Chronic plaque psoriasis is characterized by erythematous scaly patches which are more commonly present on extensor surface of limbs, face, palms and soles[6, 9]. Lesions may range from small papules to large plaques and can form at trauma sites (Koebner phenomenon)[6, 10] and exhibits the Auspitz sign[10].

The pathophysiology of plaque psoriasis involves immune system dysregulation and chronic inflammation[7].

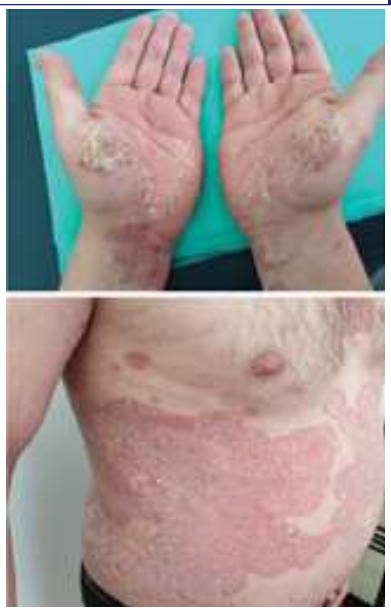

Figure 3 Clinical presentation of plaque psoriasis on palms and trunk[9].

Current topical treatments for psoriasis include corticosteroids, vitamin D analogs (such as calcipotriene or calcitriol), tazarotene, and coal tar, vitamin A [11]. However, their use is often limited due to various short- and long-term adverse effects[12]. While biologics targeting specific immune pathways have greatly improved psoriasis treatment, there remains a limited availability of newer topical agents with innovative mechanisms of action[11]. Although these agents are effective in treating psoriasis and atopic dermatitis, their long-term use is restricted by adverse effects. Currently, new topical treatments designed to target pathological skin processes are under development[13].

The Aryl Hydrocarbon Receptor (AhR) and its Role in Plaque Psoriasis

In the plaque psoriasis, there is the activation of aryl hydrocarbon receptor (AhR) which is a ligand-dependent transcription factor found in both immune and skin cell[12]. It helps to maintain skin homeostasis by regulating the immune responses, differentiation of keratinocytes, barrier function, and gene expression. It can be activated by endogenous and exogenous compounds, including pollutants, PAHs (polycyclic aromatic hydrocarbons), microbial metabolites, dietary components, and phytochemicals. Upon activation, the AhR-ligand complex translocates to the nucleus, dimerizes with the AhR nuclear translocator (ARNT), and binds to DNA, altering gene transcription[14]. AhR is required for normal development, as it helps prevent phenotypic abnormalities. It also plays a crucial role in regulating the innate immune system at barrier sites that comes in contact to the external environment[14]. Tapinarof is a small-molecule AhR agonist that specifically binds to and activates the receptor. In vitro and animal studies suggest that AhR activation by Tapinarof modulates gene expression, reducing skin inflammation by downregulating Th17 cytokines (IL-17A, IL-17F) involved in psoriasis. It also supports skin barrier function by increasing keratinocyte differentiation proteins and reduces oxidative stress through the Nrf2 pathway and direct reactive oxygen species scavenging[11–13].

Tapinarof

Tapinarof is a novel, non-steroidal topical treatment which is being developed for psoriasis and atopic dermatitis. By binding to and activating AhR, a ligand-dependent transcription factor, Tapinarof reduces pro-inflammatory cytokines like interleukin-17 and enhances the expression of skin barrier proteins such as filaggrin and loricrin, supporting skin barrier restoration[15, 16]. The clinical efficacy of Tapinarof in psoriasis treatment is linked to reduction of the proinflammatory (Th17/Th22) cytokines, including IL-17 and IL-22. Additionally, AhR activation by Tapinarof promotes the expression of skin barrier genes like filaggrin, loricrin and involucrum which are typically reduced in psoriasis[15, 17].

The pharmacokinetics analysis showed systemic absorption of tapinarof cream, with higher plasma concentrations in the two percentage cohort. Median Tmax ranged two to four hours and plasma exposure decreased from day 1 to day 21 due to improved skin barrier function. No drug accumulation occurred, and metabolism involved glucuronidation, sulfation, and CYP enzymes (mainly CYP1A2 and CYP3A4). Systemic exposure diminished as inflammation subsided, with no significant adverse effects[18]. Tapinarof plasma concentrations were highest on day one and decreased significantly by day 29, with most samples showing concentrations below the quantifiable limit. Tapinarof sulfate concentrations were consistently undetectable. Pharmacokinetic parameters showed reduced exposure on day 29 compared to day one, with Cmax and AUC values lower, and the half-life could only be calculated for a few patients on day one.

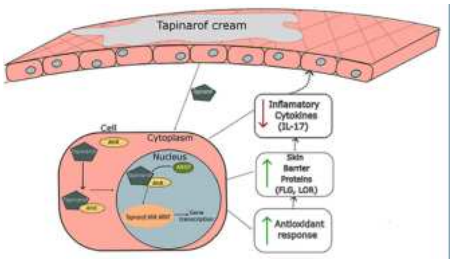

Figure 4 Mechanism of action of Tapinarof[12].

Efficacy

This randomized, double-blind, placebo-controlled phase II trial assessed the efficacy and safety of WBI-1001 (one percentage) in 61 patients with mild to moderate plaque psoriasis over 12 weeks. Patients applied either WBI-1001 cream or placebo twice daily. At 12 weeks, the WBI-1001 group showed a 62.8% improvement in Physician's Global Assessment (PGA) scores, compared to 13.0% for placebo ($p<0.0001$), along with significant reductions in Psoriasis Area and Severity Index (PASI, 71.0%) and body surface area (BSA, 79.1%). Adverse events, mainly mild to moderate dermatological reactions, were more frequent in the WBI-1001 group. The study concluded that WBI-1001 is a safe, effective, and fast-acting topical treatment for mild to moderate psoriasis, warranting further research on long-term use[19].

Additionally in a different phase IIb randomized, double-blind, dose-finding study evaluated the safety and efficacy of tapinarof cream at two concentrations (0.5% and 1%) and two dosing frequencies (once or twice daily) compared to a vehicle in 227 adults with plaque psoriasis. The primary endpoint, defined as achieving a Physician Global Assessment (PGA) score of 0 or 1 with a 2-grade improvement at week 12, was met by 65% of patients on 1% tapinarof twice daily, significantly outperforming vehicle groups (5-11%). Secondary endpoints, including ≥75% improvement in Psoriasis Area and Severity Index (PASI75), were similarly superior for tapinarof, with effects maintained 4 weeks post-treatment. Adverse events, primarily mild to moderate dermatological reactions such as folliculitis and contact dermatitis, were more frequent in tapinarof groups. The study concluded that Tapinarof is an effective and well-tolerated topical treatment for plaque psoriasis, indicating the need for further evaluation [19].

Two identical, multicenter, randomized, double-blind, vehicle-

controlled Phase III trials PSOARING 1 (NCT03956355) and PSOARING 2 (NCT03983980) with sample size of 510 and 515 respectively, were conducted across the U.S. and Canada, involving adults with mild-to-severe plaque psoriasis. Participants were randomized in a 2:1 ratio to receive either tapinarof 1% cream or a vehicle cream once daily for 12 weeks. The primary endpoint was achieving a Physician's Global Assessment (PGA) score of 0 or 1 with at least a 2-grade improvement. Secondary endpoints included achieving PASI 75 and PASI 90, changes in the percentage of body surface area affected, and patient-reported outcomes, such as pruritus relief and quality-of-life improvements. Adverse events were rigorously monitored.

In Trial 1, 35.4% of patients in the tapinarof group achieved the primary endpoint of a PGA score of 0 or 1 with at least a 2-grade improvement at week 12, compared to 6.0% in the vehicle group (adjusted difference: 29.4%; relative rate: 5.8; $p<0.001$). Similarly, in Trial 2, the tapinarof group achieved a PGA response in 40.2% of cases compared to 6.3% in the vehicle group (adjusted difference: 33.9%; relative rate: 6.1; $p<0.001$). Secondary outcomes supported these findings, with PASI 75 achieved by 36.1% (Trial 1) and 47.6% (Trial 2) of patients in the tapinarof group versus 10.2% and 6.9% in the vehicle group, respectively ($p<0.001$). The proportion of patients achieving PASI 90 was 18.8% (Trial 1) and 20.9% (Trial 2) in the tapinarof group compared to 1.6% and 2.5% in the vehicle group ($p<0.001$).

Patient-reported outcomes also improved significantly in the tapinarof group. Pruritus scores decreased by an average of 3.6 points compared to 2.7 reduction in the vehicle group in Trial 1 and 3.0 points reduction as compared to reductions of 1.4 points in the vehicle group in Trial 2. Quality of life, measured by the Dermatology Life Quality Index (DLQI), showed mean reductions of 4.6 (Trial 1) and 4.4 (Trial 2) in the tapinarof group, compared to 2.8 and 1.1 in the vehicle group. Psoriasis Symptom Diary scores showed significant reductions, further highlighting the treatment's impact on patients' day-to-day experiences with psoriasis.

Tapinarof showed solid efficacy across multiple endpoints, significantly better than the vehicle group in clearing psoriasis lesions and improving patient's quality of life. Its favorable safety profile, and manageable local side effects, makes it a promising novel topical option for plaque psoriasis. However, side effects like folliculitis needs to be further explored. The trials also highlighted tapinarof's distinctive mechanism of leveraging immune modulation and antioxidant activity, which is an important step forward in addressing unmet needs in psoriasis management.

Tapinarof 1% cream represents a promising new treatment for plaque psoriasis, with significant improvements in both disease severity and patient-reported outcomes over 12 weeks. Despite some local adverse effects, its efficacy and tolerability warrant further exploration in larger, longer-term studies to establish its position among current treatment options.

The PSOARING 3[20] trial was maximal use study to evaluate the long-term safety, efficacy, and tolerability of tapinarof 1% cream in adults with mild to severe plaque psoriasis. This open-label extension included 763 participants from prior 12-week phase 3 trials. Patients received up to 40 weeks of treatment, followed by 4 weeks of follow-up, with treatment tailored based on Physician Global Assessment (PGA) scores. Results demonstrated significant efficacy, with 40.9% of patients achieving complete disease clearance (PGA = 0) during the trial. Among patients entering the trial with moderate or severe psoriasis (PGA ≥ 2), 58.2% achieved at least a near-clearance (PGA = 0 or 1) at some point. The average duration of disease remission off therapy was 130.1 days, with 24.1% of patients maintaining clearance without needing retreatment. No evidence of tachyphylaxis (loss of treatment effect over time) was observed, and efficacy was consistent with intermittent use[20].

Overall, the trial highlighted the long-term benefits of tapinarof as a nonsteroidal topical treatment for plaque psoriasis, with durable efficacy, a substantial remittive effect supporting its potential as a novel therapy for psoriasis management[20].

Safety

A phase II trial for WBI-1001[21], a 1% non-steroidal topical cream, involved 61 patients with mild to moderate plaque psoriasis randomized to receive either WBI-1001 or placebo twice daily for 12 weeks. Efficacy was assessed using the Physician's Global Assessment (PGA), Psoriasis Area and Severity Index (PASI), and changes in body surface area (BSA) affected. Safety monitoring included adverse events (AEs), lab tests, and electrocardiograms. Treatment-related AEs in the WBI-1001 group included application site discoloration (27.5%), dermatitis (15%), folliculitis (10%), and papules (7.5%), all mild or moderate, leading to discontinuation in two cases. Overall, 80% of WBI-1001-treated patients experienced AEs, compared to 52.4% in the placebo group, with no serious AEs linked to the treatment[21].

In another clinical trial, the tapinarof cream 1% trial, adverse events (AEs) were reported in 12 out of 21 patients (57.1%) treated under maximal use conditions for 29 days. The most frequently observed AEs were folliculitis (19.0%) and headache (19.0%). Both folliculitis and headache were considered treatment-related; folliculitis was mild in three patients and moderate in one. Other reported AEs included back pain and pruritus, each affecting 9.5% of patients. Notably, no patients discontinued treatment due to these events. Local tolerability was favorable, with no significant irritation reported, even in sensitive areas such as the face, axilla, and genital regions. No clinically relevant changes were observed in laboratory values, vital signs, or electrocardiograms (ECGs). A serious adverse event (SAE) of pancreatitis occurred in one patient, but it was deemed unrelated to the study drug. Overall, tapinarof demonstrated a strong safety and tolerability profile, with most AEs being mild and transient[15].

In the phase 3 PSOARING trials[22], adverse events associated with tapinarof cream 1% were common but typically mild to moderate in severity. The most frequent adverse events included folliculitis (23.5% in trial 1 and 17.8% in trial 2), contact dermatitis (5.0% and 5.8%, respectively), and headache (3.8% in both trials). Severe events were rare, with only one severe case reported for folliculitis, contact dermatitis, and headache across the trials. Discontinuations due to adverse events were relatively low, occurring in 5.6% of patients in trial 1 and 5.8% in trial 2, primarily related to folliculitis and contact dermatitis. Investigators highlighted that these adverse events were generally self-limiting, manageable, and did not significantly impact overall treatment adherence. The trials underscored that the safety profile of tapinarof cream was acceptable for patients with mild-to-severe plaque psoriasis, with no significant differences in systemic safety outcomes such as laboratory values, vital signs, or electrocardiograms between the tapinarof and vehicle groups[22].

Summary

Tapinarof 1% cream is being developed as a novel, non-steroidal topical treatment for plaque psoriasis in adults, leveraging its role as an aryl hydrocarbon receptor (AhR) modulator to target key inflammatory pathways involved in

the disease. Preclinical studies have demonstrated its anti-inflammatory properties and skin barrier-restoring capabilities, supported by a favorable safety profile. Clinical trials, including Phase II and III studies, have shown significant improvements in psoriasis severity scores such as PASI, with many patients achieving sustained remission. Tapinarof is well-tolerated, with minimal adverse events, primarily mild skin irritation. It offers a promising long term treatment alternative to steroidal therapies while avoiding steroid-related side effects. The clinical development plan aligns with regulatory requirements, paving the way for FDA approval and promising to establish Tapinarof as a safe and effective choice for managing plaque psoriasis in adults.

Abbreviations

AEs	Adverse Events
AhR	Aryl Hydrocarbon Receptor
ARNT	AhR Nuclear Translocator
BSA	Body Surface Area
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
Nrf2	Nuclear factor erythroid 2-related factor 2
PASI	Psoriasis Area and Severity Index
PASI 75	≥75% improvement in Psoriasis Area and Severity Index
PASI 90	≥90% improvement in Psoriasis Area and Severity Index
PGA	Physician's Global Assessment
SAE	Serious Adverse Events

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