Journal Club
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Title: Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis

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Background: Plaque psoriasis, which represents 80 to 90% of clinical psoriasis manifestations, is disease characterized by sharply demarcated, erythematous, scaly patches or plaque on the body. These are mostly found on the scalp, trunk, gluteal fold, and extensor surfaces such as the elbows and knees.[1] The pathophysiology of plaque psoriasis is complex and not fully understood, but it is thought that excessive activation of parts of the adaptive immune system leads to activation of key inflammatory mediators causing the lesions.[1] In the United States, the adult incidence is nearly 80 new cases per 100,000 person-years.[2] A variety of medication classes are used to treat plaque psoriasis. These include topical, systemic, and biologic agents, each with their own risk-benefit assessment.[1] When considering topical therapy, the joint American Academy of Dermatology-National Psoriasis Foundation (AAD-NPF), provides clinicians with several options. Topical steroids have remained a top recommendation; however, these agents are limited to a short duration to avoid adverse events associated with long-term use. Other topical agents that are recommended include calcineurin inhibitors, vitamin D analogs, or salicylic acid.[3] Previous phase 2 studies have evaluated tapinarof, a novel nonsteroidal, topical aryl hydrocarbon receptor–modulating agent, in development for plaque psoriasis and atopic dermatitis.[4,5] This article is presenting the PSOARING 1 and PSOARING 2 trials which were looking to establish the efficacy and safety of tapinarof cream in patients with plaque psoriasis.[6]

Primary Objective: To determine if tapinarof 1% cream is superior to placebo in the treatment of plaque psoriasis.

Primary Efficacy Measure: Physician Global Assessment (PGA) response, defined as a PGA score of zero (clear) or 1 (almost clear) and a decrease from baseline of at least 2 points on the 5-point PGA scale at week 12.

Study Design: This was two identical phase III, randomized, double-blind, placebo-controlled studies that took place in the United States of America and Canada. Patients were screened for a maximum of 34 days prior to beginning the 12-week treatment period, after which patients could enroll in an open label long-term extension trial (PSOARING 3) or complete a follow up at week 16. Patients were not allowed to use other medications for treatment of plaque psoriasis during the trial.

Subjects: Both trials used 2:1 randomization. PSOARING 1 randomization resulted in similar group with regards to age, weight, body-mass index, and baseline PGA score. This trial did have marked differences between groups, most noticeably, distribution of sex, races,

and duration of psoriasis. PSOARING 2 randomization resulted in a very similar profile to PSOARING 1, including differences in distribution of sex, races, and duration of psoriasis.

Inclusion Criteria:

- Male and female subjects ages 18 to 75 years with clinical diagnosis of chronic plaque psoriasis and stable disease for at least 6 months prior to the study .
- Body surface area involvement 3% and 20% (The subject's scalp, palms, fingernails, toenails, and soles should be excluded from the %BSA calculations).
- A PGA score of 2 (mild), 3 (moderate) or 4 (severe) at screening and baseline (pre-randomization). Subjects with mild and severe psoriasis will be limited to approximately 10% each of the total randomized population; the majority of the enrolled subjects (approximately 80%) will have a PGA of 3, signifying moderate disease.
- Females of child-bearing potential and male subjects who are engaging in sexual activity that could lead to pregnancy must use at least 1 of the following adequate birth control methods while on study and for 4 weeks after the last exposure to study drug. Acceptable contraception methods are:
    a. Male partner with vasectomy, OR Male condom AND partner use of one of the contraceptive options below:
    b. Spermicide
    c. Contraceptive subdermal implant that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label
    d. Intrauterine device or intrauterine system that meets effectiveness criteria including a < 1% rate of failure per year, as stated in the product label
    e. Oral contraceptive, either combined or progestogen alone
    f. Injectable progestogen
    g. Contraceptive vaginal ring
    h. Percutaneous contraceptive patches

    NOTE: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before baseline.
    These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

    Non-child-bearing potential is defined as premenarchal or pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy, or hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 IU/mL is confirmatory. Documented verbal history from the subject is acceptable.

    Subjects who are abstinent are eligible, but they must agree to use one of the birth control methods listed above if they start engaging in sexual activity that could lead to pregnancy during the study.

Female subjects of childbearing potential must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

- Capable of giving written informed consent, as applicable, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF); written informed consent must be obtained prior to any study related procedures.

Exclusion Criteria:

- Psoriasis other than plaque variant.
- Any sign of infection of any of the psoriatic lesions.
- Concurrent conditions or history of other diseases:
    a. Immunocompromised (eg, lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus (HIV) antibody at Screening
    b. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to the Baseline visit
    c. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, chicken pox) skin infection within 1 week prior to the Baseline visit
    d. Significant dermatologic or inflammatory condition other than plaque psoriasis that, in the Investigator's opinion, would make it difficult to interpret data or assessments during the study
- Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) 1.5x the upper limit of normal (ULN)
- Screening total bilirubin > 1.5 x ULN; total bilirubin > ULN and 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%.
- Corrected QT (QTcF) interval > 475 msec.
- Current or chronic history of liver disease, known hepatic or biliary abnormalities (withthe exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result, or a positive antihepatitis B core antigen (anti-HBc) result.
- Ultraviolet (UV) light therapy or prolonged exposure to natural or artificial sources of UV radiation (eg, phototherapy, tanning beds/booths, or therapeutic sunbathing) within 4 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the subject's psoriasis (as determined by the Investigator).
- Use of any prohibited medication within the indicated period before the Baseline visit.

  NOTE: Prohibited concomitant medications, therapy, etc., during the defined period are as listed in the bullets below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study.

a. Minimum of 5 half-lives for biologic agents: eg, 12 months for rituximab; 8 months for ustekinumab; 5 months for secukinumab; 12 weeks for golimumab; 10 weeks for ixekizumab; 8 weeks for infliximab, adalimumab, or alefacept; and 4 weeks for etanercept.
b. 4 weeks for systemic treatments: cyclosporin, interferon, methotrexate, apremilast, tofacitinib, mycophenolate, thioguanine, hydroxyurea, sirolimus, azathioprine, other systemic immunosuppressive or immunomodulating agents, fumaric acid derivatives, vitamin D3 and analogs, retinoids (eg, acitretin, isotretinoin), psolarens, corticosteroids, or adrenocorticotropic hormone analogs.
c. 2 weeks for immunizations with a live viral component; drugs known to possibly worsen psoriasis, such as beta-blockers (eg, propranolol), lithium, iodides, angiotensin-converting enzyme inhibitors, and indomethacin, unless on a stable dose for > 12 weeks.
d. With the exception of non-medicated emollients, 2 weeks for topical treatments including corticosteroids, immunomodulators, anthralin (dithranol), Vitamin D derivatives (eg, calcipotriene, calcipotriol), retinoids (Note: 4 weeks for tazarotene), or coal tar.

- A history of or ongoing serious illness or medical, physical, or psychiatric condition(s)That, in the Investigator's opinion, may interfere with the subject's participation in the study and ability to understand and give informed consent.
- Pregnant females as determined by positive serum (screening) or urine (baseline) human chorionic gonadotropin test at screening or prior to dosing.
- Lactating females
- History of sensitivity to the study drugs, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the subject's participation in the study.
- The subject has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the study drug (whichever is longer).
- Current or a history of cancer within 5 years except for fully excised skin basal cell carcinoma, squamous cell carcinoma or carcinoma in situ of the cervix.
- Subjects with active infection that required oral, intramuscular, or intravenous administration of antibiotics, antifungal or antiviral agents within 7 days of Baseline/Day 1.
- Concurrent skin lesions in the treatment area that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject.
- Subjects with advanced disease or abnormal laboratory test values that could affect the safety of the subject or the implementation of this study.
- Previous known participation in a clinical study with tapinarof.
- Evidence of significant hepatic, renal, respiratory, endocrine, hematologic, neurologic, psychiatric, or CV system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results

Study Period: PSOARING 1 took place from April 25, 2019, to May 26, 2020, and PSOARING 2 took place from May 30, 2019, to May 13, 2020. After a maximum 34-day

screening period, patients were randomized to receive tapinarof 1% cream or vehicle placebo with directions to apply a thin layer of cream once daily to cover psoriasis lesions completely, including newly appearing lesions and any lesions or areas in which psoriasis abated or cleared during the trial for 12 weeks.

Monitoring: Patients were monitored for psoriasis severity and adverse events including laboratory monitoring at baseline, weeks 2, 4, 8, and 12 during the study period. Patients were instructed to complete a daily diary to assess adherence to the treatment regimen.

Data Analysis: Analysis of an intent-to-treat population was performed in both trials. PSOARING 1 analyzed 340 patients assigned to tapinarof and 170 patients assigned to placebo. PSOARING 2 analyzed 343 patients assigned to tapinarof and 172 patients assigned placebo. Both trials set power at 99% with 500 patients total required. Alpha was set at 0.05.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Percent of patients achieving PGA response	Nominal	Cochran-Mantel-Haenszel	Appropriate

Results: In both trials, once daily tapinarof cream was found to have a statistically significant difference versus placebo in the percentage of patients achieving PGA response at week 12. This is shown by the confidence interval not crossing the absolute equivalency of 1 and further supported by a p value less than alpha.

	PSOARING 1			
	Tapinarof (n=340)	Placebo (n=170)	Relative Rate vs. Placebo (95% CI)	P Value
Percent of Patients achieving PGA response	35.4 ± 2.8	6.0 ± 2.1	5.8 (2.9 to 11.6)	<0.001
	PSOARING 2			
	Tapinarof (n=343)	Placebo (n=172)	Relative Rate vs. Placebo (95% CI)	P Value
Percent of Patients achieving PGA response	40.2 ± 2.8	6.3 ± 2.0	6.1 (3.3 to 11.4)	<0.001

Tolerability: Between both trials, the number of adverse events and most common reported adverse events were similar.

	PSOARING 1		PSOARING 2	
	Tapinarof (n=340)	Placebo (n=170)	Tapinarof (n=343)	Placebo (n=172)
Any Adverse Event (%)	171 (50.3)	39 (22.4)	187 (54.5)	45 (26.2)
Adverse Event Leading to Trial Discontinuation (%)	19 (5.6)	0	20 (5.8)	1 (0.6)
Folliculitis (%)	80 (23.5)	2 (1.2)	61 (17.8)	1 (0.6)
Nasopharyngitis (%)	25 (7.4)	10 (5.9)	14 (4.1)	5 (2.9)
Contact Dermatitis (%)	17 (5.0)	1 (0.6)	20 (5.8)	0
Headache	13 (3.8)	4 (2.4)	13 (3.8)	1 (0.6)
Upper Respiratory Tract Infection (%)	5 (1.5)	4 (2.4)	12 (3.5)	8 (4.7)
Pruritis (%)	8 (2.4)	0	7 (2.0)	2 (1.2)
Viral Upper Respiratory Tract Infection (%)	7 (2.1)	2 (1.2)	3 (0.9)	0

Author's Conclusion: Both PSOARING 1 and PSOARING 2 showed that once daily topical tapinarof 1% cream is superior to a vehicle placebo cream in reducing the severity of plaque psoriasis over a period of 12 weeks.

Strengths:

- Power was set and met
- Treatment was appropriate and accepted
- Length of study was appropriate to show affect
- Inclusion and exclusion criteria were appropriate
- Blinding was present
- Biostatistical test was appropriate
- Primary outcome is standard and accepted
- Authors' conclusion supported by results

Limitations:

- Randomization produced groups with marked differences
- Mostly white population
- Local adverse events may have unmasked the active treatment in the trials
- Only included patients from the United States and Canada
- Only including patients with plaque psoriasis
- Excluded patients with very limited and very extensive body-surface area affected

Level of Evidence: Level I – interventional, placebo-controlled, randomized trial that met power with Major Limitations

Recommendation: I recommend that topical tapinarof 1% cream be used in the treatment of moderate plaque psoriasis versus no therapy for the following reasons:

- Efficacy
  - Percentage of patients achieving PGA response was statistically significant in both trials
    - PSOARING 1: Tapinarof (n=340) vs. Placebo (n=170) – 35.4%±2.8 vs. 6.0%±2.1; RR 5.8, 95% CI [2.9 to 11.6]; p<0.001
    - PSOARING 2: Tapinarof (n=343) vs. Placebo (n=172) – 40.2%±2.8 vs. 6.3%±2.0; RR 6.1, 95% CI [3.3 to 11.4]; p<0.001
- Safety
  - There were no serious adverse events that were related to tapinarof or placebo cream
  - Most commonly reported adverse events with > 2% frequency in the treatment groups in PSOARING 1 and PSOARING 2 were folliculitis (23.5% and 17.8%), nasopharyngitis (7.4% and 4.1%), contact dermatitis (5.0% and 5.8%), headache (3.8% and 3.8%), upper respiratory tract infection (1.5% and 3.5%), pruritis (2.4% and 2.0%), and viral upper respiratory tract infection (2.1% and 0.9%).
- Cost[7]
  - Cost of tapinarof 1% cream is currently unknown
  - Betamethasone
    - 0.05% augmented dipropionate cream: $0.31 to $5.58 per gram
    - 0.05% augmented dipropionate ointment: $4.23 to $5.55 per gram
    - 0.05% dipropionate cream: $2.77 to $3.52 per gram
    - 0.05% dipropionate ointment: $3.36 to $4.10 per gram
    - 0.1% valerate cream: $0.17 to $1.27 per gram
    - 0.1% valerate ointment: $1.36 to $1.39 per gram
  - Calcipotriene
    - 0.005% cream: $7.06 to $15.83 per gram
    - 0.005% ointment: $6.03 to $6.38 per gram
  - Calcipotriene and Betamethasone
    - 0.005-0.064% cream: $23.00 per gram
    - 0.005-0.064% ointment: $13.15 to $22.43 per gram
  - Triamcinolone
    - 0.1% acetonide cream: $0.24 to $0.39 per gram
    - 0.1% acetonide ointment: $0.37 to $0.39 per gram
    - 0.5% acetonide cream: $0.67 to $0.76 per gram
    - 0.5% acetonide ointment: $0.67 per gram
- Special Considerations/Populations
  - There is currently no data comparing tapinarof 1% cream to existing treatments for plaque psoriasis
  - Further studies are needed to establish long-term safety of tapinarof
  - Mostly white population limits generalizability to other races

- Patients included were from the United States and Canada only, limiting generalizability to other populations
- Only studied in plaque psoriasis limiting generalizability to all forms of psoriasis
- Excluded patients with very limited and very extensive body-surface area affected limiting generalizability to the full spectrum of severity of plaque psoriasis
- Current data set limits treatment to 12 weeks
    - PSOARING 3
- Further studies needed to determine ability to sustain PGA response

Grade of Recommendation: A

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