CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215272Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Original NDA
Application Number(s)	215272
Priority or Standard	Standard
Submit Date(s)	May 26, 2021
Received Date(s)	May 26, 2021
PDUFA Goal Date	May 26, 2022
Division/Office	Division of Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	
Established/Proper Name	tapinarof
(Proposed) Trade Name	Vtama
Pharmacologic Class	Aryl hydrocarbon receptor (AhR) modulating agonist
Code name	N/A
Applicant	Dermavant Sciences GMBH
Doseage form	Cream, 1%
Applicant proposed Dosing Regimen	Apply a thin layer to affected area(s) once daily
Applicant Proposed Indication(s)/Population(s)	For the topical treatment of plaque psoriasis in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Plaque psoriasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the topical treatment of plaque psoriasis in patients 18 years and older
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Plaque psoriasis (disorder)
Recommended Dosing Regimen	Apply a thin layer to affected area(s) once daily

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant, Dermavant Sciences GMBH, submitted a new drug application (NDA) 215272, VTAMA (tapinarof) cream, 1%, under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the treatment of plaque psoriasis in adults. Tapinarof, the active ingredient, is a small molecule aryl hydrocarbon receptor (AhR) modulating agent, which activates AhR, a cytosolic ligand-dependent transcription factor. The activation of the AhR signaling pathway downregulates the expression of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-13, IL-17A and F, and eotaxin, and upregulates the expression of several skin barrier proteins, including filaggrin, hornerin, and involucrin. In addition, AhR also activates antioxidative transcription factor nuclear factor-erythroid 2-related factor-2 (Nrf2), upregulating the expression of antioxidative enzymes, which protect against oxidative damage resulting from inflammation and injury.

The proposed indication is topical treatment of plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is to apply a thin layer to affected areas once daily. It will be packaged and dispensed as a 60 g tube.

The Agency concluded that the proposed proprietary name, VTAMA, was acceptable from both a promotional and safety perspective under NDA 215272 (proprietary name review by Dr. Madhuri R. Patel, Division of Medication Error Prevention and Analysis dated September 28, 2021).

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the efficacy of VTAMA in the treatment of adults with plaque psoriasis, the Applicant submitted the data from two adequate and well-controlled Phase 3 trials (DMVT-505-3001, henceforth referred to as Study 3001; and DMVT-505-3002, henceforth referred to as Study 3002). The trials assessed the primary endpoint of "treatment success" at Week 12. Treatment success was defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear") and a minimum two-point decrease from Baseline (i.e., PGA score of 0 or 1 if moderate disease at Baseline or PGA score of 0 if mild disease at Baseline).

Tapinarof cream, 1%, was superior to vehicle cream ($p<0.001$, difference [95% confidence interval (CI)]) for the primary endpoint of treatment success at Week 12. The Applicant demonstrated that tapinarof cream, 1%, is effective for its intended use in the target population and met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant, Dermavant Sciences GMBH, submitted NDA 215272 for VTAMA (tapinarof) cream, 1%. The proposed indication is topical treatment of plaque psoriasis in patients 18 years of age and older.

Tapinarof cream is a small molecule, an aryl hydrocarbon receptor (AhR) modulating agent. Activation of the AhR signaling pathway in the nucleus downregulates the expression of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5, IL-6, IL-13, IL-17A and F, and eotaxin, and upregulates the expression of several skin barrier proteins, including filaggrin, hornerin, and involucrin.

The Applicant conducted two Phase 3 randomized, multicenter, vehicle-controlled studies in 1025 subjects ≥18 years of age with mild-to-severe plaque psoriasis. A total of 683 subjects were randomized to tapinarof cream, 1% and 342 subjects were randomized to vehicle cream. Subjects had a baseline disease severity of 2 ("mild"), 3 ("moderate") or 4 ("severe") on a 5-point scale of overall disease severity, and an affected body surface area (BSA) involvement of 3% to 20%. The primary efficacy endpoint was defined as a Physician's Global Assessment (PGA) score of 0 ("clear") or 1 ("almost clear") with at least a two-grade reduction from baseline, assessed at Week 12.

For both trials, tapinarof cream, 1% was superior to vehicle on the primary efficacy endpoint (Study 3001: 35% vs 6% and in Study 3002: 40% vs 6%; p-values < 0.001).

The safety database that consisted of data pooled from vehicle-controlled studies (3001 and 3002) and the Long Term Extension (LTE) study (3003) was adequate to characterize the safety profile of tapinarof cream, 1%. One death (myocardial infarction) reported in long-term extension study (Study 3003) was considered unrelated to treatment with tapinarof cream, 1%. In two vehicle-controlled studies, the most frequently reported adverse reactions in subjects treated with tapinarof cream, 1% were: folliculitis (20%), nasopharyngitis (1%) and contact dermatitis (7%); compared to vehicle cream treated subjects (1%; 9% and 1%) respectfully. In the LTE study (3003), the most frequently reported adverse reactions were: folliculitis 24%, contact dermatitis 9%, pruritus 3%, headache 2%, urticaria 1%, and drug eruption 1%.

The Applicant provided evidence of safety and efficacy of tapinarof cream, 1%, for the topical treatment of plaque psoriasis in patients 18 years of age and older. In view of tapinarof's favorable overall benefit/risk assessment, the review team recommends approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Psoriasis is a common, chronic, inflammatory multisystem disorder that primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the United States is approximately 2 to 3%, and an estimated 20% of patients with psoriasis have moderate-to-severe disease.	Plaque psoriasis can be a serious disease because of its chronicity and impact on quality of life.
Current Treatment Options	Mild disease is commonly treated with topical corticosteroids or synthetic vitamin D products, but systemic treatments may be needed for more widespread and severe disease. Currently approved topical products indicated for the treatment of psoriasis include corticosteroids, synthetic vitamin D3 derivatives, retinoids, and fixed combinations of these moieties. Topical products come in a variety of formulations, including ointments, creams, solutions, oils, lotions, and foams. Systemic treatments include tumor necrosis factor antagonists (adalimumab, etanercept, infliximab), interleukin [IL]-17 antagonists (secukinumab, ixekizumab), an IL-17 receptor antagonist (brodalumab), an IL-12/-23 antagonist (ustekinumab), and the IL-23p19 antagonists (guselkumab, tildrakizumab, and risankizumab). Other approved systemic psoriasis therapies include acitretin, methotrexate, cyclosporine, and apremilast. Phototherapy, either ultraviolet (UV) A light combined with psoralen methoxsalen or UV-B light therapy (narrow or broadband) may also be an appropriate first-line or adjunctive treatment for patients with moderate-to-severe psoriasis.	There are a number of FDA-approved products with an acceptable risk-benefit profile for the topical treatment of plaque psoriasis in adults. None of these treatments provides a permanent cure. Approval of this application would add to the treatment armamentarium for plaque psoriasis by providing a new topical product with a unique mechanism of action.
Benefit	Data from two adequate and well-controlled studies (3001 and 3002) provide substantial evidence of the effectiveness of tapinarof cream, 1%, for the topical treatment of plaque psoriasis. The studies were conducted in 1025 subjects ≥18 years of age with mild-to-severe psoriasis. Tapinarof	Tapinarof cream, 1%, provides an effective and safe treatment option for the topical treatment of plaque psoriasis in patients 18 years of age and older.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cream, 1%, was superior to vehicle cream ($p<0.001$) for the primary endpoint of "treatment success" at Week 12. Treatment success was defined as a PGA score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade reduction from baseline. Review of the safety data from the clinical studies identified several adverse reactions attributable to tapinarof cream, 1%, including folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, and influenza.	
Risk and Risk Management	The primary safety database included 683 subjects who were treated with tapinarof cream, 1% in the vehicle-controlled studies 3001 and 3002 for 12 weeks; a 40-week, long-term extension study of 763 subjects (subjects who rolled over from Studies 3001 and 3002); and 21 subjects from a maximal use study. One death occurred during the open-label, long-term extension study (Study 3003); it was not related to treatment with tapinarof cream. The most frequently reported adverse reactions in subjects treated with tapinarof cream, 1% were folliculitis, nasopharyngitis, contact dermatitis, headache, pruritus, and influenza. Folliculitis was reported in 20% of subjects treated with tapinarof cream and 1% of subjects treated with vehicle. Contact dermatitis was reported in 7% of subjects treated with tapinarof cream and 1% of subjects treated with vehicle. Labeling: Prescription labeling adequately addresses the known risks associated with the moiety and those identified during product development. Assessment of the safety and PK in pediatric subjects with plaque psoriasis ages 2 to 17 is recommended as a postmarketing requirement.	The risks associated with use of tapinarof cream, 1%, appear favorable. Most adverse reactions were mostly mild or moderate in severity. Prescription labeling, patient labeling, and routine pharmacovigilance are adequate to manage the risks of the product.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	The patient experience data that were submitted as part of the application include:			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated condition that manifests on the skin, but is associated with systemic co-morbidities such as cardiovascular disease, metabolic conditions, joint disease and psychiatric impact (Parisi, et al, 2020). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines that trigger and perpetuate the inflammatory cascade.

In the United States, the prevalence of psoriasis is 3% in adults 20 years and older, which translates to 7.55 million US adults (Armstrong, et al., 2021). Approximately 70.9% of those affected by psoriasis have mild- to-moderate disease, and 27.3% have moderate-to-severe psoriasis, defined as affecting more than 10% of the body surface area (BSA) (Takeshita, et al., 2015). The rates of psoriasis between men and women is similar, 3.2% for women and 2.8% for men. It is most common in White individuals (3.6%), with prevalence rates of Asians at 2.5%, Hispanics 1.9%, and Blacks at 1.5% (Armstrong, et al., 2021).

Psoriasis can first appear at any age, from infancy to the eighth decade of life, although the most common periods are between 20 to 30 years of age and between 50 to 60 years. Approximately 75% of patients are diagnosed before the age of 40 years, and in 35% to 50%, before the age of 20 years. The age of onset is earlier in women than in men (Van de Kerkhof, et al., 2018). In 35-90% of patients, a positive family history is reported (Van de Kerkhof, et al., 2018).

Psoriasis is a chronic condition that waxes and wanes. Remission of about 5 years can occur in about 15% of patients. The most common form of psoriasis is plaque psoriasis, affecting about 55-79% of patients with psoriasis (Merola, et al., 2016; Feldman, et al., 2019) and presenting as sharply demarcated, erythematous plaques with silvery scale. The most common areas of involvement are the scalp, elbows, knees, lumbosacral area, and hands and feet. The genitalia is affected in up to 45% of patients. With more extensive involvement, plaques form on the trunk and other areas on the extremities. Other forms include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, often in association with psoriatic arthritis (Van de Kerkhof, et al., 2018).

A diagnosis of psoriasis can be made by history and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, nummular eczema, mycosis fungoides, and squamous cell cancer of the skin. Occasionally, a skin biopsy is necessary to rule out other conditions (Van de Kerkhof, et al., 2018).

The prevalence of psoriasis in the pediatric population (i.e., less than 20 years of age) is

approximately 2% worldwide, and 1/3 of psoriasis patients present during childhood. They have a 2x-higher risk for developing comorbidities in adulthood (see below) than children without psoriasis. Approximately 6 to 41% of children with psoriasis also develop psoriatic arthritis (Kim, et al., 2021).

The anogenital area is most commonly affected in psoriasis patients under the age of 2, particularly the diaper area. Due to the moist and occlusive environment, it is often thin, areas of confluent erythema, without scale. Involvement of the genitalia and the umbilicus can help distinguish it from other, more common, diaper dermatitides. Compared to adults with psoriasis, pediatric patients may also develop psoriasis on the face or present with guttate psoriasis. Children are more likely than adults to experience spontaneous remission (Kim, et al., 2021).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, dyslipidemia, pulmonary disease, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and depression (Takeshita, et al., 2015).

2.2. Analysis of Current Treatment Options

The proposed indication is the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older. The classes of topical drugs that are FDA-approved for plaque psoriasis are corticosteroids, vitamin D derivatives, retinoids, and combination drugs. Several examples of products available for the topical treatment of plaque psoriasis are listed in Table 1.

Table 1. Summary of Treatments Relevant to Proposed Indication of Plaque Psoriasis

Product Class	**Product/Year Approved**	**Relevant Indication**	**Dosage and Administration**	**Efficacy Information**	**Important Safety and Tolerability Issues**
Corticosteroid	Olux E (clobetasol propionate) Foam/2007	CSRD (one trial in mild-to-moderate plaque-type psoriasis)	Apply thin layer twice daily; treatment should be limited to 2 consecutive weeks and patients should not use more than 50 g per week.	In a randomized study of subjects 12 years of age and older with mild to moderate plaque psoriasis, 253 subjects were treated with Olux-E Foam and 123 subjects were treated with vehicle foam. 41 of 253 subjects (16%) treated with Olux-E Foam compared to 5 of 123 (4%) treated with vehicle foam achieved treatment success. Treatment success was defined by an Investigator's Static Global Assessment score of clear (0) or almost clear (1) with at least a 2-grade improvement from baseline, scores of none or faint/minimal (0 or 1) for erythema and scaling, and a score of none (0) for plaque thickness.	Use in pediatric patients under 12 years of age is not recommended because of a numerically high rate of HPA axis suppression.
Synthetic Vitamin D3 Derivative	Dovonex (calcipotriene) Cream/1996	Plaque psoriasis	Apply thin layer twice daily	Adequate and well-controlled trials have demonstrated improvement usually beginning after 2 weeks of therapy. This improvement continued with approximately 50% of patients showing at least marked improvement in the signs and symptoms of psoriasis after 8 weeks of therapy, but only approximately 4% showed complete clearance.	Reversible elevation of serum calcium has occurred.

Product Class	Example Product/Year Approved	Relevant Indication[1]	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Synthetic Vitamin D3 Derivative/ Corticosteroid Combination Product	Taclonex (calcipotriene 0.005% and betamethasone dipropionate 0.064%) Ointment/2006	Plaque psoriasis in patients 12 years of age and older	Use once daily for up to 4 weeks	1603 subjects with mild to very severe plaque psoriasis on the trunk and limbs were treated once daily for 4 weeks. Subjects were randomized to one of four treatment arms: Taclonex Ointment, calcipotriene hydrate 50 µg/g in the same vehicle, betamethasone dipropionate 0.64 mg/g in the same vehicle, and vehicle alone. Treatment effect was 48%, 16.5%, 23.3% and 7.6%, respectively. Efficacy was assessed as the proportion of subjects with absent or very mild disease according to the Investigator's Global Assessment of Disease Severity at end of treatment (4 weeks).	Hypercalcemia and hypercalciuria and HPA axis suppression have been observed. Patients aged 12 to 17 years should not use more than 60 g per week. Treatment of more than 30% of body surface area is not recommended.
Retinoid	Tazorac (tazarotene) Cream, 0.05%, 0.1%/2000	Plaque psoriasis in adults, up to 20% BSA involvement	Apply thin film once daily	Improvements in plaque elevation, scaling, and erythema were generally significantly greater with tazarotene 0.05% and 0.1% than with vehicle. The number of patients with none, minimal, or mild overall disease was significantly greater with tazarotene 0.05% and 0.1% vs. vehicle.	Retinoids may cause fetal harm when administered to a pregnant woman.

Product Class	Example Product/Year Approved	Relevant Indication[1]	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues
Corticosteroid/ Retinoid combination	Duobrii ((halobetasol propionate 0.01% and tazarotene 0.045%) Lotion/2019	Plaque psoriasis in adults	Apply a thin layer of DUOBRII Lotion once daily	418 subjects 18 years of age and older with moderate to severe plaque psoriasis that covered a body surface area (BSA) between 3% and 12% excluding the face, scalp, palms, soles, axillae, and intertriginous areas, were treated once daily for 8 weeks. Treatment success was defined as at least a 2-grade improvement from baseline in the IGA score and an IGA score equating to “clear” or “almost clear”. The efficacy for DUOBRII was 36% vs 7% vehicle in Trial 1 and 45% vs 13% vehicle in Trial 2.	Retinoids may cause fetal harm when administered to a pregnant woman. Safety is not established in patients under 18 years of age; pediatric patients are at greater risk for HPA axis suppression. The most common adverse reactions are contact dermatitis, application site pain, and folliculitis.

Sources: Table 2 from the Unireview for NDA 210566; Reviewer’s table by Dr. Amy Woitach
[1] Some corticosteroids are indicated for the “treatment (or relief) of inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses (CSRD),” which is inclusive of the psoriasis indication.
Abbreviations: CSRD, corticosteroid-responsive dermatoses; HPA, hypothalamic–pituitary–adrenal

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tapinarof is not approved for sale in the United States or worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed tapinarof cream, 1%, under investigational new drug (IND) application 104601 using the 505(b)(1) regulatory pathway. Milestone interactions are described below:

- A Pre-IND meeting was held with Welichem (Stiefel in 2012) on May 6, 2009 to discuss the overall development plan for plaque psoriasis and atopic dermatitis, including potential trial duration, trial design (b) (4)

- An End-of-Phase 2 meeting was held with the Sponsor (then GlaxoSmithKline (GSK)) on January 11, 2017. The FDA agreed with the proposed primary endpoint of the proportion of subjects with PGA (b) (4) of 0 or 1 along with a minimum of 2-grade improvement at Week 12. There was continued discussion of Phase 3 trial designs (b) (4) . The FDA recommended that long-term extension studies evaluate duration of effect and response to retreatment of their product.

- The new Sponsor (Dermavant Sciences GmbH) submitted an amended initial Pediatric Study Plan (iPSP) on March 8, 2019, addressing the indication of plaque psoriasis. The FDA agreed with the sponsor's iPSP on August 23, 2019. Refer to section 10 of this review for further details.

- (b) (4) .

Good Clinical Practice and Financial Disclosure:

The applicant stated that all clinical trials in their VTAMA development program were conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, and with Good Clinical Practice (GCP), as required by the US Code of Federal Regulations applicable to clinical studies (21 CFR Parts 11, 50, 54, 56 and 312, 42 USC 282(j), International Conference on Harmonisation, Harmonised Tripartite Guideline E6(R1): GCP and E2A: Safety Data Management, and applicable local or national regulations.

For financial disclosure information, refer to Section 18.2 of this review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The division requested that the Office of Scientific Investigations (OSI) conduct clinical site inspections. All Phase 3 trials were conducted at sites in the U.S. and Canada.

The sites in Table 2 were selected for inspection for the following reasons: high site efficacy effect, high enrollment, high discontinuation rate, and/or the fact that these clinical investigators had no prior history of good clinical practice (GCP) inspections. The OSI assessed that the overall quality of the clinical information contained in this submission is adequate.

Table 2. Inspection Sites

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects (SAFPOP)	Study Title
Bissonnette, Robert 3530 boulevard Saint-Laurent, Suite 400 Montreal, QC H2X 2V1 CAN Canada phone: (b) (6) fax:Unknown email:pirbissonnette@innovaderm.ca	1904	1. DMVT-505-3001	33	A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults
Ehst, Benjamin 9495 SW Locust Street, Suite G Portland, OR 97223 USA United States phone: (b) (6) ext: fax:Unknown email:Behst@oregonmedicalresearch.com	2024	2. DMVT-505-3002	18	A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults
Hong, Chih-Ho 15300 105th Ave, Suite 20 Surrey, BC V3R 6A7 CAN Canada phone: (b) (6) ext: fax:Unknown email:chihho@mail.ubc.ca	2901	2. DMVT-505-3002	30	A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults

Thorla, Ira 10154 Jefferson Hwy. Baton Rouge, LA 70809 USA United States phone (b) (6) fax:Unknown email:ithorla@delricht.com	1006	1. DMVT-505-3001	18	A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults

In the clinical inspection summary, the review team concluded that the conduct of the trials appears to be adequate and that the data generated appear to be acceptable to support the use of this product for the proposed indication. Refer to the Clinical Inspection Summary by Phil Phuc Nguyen, MD, dated March 31, 2022, for further information regarding the findings of the Clinical Site Inspections.

4.2. Product Quality

The Product Quality team, led by Nina Ni, PhD, and Hong Cai, PhD, made the following conclusions and recommendations:

Each gram of VTAMA cream, 1% contains 10 mg of tapinarof in a white to off-white cream intended for topical use. VTAMA cream is packaged in two configurations: 60 g in (b) (4) laminate tube with a peelable sealed membrane and a (b) (4) closure for commercial use; and 2 g in an aluminum tube with a sealed membrane and a membrane piercing (b) (4) closure for use as the physician sample.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency, and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging, and testing facilities have acceptable CGMP status. Labeling (package insert and container/ carton) negotiations have been completed, and in its present form, the labeling complies with the requirements under 21 CFR 201. The request for a categorical exclusion from an environmental assessment (EA) is accepted.The applicant has proposed adequate drug substance specification, which includes all critical drug substance attributes that affect the manufacturing and quality of the drug product.

The applicant requested an expiration dating period of 36 months with adequate supporting data, which is granted for the 60-g commercial pack. An (b) (4)-month expiration dating period is granted for the 2-g physician sample. The storage conditions recommended for labeling of the drug product are "Store at 20 to **25˚C** (68 to **77˚F)** with excursions permitted to 15 to **30˚C** (59 to **86˚F).** Do not freeze."

With no outstanding product quality issues, the Quality Assessment team recommended that the application be approved.

The complete Integrated Quality Review dated April 22, 2022 is archived in the CDER Informatics Platform.

4.3. Clinical Microbiology

The Clinical Microbiology review was included in the Integrated Quality Review dated April 22, 2022, and their recommendations and conclusions are integrated into the Product Quality section above.

The complete Integrated Quality Review dated April 22, 2022 is archived in the CDER Informatics Platform.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted a 505(b)(1) application for their proposed product, tapinarof cream, 1% to treat plaque psoriasis in adults. The active ingredient of the product, tapinarof, is an aryl hydrocarbon receptor agonist and it is a new molecular entity.

The nonclinical studies submitted in this NDA include pharmacology, pharmacokinetics and toxicology studies of tapinarof.

Tapinarof (GSK2894512; WBI-1001) has been evaluated in single- and repeat-dose dermal toxicity studies of up to 13 weeks in mice and rats, 28 days in rabbits, and up to 39 weeks in minipigs. Tapinarof was also evaluated in repeat-dose subcutaneous toxicity studies of up to 26 weeks in rats. The major test article-related findings observed in repeat-dose dermal and subcutaneous studies were related to the skin, liver, kidney, and thymus with associated secondary clinical pathology findings. For the no-observed-adverse-effect-level (NOAEL) determined in the general toxicity studies with tapinarof, there are modest (dermal studies) to large (subcutaneous studies) safety margins when systemic tapinarof exposure is compared between animals and humans topically treated with tapinarof cream, 1%.

Tapinarof was not mutagenic or clastogenic in the Ames bacterial reverse mutation assay, the in vitro mammalian chromosome aberration test, and the in vitro mouse lymphoma assay. Tapinarof was not genotoxic in two in vivo micronucleus assays in mice and rats.

In a 2-year dermal mouse carcinogenicity study, topically applied tapinarof cream at once daily doses up to 3.0% did not result in a significantly increased incidence of drug-related neoplasms in CD-1 mice.

In a 2-year subcutaneous rat carcinogenicity study, tapinarof were tested in Wistar-Han rat at subcutaneous doses up to 1.0 mg/kg/day. The study is negative for drug-related neoplasms in female rats. The male portion of the study, while it did not show any statistical increase in tumors, was of an inadequate duration. Therefore the male animal carcinogenicity data (b) (4) .

The effect of tapinarof on reproductive toxicity, including fertility, embryofetal development, and prenatal and postnatal development was investigated in rats or rabbits following subcutaneous administration:

- Tapinarof at 0 (vehicle), 1.2, 6.9, and 34 mg/kg/day given subcutaneously to pregnant rats during the period of organogenesis resulted in decreased mean fetal body weights and an increased incidence of the fetal variation, incomplete ossification of the nasal bones at 34 mg/kg/day. The subcutaneous NOAEL for rat embryo-fetal development toxicity is 6.9 mg/kg/day.
- Tapinarof given subcutaneously twice daily to pregnant rabbits during the period of organogenesis resulted in maternal toxicity at 3 mg/kg/day. Based on increased post-implantation loss and fetal skeletal variations (extra sutures in the interparietals and intraparietal ossification site) observed at 3 mg/kg/day, the NOAEL for tapinarof effects on rabbit embryo-fetal development toxicity is 1 mg/kg/day.
- Tapinarof given to pregnant rabbits during the period of organogenesis through continuous subcutaneous infusion showed no maternal or fetal toxicity at dose up to 3 mg/kg/day. The NOAEL for this study is 3 mg/kg/day.
- No findings were noted on rat female fertility and early embryonic development at subcutaneous doses up to 30 mg/kg/day.
- Although there was no separate male fertility study in this drug development program, it is not considered an approvability issue. Assessment of tapinarof effects on male fertility was conducted in the 4-week subcutaneous rat study. Normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present at subcutaneous doses up to 30 mg/kg/day. The 4-week subcutaneous rat study data concerning male fertility effects (b) (4) due to use of immature rats. The proposed product is a topical product with limited systemic exposure. Therefore, the potential effect of tapinarof cream on male fertility is considered negligible.
- In the prenatal and postnatal development study, tapinarof given subcutaneously to pregnant female rats from gestational day 6 through lactation day 20 resulted in maternal toxicity at 30 mg/kg/day. There were test article-related decreases in F1 pup survival and viability at ≥6 mg/kg/day that resulted in reduced litter sizes and decreased pup weights. The NOAEL was 1 mg/kg/day for tapinarof effects on prenatal and postnatal development of the offspring in rats. Quantifiable tapinarof exposures were noted in offspring in the 6 and 30 mg/kg/day groups, suggesting that tapinarof is present in rat milk.
- In a juvenile animal toxicity study, tapinarof was administered by subcutaneous injection to juvenile rats at doses of 1, 10 and 20 mg/kg/day from postnatal day

(PND) 7 to 21 and at doses of 1.5, 15 and 30 mg/kg/day from PND 22 to 77. The dose escalation conducted at PND 22 was implemented to maintain consistent systemic exposure across the duration of the dosing period. Microscopic changes in the form of renal pelvic dilatation was noted in both male and female rats. The NOAEL was 1.5 mg/kg/day. The findings in the kidney observed in this study were not noted in the prenatal and postanal development study in rats.

Special toxicity studies with tapinarof including in vitro assessments of hemolytic potential, local lymph node assay, skin sensitization and irritation, dermal irritation, ocular irritation, and phototoxicity did not identify any safety comcerns with tapinarof.

There are no novel excipients in the proposed topical drug product.

Two drug-related impurities are of potential mutagenic concern, as indicated by positive results in Ames assays. The specification limit that is proposed to be set at (b) (4) times the threshold of toxicological concern (TTC) of 1.5 µg/day for these two impurities is acceptable from a pharmacology/toxicology perspective.

In summary, the nonclinical assessment did not identify any safety concerns for the proposed tapinarof cream formulation. This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

To identify possible molecular targets, tapinarof was profiled against more than 800 potential cellular targets, including enzymes implicated in cell health, a diverse array of kinases, nuclear receptors, and mediators of epigenetic signaling. Tapinarof was inactive in most of the molecular target assays tested. However, it was found to be an agonist of aryl hydrocarbon receptor as measured by induction of CYP1A1 gene and AhR nuclear translocation in human keratinocytes.

- Tapinarof dose dependently induced nuclear translocation of AhR in immortalized keratinocytes (HaCaT cells) (half excitatory concentration [EC_{50}]= 0.16 nM].
- Exposure of ex vivo skin cultures to tapinarof results in significant CYP1A1 gene induction in a dose-dependent manner under both normal as well as Th17-stimulating conditions.
- CYP1A1 gene expression was significantly increased in both fetal cord and adult peripheral blood CD4+ cells treated with 0.003 to 3 µM tapinarof, suggesting the AhR– agonist mechanism of action of tapinarof may be similar among infants and adults.

- Direct binding of tapinarof to AhR was assessed using either the human or mouse AhR Per-Arnt-Sim (PAS) domains, expressed as a heterodimer with the Aryl hydrocarbon Receptor Nuclear Translocator (ARNT) PAS domains. An increase in fluorescence signal was observed with increasing concentrations of unbound heterodimer indicating that tapinarof binds to both human and mouse AhR PAS domains.

Tapinarof also exhibited activities as an activator of nuclear factor erythroid 2-related factor-2 and cannabinoid receptor-2, and as an inhibitor of the monoamine oxidase B pathway. Tapinarof also demonstrated specific inhibition of pro-inflammatory mediators, including interleukin (IL)-6, IL-17A, and eotaxin-3.

Treatment with tapinarof reduced reactive oxygen species in chemically redox-stressed keratinocytes, indicating that tapinarof possesses antioxidant properties. In the micromolar range, tapinarof exhibited dose-dependent inhibition on cell growth and survival of both T-cells and epidermal keratinocytes.

In animal models, the anti-inflammatory activity of tapinarof has been demonstrated in the imiquimod mouse model of psoriasis. It led to reductions in epidermal thickness and mRNA expression of key pro-inflammatory cytokines (IL-17a, IL-17f, IL-19, IL-1β, and IL-23a). In a LPS-induced mouse ear edema model, a dose-dependent reduction in both skin erythema and ear thickness was observed following tapinarof treatment. Furthermore, in a mouse model of dermatitis, 2,4-dinitrofluorobenzene-induced epidermal and dermal thickening, as well as mRNA expression of pro-inflammatory mediators, were significantly reduced following tapinarof treatment.

Safety pharmacology

- Neurological effects:

Four groups of 6 male SD rats received a single subcutaneous dose of 0 (Vehicle, propylene glycol), 1, 3, or 10 mg/kg tapinarof. Evaluation of neurological effects was based on observations collected pre-dosing and approximately 1, 2, 4, 6, and 48 hours post-dosing. The evaluation used a modified Irwin battery of neurological assessments, including home cage, hand-held, open-field, and elicited response observations. Low body tone was observed in 1, 1, 1, and 3 rats treated at 0, 1, 3, and 10 mg/kg, respectively. Unusual behavior (head tilt left) was also seen in 1 out of 6 rats treated at 10 mg/kg at 4, 6, and 48 hours post-dosing. The physiological significance of these observations at 10 mg/kg without related neurological findings was considered minimal.

- Respiratory effects:

Four groups of 8 male SD rats received a single subcutaneous dose of 0 (Vehicle, propylene glycol), 1, 3, or 10 mg/kg tapinarof. Plethysmography data were continuously collected for approximately 2.5 to 2.75 hours pre-dosing (baseline), at least 6 hours post-dosing, and for approximately 2.7 hours beginning at approximately 46.5 hours post-dosing. Plethysmography parameters were analyzed as 30-minute averages at baseline, 1 through 6 hours post-dosing,

and 48 hours post-dosing. There were no treatment-related effects on clinical signs or respiratory function as measured by tidal volume, respiration rate, and minute volume.

- Cardiovascular effects:

The effects of tapinarof on the potassium selective IKr tail current were tested in human embryonic kidney (HEK293) cells at target concentrations of 100, 200, 660, and 2000 ng/mL. No statistically significant inhibition of hERG tail current was noted at any of the four concentrations tested. An IC_{50} value could not be determined. Analysis of the dosing solutions over 3 months after the experiment indicated that the tapinarof concentrations were <20, 32, 146, and 914 ng/mL for the targeted concentrations of 100, 200, 660, and 2000 ng/mL, respectively.

The effect of tapinarof on hERG tail current in HEK-293 cells was tested at concentrations of 0.12, 0.35, 1.16, 3.47, 11.56, and 34.7 μM (0.03, 0.09, 0.29, 0.88, 2.94 and 8.83 μg/mL, respectively). Tapinarof inhibited hERG channel tail current in a concentration-dependent manner. The IC_{25}, IC_{50} and IC_{75} values were estimated to be 1.72, 4.02, and 9.37 μM, respectively.

Four male and four female Dunkin Hartley guinea pigs were instrumented with continuous telemetric monitoring and topically exposed to increasing concentrations of 0, 1, 4, and 6% (0, 20, 80, and 180 mg/kg) tapinarof cream for 6 hours at each concentration. The dosing phase of the study began with the application of the vehicle control (0 mg/kg). The guinea pig was fitted with an Elizabethan collar and returned to its home/monitoring cage. Approximately 6 hours after application, the Elizabethan collar was removed, the application site was gently cleansed with gauze and deionized water, and the guinea pig was returned to its home/monitoring cage. After at least 72 hours, this regimen was repeated for each subsequent dose. A slight increase in heart rate (up to 16%) was observed throughout the majority of early exposure (1-8 hours) following 6% tapinarof cream treatment. Reductions in PR interval, uncorrected QT interval (6%), and corrected mean QT intervals (QTcV, QTcB, and QTcF) were also noted at 4 or 6 hours with 6% tapinarof cream treatment.

Four telemeterized male minipigs received intravenous doses of 0, 1, 3, and 10 mg/kg tapinarof. Systolic, diastolic, and mean arterial pressure, heart rate, pulse pressure, QA interval (a measure of cardiac contractility), electrocardiographic parameters (RR, PR, QRS, QT, QTc), and body temperature were collected continuously for at least 24 hours post-dosing. There were no treatment-related effects.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	

Type of Study	Major Findings
An In Vitro Investigation of the Passive Membrane Permeability of [^{14}C] GSK2894512E in MDCKII-MDRI Cells (16DMM021)	[^{14}C]-tapinarof was determined to have a high passive membrane permeability of 670 nm/s at pH 7.4 and 500 nm/s at pH 5.5 in Madin-Darby canine kidney (MDCKII-MDR1) cells in the presence of the potent P-glycoprotein (P-gp) inhibitor, GF120918.
Distribution	
A study to investigate the in vitro protein binding of GSK2894512 in pooled rat, minipig, and human plasma using equilibrium dialysis (2013N176703)	The plasma protein binding of tapinarof was very high, ranging from 99.1% to 99.4%, with no apparent concentration dependence in the three species tested (rat, minipig, and human) over the concentration range from 20 to 1000 ng/mL.
In Vitro Protein Binding of GSK2894512A in Human and Minipig Skin Homogenate and Human Plasma (2015N242613) (8310655)	In vitro protein binding study of tapinarof showed that the skin protein binding values for the minipig and human homogenates were 90.7% and 92.7%, respectively. The binding appeared to be concentration dependent at high concentrations.
Quantitative Whole Body Autoradiography Tissue Distribution Study in Rat after Single Subcutaneous Dosing (2015N243602)	In male pigmented rats following a single SC administration of [^{14}C]-tapinarof at 2 mg/kg, radioactivity was rapidly and widely distributed throughout the body with all tissues containing quantifiable radioactivity concentrations by 1-hour post-dose. Tissue radioactivity concentrations were generally greater in the skin at the dosing site, urinary bladder wall, adrenal cortex, small intestine wall, liver, brown fat, and the kidney cortex. Lower concentrations were present in the skin (distal to the dosing site), preputial gland, large intestine wall, and the bone surface. The T_{max} for majority of tissues was 1 hour following dose administration. Radioactivity was still quantifiable in all tissues at 72 hours post administration. Majority of tissues were more highly exposed to [^{14}C]-tapinarof and its metabolites than whole blood.

Type of Study	Major Findings
Metabolism	
Metabolite profiling of WBI-1001 in human liver microsomes and cryopreserved hepatocytes from rat, rabbit, Gottingen minipig and human (2013N163811) An In Vitro Investigation of the Hepatic Metabolism of [^{14}C]GSK2894512 in the Human, Crl:WI (Han) and Crl:ICR (CD-1) Mouse (15DMM042) Metabolism of GSK2894512 in Male Mice following a Single Subcutaneous Administration of [^{14}C]GSK2894512 at a Target Dose Level of 2 mg freebase/kg (I7DMW028) Metabolism of GSK2894512 in Male Rats following a Single Subcutaneous Administration of [^{14}C]GSK2894512 at a Target Dose Level of 2 mg freebase/kg (I7DMW029)	The major in vitro biotransformation pathways of the test article in all of the species were attributed to the Phase II enzyme activities, e.g. sulfate and glucuronic acid conjugations on the phenolic group, alone or in combination with oxidation. All metabolites noted in human hepatocyte incubations were observed in rat or minipig hepatocyte incubations. Only incubation of the test article with rabbit hepatocytes produced a Phase I metabolite, which was formed likely due to aromatic hydroxylation reaction. The major routes of metabolism in vivo in mice and rats were oxidation, glucuronidation and combinations thereof.
Excretion	
[^{14}C]GSK2894512: Excretion Study In The Rat After Single Subcutaneous Dosing (2 mg/kg) (2015N243603) [^{14}C]GSK2894512: Excretion Study In The Mouse After Single Subcutaneous Dosing (2 mg/kg) (2015N243607) The Excretion of Radioactivity Following a Single Subcutaneous Administration of [^{14}C]-GSK2894512 free base to the CD-1 Mouse (2018N389035) Excretion of Radioactivity Following Subcutaneous Administration of [^{14}C]GSK2894512 free base to the Rat (2 mg/kg) (2018N389055) Excretion of Radioactivity Following Dermal Administration of [^{14}C]GSK2894512 free base to the Mini-pig (10 mg/kg) (2018N389316)	Excretion studies were conducted in rats and mice following a single SC administration of 2 mg/kg [^{14}C]-tapinarof. In rats and mice, the major route of elimination was in the feces. For bile duct-cannulated rats, the major route of elimination was in the bile. Elimination of drug-related material was rapid following SC administration, with 80% to 88% of the dose recovered by 24 hours post-dose. Blood to plasma ratios ranged from 0.66 to 1.2 in the rat and 0.60 to 0.77 in the mouse. Liver to plasma ratios ranged from 7.1 to 14.0 in the rat and 4.0 to 14.1 in the mouse. In the minipig study, the majority of the radioactivity (82.5% of the dose) was recovered in the interim dressing removed from the dose site 10 hours after dosing. Less than 1% of the administered radiolabeled material was recovered in excreta (urine and feces), suggesting minimal absorption of the radioactive test material. Blood and plasma concentrations of radioactivity were below the limit of detection.

Type of Study	Major Findings
TK data from repeat dose toxicology studies:	
A Once Daily 26-Week Subcutaneous Injection Toxicity Study in Rats Followed by a 6-Week Off-Dose Period (2015N254469)	<u>Rat</u> T_{max}: 0.5 hour AUC_{0-t}: 63.2 ng·hr/mL at 1 mg/kg/day C_{max}: 37.6 ng/mL at 1 mg/kg/day Accumulation: No Dose proportionality: Exposure generally increased greater than proportionally on Weeks 13 and 26
GSK2894512A: Toxicity Study by Dermal Administration to Göttingen Minipigs for 9 Months Followed by a 1-Month Off-Dose Period (2016N299302)	<u>Minipig</u> T_{max}: 6 hour AUC_{0-t}: 5.09 ng·hr/mL at 3% C_{max}: 0.686 ng/mL at 3% Accumulation: No Dose proportionality: Exposure generally increased dose proportionally on Week 39
4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats (2013N166805) (The TK parameters of this study was used for extrapolation of reproductive and development studies in rats.)	<u>Rats</u> T_{max}: 0.5-1 hour AUC_{0-t} and C_{max} on Day 28: • 1 mg/kg/day: AUC_{0-t} of 54.4 (male) and 48.0 (female) ng·hr/mL; C_{max} of 27.5 (male) and 24.4 (female) ng/mL • 6 mg/kg/day: AUC_{0-t} of 543 (male) and 358 (female) ng·hr/mL; C_{max} of 278 (male) and 132 (female) ng/mL • 30 mg/kg/day: AUC_{0-t} of 3060 (male) and 2140 (female) ng·hr/mL; C_{max} of 1100 (male) and 673 (female) ng/mL Accumulation: No Dose proportionality: Exposure approximately increased proportionally on Days 1 and 28

Type of Study	Major Findings
TK data from reproductive toxicology studies	
GSK2894512A: Subcutaneous Embryo-Fetal Development Study in Female Rabbits (2014N189059)	Rabbit at the developmental NOAEL of 1.0 mg/kg/day on GD 11 AUC_{0-t}: 128 ng·hr/mL C_{max}: 122 ng/mL
GSK2894512A: Subcutaneous Infusion Embryo-Fetal Development Study in Rabbits (2015N244027)	Rabbit at the developmental NOAEL of 3.0 mg/kg/day on GD 11 AUC_{0-t}: 159 ng·hr/mL C_{max}: 6.6 ng/mL
GSK2894512A: Subcutaneous Pre- and Postnatal Development Study in Rats (2018N368233)	The plasma values for F1 pups on PND 10 ranged from 0.326 to 0.506 ng/mL at 6 mg/kg/day and from 0.301 to 0.985 ng/mL at 30 mg/kg/day between 3 and 22 hours post maternal dosing. Tapinarof is present in maternal milk.
GSK2894512A: Subcutaneous Juvenile Toxicity Study in Rats (2014N21697)	Juvenile rat at the NOAEL of 1/1.5 mg/kg/day on PND 77 AUC_{0-t}: 86.4 ng·hr/mL C_{max}: 73.1 ng/mL Juvenile rat at 10/15 mg/kg/day on PND 77 AUC_{0-t}: 1320 ng·hr/mL C_{max}: 729 ng/mL
TK data from Carcinogenicity studies	
GSK2894512A: A 2-Year Carcinogenicity Study by Subcutaneous Injection in the Wistar Han Rat (DMVT-505-9002)	Rat at the NOAEL of 1 mg/kg/day on Day 182 AUC_{0-t}: 73.1 (male) and 63.9 (female) ng·hr/mL C_{max}: 37.7 (male) and 39.7 (female) ng/mL
GSK2894512A: A 2-Year Dermal Carcinogenicity Study in the Mouse (20097894)	Mouse at the NOAEL of 3% on Day 182 AUC_{0-t}: 259 (male) and 444 (female) ng·hr/mL C_{max}: 66.4 (male) and 95.7 (female) ng/mL

5.5. Toxicology

5.5.1. General Toxicology

Repeat-Dose Toxicity Studies through Dermal Administration

Tapinarof was evaluated in repeat-dose dermal toxicity studies of up to 13 weeks in mice and rats, 28 days in rabbits, and up to 39 weeks in minipigs. These studies utilized multiple formulations of tapinarof cream (Formulations A through F). Pivotal repeat-dose dermal studies

(13-week study in mice, and 28-day and 39-week studies in minipigs) were conducted with the final clinical formulation, Formulation F, at concentrations up to 3% (the maximum feasible concentration of tapinarof in this formulation).

13-Week Repeat-Dose Dermal Toxicity Study in Mice
Tapinarof cream was administered topically to CD-1 mice at concentrations of 0% (vehicle cream), 0.5%, 1%, or 3% for approximately 23 hours/day nonoccluded once daily for 13 weeks. A no observed adverse effect level (NOAEL) was considered to be greater than or equal to 3%, the highest formulation concentration tested, for both males and females.

13-Week Repeat-Dose Dermal Toxicity Study in Rats
Tapinarof cream was administered topically to Han Wistar rats at concentrations of 0% (vehicle cream), 0.5%, 1.5%, or 3% for a period of 22 hours and semi-occluded for 6 hours once daily for 13 weeks. The NOAEL for both sexes was considered to be 3%, the highest concentration tested (b) (4).

28-Day Repeat-Dose Dermal Toxicity Study in Rabbits
In a 28-day study, tapinarof was given to New Zealand White rabbits at 0 (vehicle cream), 1%, 3%, 4%, or 6% for 6 hours/day by occluded dermal application to not less than 10% BSA.

The test article induced dose dependent skin reactions (skin dryness, erythema/edema, hyperkeratosis and occasional fissures) at the application sites. Underlying dermal responses ranged from foci of increased numbers of fibroblasts or neutrophils, to small areas of inflammation, edema, and fibrin exudation.

At necropsy, there was a dose dependent increases in liver weight in both genders. Histological findings in the liver included multifocal necrosis/inflammation, hepatocellular hypertrophy/ regeneration, and cholangiolar proliferation at ≥3%. Thymic atrophy was noted in animals treated with 6% tapinarof cream.

The skin reactions and effects on the liver are known effects when occlusion is used after dermal application in rats or rabbits. This study did not use the preferred dermal study design of no occlusion at the topical test article site.

The NOAEL was estimated to be 1% tapinarof cream under the conditions of the study.

28-Day Repeat-Dose Dermal Toxicity Studies in Minipigs
Tapinarof cream was applied onto the skin of Göttingen minipigs at 0 (vehicle cream), 1.5%, 3%, or 6% for 6 hours/day for 28 days by nonoccluded dermal application. The NOAEL for this study was considered to be 6% tapinarof cream.

In another 28-day study, tapinarof was applied onto the skin of Göttingen minipigs at 0 (vehicle cream), 1%, 2%, or 4% cream for 24 hours/day for 28 days by semi-occluded dermal application. The NOAEL was 4% tapinarof cream, the highest dose tested.

In an additional 28-day study, tapinarof was dermally administered to Göttingen minipigs at 0 (vehicle cream), 0.5, 1, or 3% tapinarof cream twice daily for 20 hours/day for 28 days by semi-occluded dermal application. The NOAEL was 3% tapinarof cream.

13-Week Repeat-Dose Dermal Toxicity Studies in Minipigs

Tapinarof was applied to the skin of Göttingen minipigs at 0 (vehicle cream), 1%, 2%, or 4% tapinarof cream twice daily for 13 weeks by occluded dermal application. A female in the 4% tapinarof cream group was found dead. The cause of death was undetermined.

Skin changes observed at the application sites in all groups were attributed to effects of the vehicle and/or accumulation of test article remnants. Reversible, test article-related clinical pathology effects were noted at ≥ 2% tapinarof cream. The skin effects noted in minipigs are known effects when occlusion is used after dermal application in minipigs. This study did not use the preferred dermal study design of no occlusion at the topical test article site.

In another 13-week study, tapinarof was applied onto the skin of Göttingen minipigs at 0 (vehicle cream), 0.1%, and 1% QD, 2% and 4% BID tapinarof cream (Formulation E) for 13 weeks by semi-occluded dermal application. Slight-to-moderate erythema was noted in all all groups including vehicle control group. The NOAEL for tapinarof dermally administered BID for 13 weeks to minipigs was 4% cream, the highest dose tested. The erythema noted in minipigs is a known effect when occlusion is used after dermal application in minipigs. This study did not use the preferred dermal study design of no occlusion at the topical test article site.

39-Week Repeat-Dose Dermal Toxicity Study in Minipigs

Twice daily dermal administration of tapinarof cream at doses of 0 (vehicle), 0.5, 1.0 and 3.0% (Formulation F; 0, 10, 20, and 60 mg/kg/day) were applied onto 10% of total BSA of minipigs (3/sex/group) with no occlusion for 39 weeks. There were no dermal irritation nor systemic toxicity noted. The NOAEL was 3% tapinarof cream, the highest dose tested.

Repeat-Dose Toxicity Studies through Subcutaneous Administration

Repeat-dose studies of tapinarof given subcutaneously were conducted in the rat only and the pivotal GLP toxicology studies included 28-day, 13-week, and 26-week studies.

28-Day Repeat-Dose Toxicity Study in Rats

In a 28-day study, tapinarof was given to Han Wistar rats at doses of 0 (30% Captisol™), 1, 6, or 30 mg/kg/day once daily by subcutaneous injection. Slight increases in liver weights in males and females at 30 mg/kg/day and decreases in thymus weights in males and females at ≥6 mg/kg/day were noted.
Treatment-related findings at the injection site included inflammatory cell infiltrate and hemorrhage/edema in the subcutis at dose levels of ≥1 mg/kg/day, and serocellular exudate and hyperplasia of the epidermis, ulceration of the epidermis, and mixed inflammatory cell

infiltrate in the dermis of rats in the 30 mg/kg/day group. These injection site reactions are not clinically relevant for the clinical topical use of tapinarof cream.

The NOAEL for systemic toxicity was 30 mg/kg/day under the conditions of the study. Additionally, tapinarof was negative in the in vivo rat bone narrow micronucleus assay that was incorporated into this study. Normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present.

13-Week Repeat-Dose Toxicity Study in Rats

Tapinarof was administered to Sprague Dawley rats at 0 (propylene glycol USP vehicle), 3, 10, or 40 mg/kg/day once daily by subcutaneous injection for 13 weeks.

Swelling, discolored skin, firmness, and/or scabs or sores were observed at the treatment sites in a dose dependent manner. Two males and two females at 40 mg/kg/day were euthanized during the dosing phase because of treatment-related dermal lesions, including ulcerative dermatitis and necrosis. These injection site reactions are not clinically relevant for the clinical topical use of tapinarof cream.

Mildly to moderately higher mean interpolated anti-KLH IgG values were noted in animals at ≥3 mg/kg/day as compared to the corresponding controls, but the responses were not dose-dependent. Decreases in thymus weights and increases in liver and lung weights were also noted in males and females at doses of ≥10 mg/kg/day.

Treatment-related microscopic findings at the injection site included inflammation, necrosis of subcutaneous tissue, degeneration/necrosis of the panniculus muscle, acanthosis, erosion/ ulcer, epidermal surface exudate, hemorrhage, brown pigment, mineralization, and intraepidermal vesicles. The microscopic lesions at the injection sites persisted in males and females at 40 mg/kg/day at the recovery phase. These injection site reactions are not clinically relevant for the clinical topical use of tapinarof cream.

Additionally, lymphoid depletion was seen in males and females at doses of 10 or 40 mg/kg/day and correlated with thymus weight decreases. The NOAEL for local effects at the injection site was not established in this study. However, the systemic NOAEL was 3 mg/kg/day under the conditions of this study.

26-Week Repeat-Dose Toxicity Study in Rats

Tapinarof was administered once daily by subcutaneous injection at doses of 0 (vehicle alone; aqueous 30% CaptisolTM in sterile water for injection), 1, 6 or 30 mg/kg/day to rats (12 animal/sex/group) for 26 weeks with additional rats (10/sex/group) included in the 6 and 30 mg/kg/day dose groups to explore reversibility of potential tapinarof-related findings following a 6-week recovery period.

One male rat was found dead in the 30 mg/kg/day group. The mortality was considered to be due to a malignant fibrous histiosarcoma, secondary to inflammation noted at injection site due

to chronic subcutaneous injection. Sarcomas were also noted at the injection site in one male of each group of 6 mg/kg/day and 30 mg/kg/day at the end of the recovery period.

Minimal, reversible changes were observed in clinical pathology (mostly at ≥6 mg/kg/dose: increased mean neutrophil, monocyte, lymphocyte, total white blood cell and reticulocyte counts, decreased mean hemoglobin and hematocrit, and increased mean triglyceride concentration). Studies of immunophenotyping parameters demonstrated increases in total T, helper T, cytotoxic T and regulatory T lymphocytes (30 mg/kg/day) and B lymphocytes (≥6 mg/kg/day) as well as decreases in NK cells (≥1 mg/kg/day; partial recovery) and stimulated Th17 cells (30 mg/kg/day).

Decreases in the thymus weights were observed in male and female rats at doses of 30 mg/kg/day. At the end of the dosing phase, tapinarof-related microscopic findings were noted in the thymus and injection sites. Reversible, decreased lymphoid cellularity was observed in the thymus of the 30 mg/kg/day dose group. Dose-dependent microscopic findings at the injection sites were observed in ≥1 mg/kg/day dose groups. These findings included chronic inflammation, ulceration, follicular atrophy, acanthosis, necrosis and/or mineralization and correlated with macroscopic and clinical observations at injection site. Inflammation and follicular atrophy were also noted at injection site in control animals but were of lower incidence and/or severity. The injection site findings were partially resolving at the end of 6-week recovery period. These injection site reactions are not clinically relevant for the clinical topical use of tapinarof cream.

Based on the incidence and severity of the microscopic findings observed at the injection site of animals, the NOAEL for the local toxicity was considered to be 1 mg/kg/day.

A complete review of the two pivotal chronic repeat dose general toxicity studies is provided below.

Study title/ number: GSK2894512A: A Once Daily 26-Week Subcutaneous Injection Toxicity Study in Rats Followed by a 6-Week Off-Dose Period / 2015N254469

- There was one mortality in the 30 mg/kg/day male group due to chronic subcutaneous injection. Sarcomas were also noted at the injection site in one male of each group of 6 mg/kg/day and 30 mg/kg/day at the end of the recovery period.
- Dose-dependent microscopic findings were noted at the injection sites in rats given ≥1 mg/kg/day.
- The NOAEL for the local toxicity was considered to be 1 mg/kg/day.

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods

Doses:	0 (vehicle), 1, 6, and 30 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Subcutaneous
Dose volume	3 mL/kg
Formulation/Vehicle:	30% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol™) in sterile water for injection
Species/Strain:	Hsd:Sprague Dawley rats
Number/Sex/Group:	12/sex/group for main study groups;
Age:	7 Weeks
Satellite groups:	6/sex/groups for 4 groups
Unique study design:	Injections rotated among 4 subcutaneous sites in the dorsal region
Deviation from study protocol:	No deviations affect the conclusions

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	One male mortality in HD group. It was considered to be due to a malignant fibrous histiosarcoma, secondary to inflammation at injection site because of chronic subcutaneous injection.
Clinical Signs	Skin scabbing, thin cover of the fur, swollen or reddened skin and/or fur staining at injection sites in both males and females in all groups, including the vehicle controls.
Body Weights	No test article-related effects
Ophthalmoscopy *[*	No test article-related effects
Hematology	Dose dependent changes (up to 1.72x) in both genders in MD and HD: ↑ in neutrophil, monocyte and lymphocyte counts ↓ in hemoglobin, hematocrit and reticulocyte counts
Clinical Chemistry	Dose dependent ↑ in mean triglycerides concentration in males in MD and HD (up to 1.78X of control)
Urinalysis	No test article-related effects
Gross Pathology	• Scabs and thickening at injection sites of male and female rats at all dose levels • Pale discoloration and enlargement in the kidney noted in all groups; signs reduced at the recovery. It was considered to be related to the vehicle (Captisol™). • Sarcomas noted at the injection site in one male of each MD and HD group at recovery
Organ Weights	HD: decreases in the thymus weights in both gender (0.72X-0.77X)

Histopathology Adequate battery: Yes/No	Yes. • Chronic inflammation, ulceration, follicular atrophy, acanthosis, necrosis and/or mineralization noted at the injection sites: dose-dependent in all groups including controls; correlated with macroscopic and clinical observations; partially resolved at recovery. • ↓ in cellularity In the thymus in HD. • Vehicle (Captisol™)-related vacuolation in kidney, bladder, bone femur, prostate, mandibular and mesenteric lymph nodes, and aorta; reduced at recoevery
Immunophenotyping	HD: ↑ total T, helper T, cytotoxic T and regulatory T lymphocytes; ↓ stimulated Th17 cells MD, HD: ↑ B lymphocytes LD, MD, HD: ↓ in NK cells

LD: low dose; MD: mid dose; HD: high dose.

Study title/ number: GSK2894512A: Toxicity Study by Dermal Administration to Göttingen Minipigs for 9 Months Followed by a 1-Month Off-Dose Period / 2016N299302

- The NOAEL of the study was considered to be 3% tapinarof cream, the highest dose tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Doses:	0 (Vehicle), 0.5%(low-dose), 1% (mid-dose), and 3% (high-dose) tapinarof cream
Frequency of dosing:	Twice daily (10 hour apart)
Route of administration:	Topical
Formulation/Vehicle:	Cream (Formulation F, final clinical formulaiton)/ (b) (4) Water, (b) (4) sodium Citrate, Dihydrate, (b) (4) Citric Acid, (b) (4) EDTA disodium, (b) (4) Triglycerides, (b) (4) Polysorbate 80, (b) (4) BHT, (b) (4) Benzoic Acid, (b) (4) Propylene Glycol and (b) (4) Diethylene glycol monoethyl ether
Species/Strain:	Gottingen Minipigs
Number/Sex/Group:	4/sex/group for main study groups;
Age:	4-5 months
Satellite groups:	6/sex/groups for 4 groups
Unique study design:	2/sex/group for vehicle and high-dose group for one month recovery period
Deviation from study protocol:	No deviations affect the conclusions

Observations and Results: Changes From Control

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	No test article-related effects
Dermal Observations	Erythema, slight eschar and desquamation in all groups
Body Weights / Food Consumption	No test article-related effects
Ophthalmoscopy *[*	No test article-related effects
ECG	No test article-related effects
Hematology	No test article-related effects
Clinical Chemistry	No test article-related effects
Urinalysis	No test article-related effects
Gross Pathology	No test article-related effects
Organ Weights	No test article-related effects
Histopathology Adequate battery: Yes/No	Yes. No test article-related effects

LD: low dose; MD: mid dose; HD: high dose.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title/ number: Bacterial reverse mutation test of WBI-1001 / 2013N163822
Key Study Findings:

- Tabinarof did not induce an increase in the number of revertants per plate in any tester strain with or without S9. It showed no mutagenic effects under the conditions of this Ames assay.

GLP compliance: Yes
Test system: *S. typhimurium* TA98, TA100, TA1535, TA1537, and *E. coli* WP2 uvrA; 48-72 hr treatment +/-S9; up to 62 µg/plate for TA98, TA100, TA1535, and TA1537; up to 190 µg/plate for WP2 uvrA.
Study is valid: Yes. Maximum concentrations tested was limited by signs of bacterial toxicity.

In Vitro Assays in Mammalian Cells
Study title/ number: Chromosome aberration test of WBI-1001 in cultured chinese hamster ovary cells/ 2013N163824
Key Study Findings:

- Tabinarof exhibited no in vitro clastogenic effects under the conditions of this assay.

GLP compliance: Yes
Test system: Chinese hamster ovary cell line WB_L; -S9: 3-hour and 18-hour incubation; +S9: 3-hour incubation; at up to 20 µg/mL
Study is valid: Yes. Maximum concentrations tested was limited by toxicity.
Study title/ number: GSK2894512A: In vitro mutation assay with L5178Y mouse lymphoma cells at the TK locus / 2013N173392

Key Study Findings:

- Tabinarof was not genotoxic in the mouse lymphoma L5178Y TK+/- assay.

GLP compliance: Yes
Test system: Mouse peripheral blood lymphocytes; 3-hr treatment +/-S9: up to 254.32 µg/mL; 24-hr treatment -S9: up to 40 µg/mL.
Study is valid: Yes. Maximum concentrations tested was limited by toxicity.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: In vivo mouse micronucleus assay of WBI-1001 / 2013N163826
Key Study Findings:

- Tabinarof exhibited no in vivo clastogenic effects in the mouse bone marrow micronucleus assay when administered intraperitoneally at doses up to 31.3 mg/kg/day

GLP compliance: Yes
Test system: Mouse, bone marrow cell micronuclei; single Intraperitoneal dose of 0 (vehicle), 7.8, 15.6 or 31.3 mg/kg/day; assessments at 24, 36 and 48 hours post-dose.
Study is valid: Yes.

Study title/ number: GSK2894512A: 4-Week Subcutaneous Toxicity Study and Bone Marrow Micronucleus Assay in Rats / 2013N166805
Key Study Findings:

- Tabinarof exhibited no in vivo clastogenic effects in the rat bone marrow micronucleus assay when administered subcutaneously for 28 days at doses up to 30 mg/kg/day

GLP compliance: Yes
Test system: Rat, bone marrow cell micronuclei; 28 days of subcutaneous doses of 0 (vehicle), 1, 6 and 30 mg/kg/day.
Study is valid: Yes

5.5.3. Carcinogenicity

In a 2-year dermal mouse carcinogenicity study, topical once daily doses of 0 (untreated control), 0 (vehicle control), 0.5%, 1.5%, and 3.0% tapinarof cream were tested in CD-1 mice. Tapinarof cream treatment did not result in a significantly increased incidence of drug-related neoplasms in either male or female CD-1 mice.

In a 2-year subcutaneous rat carcinogenicity study, subcutaneous doses of 0 (untreated control), 0 (vehicle control), 0.1, 0.3, and 1.0 mg/kg/day tapinarof were tested in Wistar-Han rat. The vehicle formulation changed from 30% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol™) to 10% (w/v) beginning day 372 due to vehicle-related toxicities noted. The male groups were terminated during week 60 and the female groups were terminated during week

82/83 when the number of surviving vehicle control reached 20 animals. The subcutaneous carcinogenicity study in Wistar-Han rats is negative for drug-related neoplasms in female rats but the male portion of the study, while it did not show any statistical increase in tumors, was of an inadequate duration. Therefore, the male carcinogenicity data (b) (4) .

Refer to Appendix 19.3.3 for full carcinogenicity study reviews.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

There was no separate male fertility study in this drug development program. This is not considered an approvability issue. Assessment of tapinarof effects on male fertility was conducted in the 4-week subcutaneous rat study. Normal progression of the spermatogenic cycle and the expected cell associations and proportions in the various stages of spermatogenesis were present at subcutaneous doses up to 30 mg/kg/day. The 4–week subcutaneous rat study data concerning male fertility effects (b) (4) due to use of immature rats. The proposed product is a topical product with limited systemic exposure. Therefore, the effect of tapinarof cream on male fertility is considered negligible.

Study title/ number: GSK2894512A: Subcutaneous Female Fertility and Early Embryonic Development Study in Rats / 2014N211242

Key Study Findings

- The NOAEL for effects on female fertility and early embryonic development was 30 mg/kg/day.

Conducting laboratory and location:	GlaxoSmithKline (GSK) Safety Assessment, 709 Swedeland RoadKing of Prussia, PA, USA
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1, 6, and 30 mg/kg/day
Route of administration:	Subcutaneous
Formulation/Vehicle:	30% Captisol™
Species/Strain:	Wistar Han (Crl:WI[HAN]) rats
Number/Sex/Group:	22 mated females / group
Study design:	Females were dosed once daily beginning 15 days before cohabitation (with untreated male breeders), during cohabitation, and continued until Day 6 of presumed gestation (GD 6); The mated female rats and their litters were euthanized on GD 20 and fetal examinations were conducted. The high dose was the maximum feasible dose.

Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	Does dependent scabs at injection-sites on back
Body Weights /Food Consumption	No test article-related effects
Necropsy findings	No test article-related effects on measured fertility parameters

Embryo-Fetal Development

Study title/ number: GSK2894512A: Subcutaneous Embryo-Fetal Development Study in Rats / 2013N166695

Key Study Findings

- There was a dose-dependent increase in the incidence of scabs at the injection site at 6.9 and 34 mg/kg/day.
- There was a slight decrease in mean fetal body weights and an increased incidence of the skeletal variation (incomplete ossification of the nasal bones) at 34 mg/kg/day.
- The NOAEL for malformations in the rat embryo-fetal development toxicity was 34 mg/kg/day.

Conducting laboratory and location:	GlaxoSmithKline (GSK) Safety Assessment, 709 Swedeland Road, King of Prussia, PA, USA
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1.2, 6.9, and 34 mg/kg/day
Route of administration:	Subcutaneous
Formulation/Vehicle:	30% Captisol™
Species/Strain:	Wistar Han (CrI:WI[HAN]) rats
Number/Sex/Group:	22 mated females / group
Study design:	The planned dose levels were 0, 1, 6, or 30 mg/kg/day once daily on gestational days (GD) 6 through 17. However, the dose levels actually achieved were 1.2, 6.9, or 34 mg/kg/day. The mated female rats and their litters were euthanized on GD 21 and fetal examinations were conducted. The high dose was the maximum feasible dose.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	MD and HD: scabs at injection-sites
Body Weights /Food Consumption	No test article-related effects
Necropsy findings Cesarean Section Data	HD: ↓ mean fetal weights (4% and 5% for male and female fetuses)
Necropsy findings Offspring	HD: ↑ fetal variation, incomplete ossification of the nasal bones (31 fetuses / 7 litters)

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: GSK2894512A: Subcutaneous Embryo-Fetal Development Study in Female Rabbits / 2014N189059

Key Study Findings

- Maternal toxicity with reduced body weight gains was noted at 3 mg/kg/day.
- Increased postimplantation loss and fetal skeletal variations were observed at 3 mg/kg/day.
- The NOAEL for effects on rabbit embryo-fetal development was 1 mg/kg/day

Conducting laboratory and location:	GlaxoSmithKline (GSK) Safety Assessment, King of Prussia, PA, USA
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 0.3, 1.0, and 3.0 mg/kg/day
Route of administration:	Subcutaneous
Formulation/Vehicle:	30% Captisol™
Species/Strain:	New Zealand White [Hra:(NZW)SPF] rabbits
Number/Sex/Group:	22 mated females / group
Study design:	Females were dosed on GD 7-19 twice daily. Surviving mated females and their litters were euthanized on GD 29 and fetal examinations were conducted.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	MD and HD: scabs at injection-sites
Body Weights /Food Consumption	HD: ↓ mean body weight gain (0.75x)
Necropsy findings Cesarean Section Data	HD: ↑postimplantation loss (8.0% versus 3.8% in control)

Necropsy findings Offspring	HD: fetal skeletal variations of extra sutures in the interparietals and intraparietal ossification site

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: GSK2894512A: Subcutaneous Infusion Embryo-Fetal Development Study in Rabbits/ 20153N244027

Key Study Findings

- The NOAEL for effects on rabbit embryo-fetal development was 3 mg/kg/day, the highest dose tested.

Conducting laboratory and location:	GlaxoSmithKline (GSK) Safety Assessment, 7333 Mississauga Road North, Mississauga, ON L5N 6L4, Canada
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1, 2, and 3 mg/kg/day
Route of administration:	Subcutaneous infusion over a 24 hour period each day
Formulation/Vehicle:	30% Captisol™
Species/Strain:	New Zealand White [Hra:(NZW)SPF] rabbits
Number/Sex/Group:	22 mated females / group
Satellite groups:	None
Study design:	Females were dosed on GD 7-19. Surviving mated females and their litters were euthanized on GD 29 and fetal examinations were conducted.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	Swollen and soft infusion sites along with skin findings (blue, red, dry, lesion, scab) in all groups due to vehicle treatment (30% Captisol™)
Body Weights /Food Consumptions	No test article-related effects
Necropsy findings Cesarean Section Data	No test article-related effects
Necropsy findings Offspring	No test article-related effects

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: GSK2894512A: Subcutaneous Pre- and Postnatal Development Study in Rats / 2018N368233

Key Study Findings

- Maternal toxicity (decreased body weight gain and food consumption) was observed at 30 mg/kg/day. Scabbing at injection site associated sparse hair coat on the back was observed across all test article groups.
- There was a test article-related decrease in F1 pup survival and viability at doses of 6 and 30 mg/kg/day that resulted in reduced litter sizes and decreased pup weights.
- The NOAEL for tapinarof effects on prenatal and postnatal development of the offspring in rats was 1 mg/kg/day. Test article was present in offspring suggesting that tapinarof is transferred in maternal milk.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1, 6, and 30 mg/kg/day
Route of administration:	Subcutaneous
Formulation/Vehicle:	30% Captisol™ aqueous solution
Species/Strain:	Wistar Han (Crl:WI[HAN]) rats
Number/Sex/Group:	24 or 26 mated females / group
Study design:	Animals were dosed from GD 6 to lactation day (LD) 20; To evaluate the potential test article effects on late gestational & neonatal kidney development, a microscopic evaluation of F1 kidneys was performed on LD 7*; An unexpected lighting issue in the study room (132 hours) caused abnormal cycling of females across all dose groups, the evaluation period was extended [starting on postnatal day (PND) 76 to 80] for a total of 31 days. * Due to the kidney findings in the Juvenile animal study, a total of 20 pups in control and 30 mg/kg/day groups (selected from 2 or 9 litters, respectively) were examined for kidney abnormalities. Renal toxicity is associated with cyclodextrin (Captisol). Therefore, it is possible that this extra evaluation for kidneys was conducted due to Capitsol renal toxicity concerns.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	• Dose-dependent ↑ in scabbing of injection site associated sparse hair coat on the back. • HD: One mortality on GD 19; ↓ body weight gain and food consumption
F1 Generation	• Dose dependent ↓in F1 pup survival and viability and ↓ litter sizes and pup weights. • Test article is present in maternal milk. • There were no microscopic kidney findings in the F1 generation pups that were considered related to test article. There were no maturation differences noted in the cortex, medulla, renal papilla, or renal pelvis between the control and 30 mg/kg/day pups on LD 7.
F2 Generation	No test article-related effects

Juvenile Animal Toxicity Study

Study title/ number: GSK2894512A: Subcutaneous Juvenile Toxicity Study in Rats / 2014N211697

Key Study Findings

- Thin fur cover or scabs was noted at the injection site in all test article-treated groups. Microscopic changes at the injection sites (hemorrhage, inflammation and/or necrosis) were noted at the high dose, and only partially recovered after 4 weeks recovery.
- At ≥ 10/15 mg/kg/day, there were adverse microscopic changes in the form of renal pelvic dilatation in both sexes; test article-related changes also included decreased thymus weight, and decreased cellularity in the thymus and changes of thymic T cell maturation populations.
- The NOAEL for juvenile animal toxicity was 1/1.5 mg/kg/day.

Conducting laboratory and location:	GlaxoSmithKline (GSK) Safety Assessment, 7333 Mississauga Road North, Mississauga, ON L5N 6L4, Canada
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 1/1.5, 10/15, and 20/30 mg/kg/day
Route of administration:	Subcutaneous
Formulation/Vehicle:	30% Captisol™
Species/Strain:	Wistar Han (Crl:WI[HAN]) rats
Number/Sex/Group:	10
Study design:	The first dose level was given from Postnatal Day (PND) 7 to 21, and the second dose level was given from PND 22 to 77. This dose escalation was done in an effort to maintain

	consistent systemic exposures across the duration of the dosing period due to decreases in exposure observed as the pups matured in a previous juvenile tolerability/dose range rat study.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No test article-related effects
Clinical Signs	Dose dependent: thin fur cover was noted at the injection site of most animals with only a few in the vehicle group. HD: Scabs were observed
Body Weights /Food Consumption	No test article-related effects
Ophthalmoscopy	No test article-related effects
Clinical Pathology	MD and HD males: reversible ↑ in total urinary glucose and protein excretion
Reproductive performance: behavior assessment, evaluation of the developing immune system, estrous cyclicity in females; and male mating, fertility and male-mediated developmental toxicity	No test article-related effects
Organ Weights	MD and HD: ↓ thymus weights in both gender
Histopathology Adequate battery: Yes/No	Yes. MD/HD: adverse microscopic changes in the form of renal pelvic dilatation in both sexes, still present at the end of recovery HD: hemorrhage, inflammation and/or necrosis at injection sites, partially recovered after recovery.
Immunology	No test article-related effects in TDAR

LD: low dose; MD: mid dose; HD: high dose.

5.5.5. Other Toxicology Studies

Skin sensitization study in guinea pigs (Buehler test method) of WBI-1001 / 2013N163830
Male guinea pigs received 8% Tapinarof cream for 6 hours on Days 0, 6, and 13. On Day 27, the animals were challenged with the test article for another 6 hours. None of the guinea pigs in the sham control, vehicle control, and test article-treated groups had any signs of local skin

irritation after the challenge period. Tapinarof cream 8% was not a sensitizer under the conditions of the study.

Acute eye irritation/corrosion test on rabbits of WBI-1001 / 2013N163833
Three female New Zealand albino rabbits received 0.1 mL 8% tapinarof cream on the conjunctival sac of one eye. The other eye remained untreated and served as the control. The treated eye of the rabbit was washed out after a 24-hour exposure period. Irritancy evaluations were performed at 1, 24, 48, and 72 hours post-dosing. Only conjunctival discharge (score 1) was observed in all animals at 1 hour post-dosing. All animals had recovered to normal by 24 hours post-dosing. The test article was classified as non-ocular irritant.

GSK2894512A (as 1, 2 and 4% creams): Local lymph node assay in the mouse / 2013N175961
Six groups of five female CBA/CaCrl mice received 50 µL of acetone/olive oil, vehicle cream, 1%, 2%, 4% tapinarof cream, or positive control (25% α-hexylcinnamaldehyde) over the outer aspect of the auditory pinnae of each mouse once daily on Days 1, 2, and 3. On Day 6 a 20 µCi dose of ^{3}H-methyl thymidine was injected intravenously into each mouse. Approximately 5 hours later the auricular lymph nodes were recovered from each animal and the proliferative response of the auricular lymph node (incorporation of ^{3}H-methyl thymidine) was assessed. No skin irritation was observed. Tapinarof cream at up to 4% was not a sensitizer under the conditions of this study.

Topical phototoxicity screening test in hairless mice / 2013N163834
Because tapinarof absorbs UV light with a peak at 315 nm, a nonclinical phototoxicity study was conducted. In a primary irritancy study, 4 groups of 3 male hairless mice topically received 100 µL of cream containing 0% (vehicle), 1%, 4%, or 8% tapinarof (Formulation A). Since no substantive primary irritation was observed, the 1%, 4%, and 8% tapinarof creams were used in the phototoxicity phase of the study.

Six groups of 6 male hairless mice received no treatment, 100 µL of 0.1% 8 methoxypsoralen (8-MOP, positive control), or 100 µL of 0%, 1%, 4%, or 8% tapinarof creams. At approximately 45 minutes post-dosing, mice were exposed to mid-range ultraviolet radiation (UVB) at 0.5 MED (Minimal Erythema Dose) in a one-half hour exposure period. Erythema grade 1 occurred at the UVB irradiated site in only 2, 1, or 1 mouse topically treated with 1%, 4%, or 8% tapinarof cream, respectively. Flaking grade 1 occurred at the UVB irradiated site in a single mouse topically treated with 8% tapinarof cream three days after UVB exposure.

The results indicated that a single dermal treatment of tapinarof followed by a single exposure to UVB irradiation did not elicit a skin reaction indicative of phototoxicity.

GSK2894512A: Study of the potential for in vitro hemolysis in minipig blood with vehicles containing SBE beta-cyclodextrin, propylene glycol, and polyethylene glycol (PEG400) / 2013N162009

Minipig whole blood samples were incubated with 0.9% sodium chloride (negative control), 10 mg/mL saponin (positive control), Captisol™ (vehicle), tapinarof at doses of 4.15 or 1.38 mg/mL, 20% propylene glycol, or 40% polyethylene glycol (PEG400) in water at 37 ºC for 10 minutes. The percent hemolysis was determined for each test article. Negative and positive control results were acceptable and the study was considered valid. Propylene glycol 20% and PEG400 were hemolytic (88.4% and 9.9% hemolysis, respectively). Tapinarof at doses of 4.15 and 1.38 mg/mL in Captisol™ and Captisol™ alone were not hemolytic in minipig whole blood (<2% hemolysis).

Excipients:
One of the excipients, Polyoxyl 20 Stearyl Ether, was not found in the FDA inactive ingredient database. However, a similar excipient Polyoxyl 20 Cetostearyl Ether was more widely used in other FDA-approved topical products. Although nonclinical studies conducted during early product development used several different formulations of tapinarof (A, B, C, D, and E) and they are slightly different from the to be marketed formulation (F) in excipient composition, pivotal repeat-dose dermal studies (13-week study in mice, and 28-day and 39-week studies in minipigs) were conducted with the final clinical formulation, Formulation F, at concentrations up to 3% (b) (4). The pivotal repeat-dose dermal studies qualify the excipients used in the final clinical formulation, that contains Polyoxyl 20 Stearyl Ether. There are no significant concerns related to the excipients, from a pharmacology/toxicology perspective.

Impurities:
The applicant has conducted a total of 15 Ames assays to investigate the genetic toxicity of the potential mutagenic impurities. Two drug-related impurities, (b) (4) and (b) (4), were tested positive in Ames assays. The applicant proposed to classify these two impurities as Class 1 ((b) (4) with a class-related acceptable intake) according to ICH M7. The applicant stated in the NDA submission that:
"This designation is based on SAR, as they are (b) (4) *in terms of DNA reactivity and there are no other substructures of concern... According to ICH M7,* (b) (4) ".

From a pharmacology/toxicology perspective, the applicant's proposal of setting the acceptable limit of these two impurities at (b) (4) times higher than TTC of 1.5 µg/day appears reasonable, because (1) the clinical route of administration for tapinarof is topical, which provides very limited amount of systemic exposure of these impurities; (2) two carcinogenicity studies have been conducted with tapinarof and no drug-related neoplasms was noted; (3) it is reasoble to

consider that [redacted] (b) (4) according to ICH M7.

An additional potential mutagen, [redacted] (b) (4), is an [redacted] (b) (4) degradant of tapinarof. This molecule was tested in the in vitro Ames test and was not mutagenic in either the presence or absence of S9-mix, and therefore this impurity was classified as Class 5 according to ICH M7 and non-mutagenic.

Assessment of the skin and eye irritation potential of [redacted] (b) (4) process intermediates has also been conducted with in vitro studies [redacted] (b) (4). There are no safety concerns from a pharmacology and toxicology perspective.

6 Clinical Pharmacology

6.1. Executive Summary

Tapinarof is a nonsteroidal aryl hydrocarbon receptor agonist that is being developed as a novel anti-inflammatory agent for the topical treatment of plaque psoriasis and atopic dermatitis. The Applicant has submitted this NDA to support the use of Tapinarof cream, 1% once daily (QD) for the treatment of plaque psoriasis in adult subjects 18 years of age and older. The clinical program consisted of seven phase 1 trials (one in patients with psoriasis and six in healthy subjects), three phase 2 studies in subjects with plaque psoriasis which include a maximal use pharmacokinetic (PK) trial in subjects with extensive plaque psoriasis, two phase 3 safety and efficacy trials, and one phase 3 long term open label long term safety trial. The Applicant has also submitted one phase 1 study in Japanese healthy subjects as supporting information.

The Clinical Pharmacology of tapinarof was evaluated in five clinical studies in healthy volunteers and in patients with psoriasis using the to-be-marketed formulation (one Phase 1 study in healthy volunteers, one Phase 1 study in Japanese healthy volunteers, one Phase 2 maximal use PK study in adult patients with psoriasis, and two Phase 3 studies in adult patients with psoriasis).

The clinical pharmacology review is focused on the appropriateness of the proposed dosing regimen of Tapinarof cream, 1% once daily in patients with plaque psoriasis.

Recommendation: This application is acceptable from a Clinical Pharmacology Perspective.

Post marketing requirement (PMR): Conduct an open-label, long-term safety and pharmacokinetic (PK) study in at least 100 pediatric subjects with plaque psoriasis ages 2 to <18 years. Subjects should be exposed to tapinarof cream, 1%, for a minimum of 52 weeks.

For PK evaluation under maximal use conditions, include at least 16 evaluable subjects ages 12 to <18 years with involved BSA ≥ 10%, and at least 8 subjects ages 2 to <12 years with involved BSA ≥ 3% exposed to tapinarof cream, 1%, for a minimum of 12 weeks, with the option of continuing for a total of 52 weeks.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Tapinarof is a nonsteroidal, small molecule therapeutic aryl hydrocarbon receptor (AhR) modulating agent, which exerts its therapeutic effects via binding to AhR, which is postulated to down regulate certain pro-inflammatory cytokines. PK of tapinarof was evaluated in five clinical studies in healthy volunteers and patients with psoriasis using the to-be-marketed formulation (one Phase 1 study in healthy volunteers, one Phase 1 study in Japanese healthy volunteers, one Phase 2 maximal use PK study in adult patients with psoriasis, and two Phase 3 studies in adult patients with psoriasis).

No accumulation was observed with repeat topical application of tapinarof. Plasma concentration of tapinarof was below the quantifiable limits (BQL) of the assay (lower limit of quantification was 50 pg/mL) in 68% of the PK samples. On Day 1, mean ± SD values of Cmax and AUC0-last were 0.90 ± 1.4 ng/mL and 4.1 ± 6.3 ng.h/mL, respectively, following a mean daily dose of 5.23 g applied to a mean body surface area involvement of 27.2% in 21 subjects with moderate to severe plaque psoriasis. On Day 29, mean plasma concentrations were lower and the mean ± SD Cmax and AUC0-last were 0.12 ± 0.15 ng/mL and 0.61 ± 0.65 ng.h/mL, respectively. The lower systemic exposure on Day 29 could have been due to resolution of disease. In Phase 3 trials in subjects with mild to severe plaque psoriasis affecting 3 to 20% body surface area, ≥95% of PK samples were BQL. Human plasma protein binding of tapinarof is approximately 99% in vitro. Tapinarof is metabolized in the liver by multiple pathways including oxidation, glucuronidation, and sulfation demonstrated by in vitro experiments. Tapinarof is the major circulating component in plasma. No other metabolites were detectable in the plasma. Due to limited systemic absorption, there was an insufficient number of quantifiable timepoints in most subjects to reliably estimate the terminal half-life. There is low potential for any drug interactions based on assessment of plasma concentrations and in vitro drug interaction studies.
At the recommended dosage, Tapinarof does not prolong the QTc interval to any clinically relevant extent.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage is a thin layer of Tapinarof cream, 1% to affected areas once daily. The proposed dosing is supported by the safety and efficacy data obtained in the phase 3 trials and the systemic exposure observed under maximal use conditions.

Therapeutic Individualization

Therapeutic individualization is not applicable for Tapinarof because it is locally administered with low systemic exposure.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK of Tapinarof was assessed in the following trials:

US trials (Formulation F: to-be-marketed formulation):

- 201661 (Skin Residency Study of Topically Applied Cream in Healthy Volunteers)
- DMVT-505-2002 (Phase 2 Maximal Use and QT Study in Subjects with Psoriasis)
- DMVT-505-3001 (Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults)
- DMVT-505-3002 (Phase 3 Efficacy and Safety Study of Tapinarof for the Treatment of Plaque Psoriasis in Adults)

Japanese trial (Formulation F: To-be-marketed formulation):

- 200920 (Skin Irritation Study in Healthy Japanese Subjects)

US trials (using earlier formulations): These studies will not be summarized in the Clinical Pharmacology review because they were conducted with a different formulations than the to-be-marketed formulation. Hence, these studies would not impact the regulatory decision on this application.

- IPS117191 (Evaluate the Cumulative Irritation Potential of Topically Applied GSK2894512 Cream in Healthy Subjects- formulation E)
- WBI-1001-101(Study to Evaluate Topically Applied WBI-1001 Cream in Patients with Psoriasis- Formulation C)

Supporting Atopic Dermatitis studies: These studies will not be summarized in the Clinical Pharmacology review because the indication is different from the targeted indication.

- 201851 (PK, safety, and clinical response of Tapinarof in subjects with AD)
- WBI-1001-201 (Evaluate Tapinarof in Subjects with Atopic Dermatitis- Formulation C)
- 203121 (Phase 2b to assess safety and efficacy of Tapinarof in subjects with AD)

Skin Residency Study (201661): The purpose of this trial was to evaluate residency time in the skin, safety, and tolerability of Tapinarof cream in healthy subjects. This study was proposed to

determine whether exploratory results in minipigs showing extended residency in the skin for up to 7 days also occurred in humans. The study consisted of a screening period for up to 28 days prior to Baseline (Day 1), a treatment period for 7 days, and a post-treatment period from Day 8 to Day 14 for biopsy collection from the Formulation F arm with a follow-up visit on Day 15. No biopsies were obtained from the Formulation E arm.
Drug administration: Tapinarof formulations were applied as a thin layer QD for 7 days to opposite volar regions of the forearms in 7 healthy male subjects.
Formulation: 2 different formulations of Tapinarof cream, 1%, Formulation E and Formulation F (to-be-marketed).
PK sampling: Skin biopsies were taken from all subjects on Day 8 and 2 additional biopsies were obtained from each subject between Days 9 and 14, in a randomized fashion. No Biopsies were collected for formulation E.
PK results: Tapinarof skin concentrations in the biopsy samples were observable through Day 9 above the LLOQ using liquid chromatography-tandem mass spectrometry (Table 3).

Table 3. Tapinarof Skin Concentration Post-Dose for Formulation F

Visit	Concentration (ng/g) Mean (SD) [Range]
Day 8 (n=6, NQ=1)	172.5 (113.0) [0, 346.6]
Day 9 (n=2, NQ=1)	20.9 (29.6) [0, 41.9]
Day 10 (n=2, NQ=2)	NQ
Day 11 (n=2, NQ=2)	NQ
Day 12 (n=2, NQ=2)	NQ
Day 13 (n=2, NQ=2)	NQ
Day 14 (n=2, NQ=2)	NQ

Source: GSK study 201661 CSR, Table 7

Tapinarof was detectable in human skin biopsy samples for up to 48 hours post dose. The extended residence time observed in healthy minipig skin were not observed in healthy human skin.

Maximal Use Study in Subjects with Psoriasis (DMVT-505-2002): The purpose of this trial was to assess safety, tolerability, PK, electrocardiogram (ECG) parameters, and efficacy of Tapinarof Cream, 1% in adult subjects with extensive plaque psoriasis.

This was a Phase 2a, multicenter, open-label, maximal use study to evaluate the safety and PK of tapinarof cream, 1% in adults with extensive plaque psoriasis (≥ 20% body surface area [BSA] involvement). The study consisted of 3 phases: Screening (up to 34 days), Treatment (29 days), and Follow-Up (7 to 10 days). Subjects returned to the clinic on Days 2, 15, 29, and 30 for study assessments and received phone calls on Days 8 and 22. Subjects returned to the clinic for the Follow-Up Visit 7 to 10 days after the Day 29 Visit. On clinic visit days, subjects applied the study drug under the supervision of site personnel after assessments were completed.

Drug administration: On Day 1 (Baseline), eligible subjects were instructed on how to apply tapinarof cream, 1% while under the supervision of site personnel in the clinic. During the treatment period, subjects applied Tapinarof cream, 1% to their affected areas QD for 29 days. They were instructed to apply study drug to all affected areas including newly appearing lesions and lesions/areas that improved during the study.
Formulation: To-be-marketed Formulation F.
PK and QT assessments: Full PK profiles and Holter monitoring were collected on Days 1 and 29 (with corresponding 24-hour time points collected on Days 2 and 30, respectively). Limited PK sampling was performed on Day 15. Pretreatment, time- matched Holter monitoring for QT assessment was conducted on Day -1 and the morning of Day 1.
PK results: Across 21 subjects (13 males/ 8 females) treated, Tapinarof plasma exposure was low with the majority of samples (284 of 418 samples [68%]) having concentrations that were BLQ. On Day 1, at 5 hours post-dose and later sample times, and at all sample times on Day 15 and 29, ≥ 50% of samples were BLQ. The highest concentration observed was 5000 pg/mL which occurred in one subject at the pre-dose time point on Day 15. Concentrations of the metabolite (Tapinarof sulfate) were BLQ (< 10 pg/mL) at all the time points.

Tapinarof concentrations were highest on Day 1 with a median T_{max} of 3.1 hours post-dose. Plasma concentrations decreased over the course of the study and this might have been due to the resolution of the disease; however, concrete conclusions could not be made due to PK data quantifiable in very small number of subjects. On Day 29, Tapinarof concentrations were approximately 10-fold lower than those observed on Day 1, with slight fluctuations in concentrations at the measured time points over the day (Table 4).

Table 4. Summary Statistics of Pharmacokinetic Parameter Estimates for Tapinarof by Day in Subjects with Extensive Plaque Psoriasis (Study DMVT-505-2002)

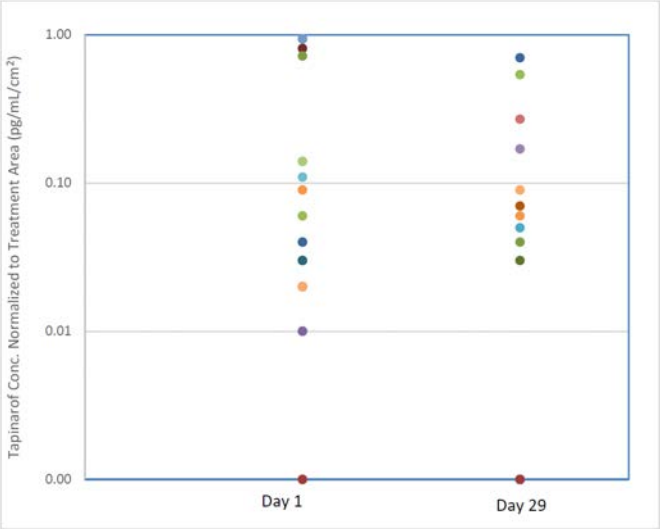
PK parameter[a]	Day 1	Day 29[b]
C_{max}, pg/mL (n)	21	19
Mean (SD), CV%	898 (1448), 161.2%	116 (148.4), 127.9%
Median (Range)	181 (0.0 – 4680)	59.4 (0.0 – 467)
t_{max}, hours (n)	18	11
Median (Range)	3.10 (1.10 – 23.8)	3.17 (1.10 – 12.2)
t_{last}, hours (n)	18	11
Mean (SD), CV%	9.50 (7.847), 82.61%	7.39 (6.650), 90.03%
Median (Range)	8.04 (1.20 – 24.2)	5.13 (2.20 – 24.1)
Geometric Mean, Geometric CV%	6.48, 123.4%	5.54, 88.32%
$AUC_{0\text{-last}}$, pg.h/mL (n)	17	11
Mean (SD), CV%	4067 (6331.2), 155.68%	608.6 (645.91), 106.13%
Median (Range)	2095 (26.80 – 22110)	278.8 (29.70 – 1994)
Geometric Mean, Geometric CV%	861.2, 1067.0%	321.3, 220.02%
$AUC_{0\text{-}\tau}$, pg.h/mL (n)	4	1
Mean (SD), CV%	8037 (6204.9), 77.200%	1986 (NC), NC
Median (Range)	6399 (2619 – 16730)	1986 (1986 – 1986)
Geometric Mean, Geometric CV%	6403, 92.560%	1986, NC
$AUC_{\tau\ extrap\ \%}$ % (n)	4	1
Mean (SD), CV%	6.19 (8.081), 130.6%	0.00 (NC), NC
Median (Range)	3.87 (0.0 – 17.0)	0.00 (0.00 – 0.00)
$t_{½}$ hours (n)	2	0
Mean (SD), CV%	6.41 (0.6910), 10.78%	NC
Median (Range)	6.41 (5.90 – 6.90)	NC
Geometric Mean, Geometric CV%	6.39, 10.83%	NC

a. Missing sampling or concentration values were not imputed but left missing in the calculation of derived PK parameters. Subjects with a minimum of 3 post-dose time points were required for determination of AUC. A minimum of 3 descending time points with quantifiable plasma concentrations after C_{max} were used in the estimation of the terminal phase rate constant, for the determination of the terminal half-life ($t_{½}$). $t_{½}$ was reported wherever the adjusted R2 value > 0.7.
b. One subject (Subject (b) (6)) had their 24-hour sample on Day 30 (Visit 7) collected outside the predetermined sample collection window and therefore was excluded from analysis.
Source: DMVT-505-2002 CSR, Table 15
Note: BQL values (concentrations < 50 pg/mL) before the first quantifiable concentration were set to zero. BQL values after the first quantifiable concentration and followed by a value above the lower limit of quantitation were set as missing. If 2 consecutive BQL values occurred after t_{max}, the subsequent values were inputted as missing.
$AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the last detectable time point; $AUC_{0\text{-}\tau}$ = area under the plasma concentration-time curve over the dosing interval at steady-state; $AUC_{\tau\ extrap\%}$ = percentage of $AUC_{0\text{-}\tau}$ extrapolated; BQL = below quantifiable limits; C_{max} = maximum observed plasma concentration; CSR = clinical study report; CV = coefficient of variation; NC = not calculated; PK = pharmacokinetics; SD = standard deviation; $t_{1/2}$ = terminal half-life; t_{last} = time of last detectable plasma concentration; t_{max} = time of maximum plasma concentration.

Source: DMVT-505-2002 CSR, Table 15

Exploratory analyses demonstrated no relationship between Tapinarof exposure and application area. When normalized by percent body surface area (%BSA) of disease, the concentration range for C_{max} demonstrated a wide range of values (Figure 1). Exploration of individual patient PK profiles further support this lack of relationship. The subject with the highest %BSA (46%) had mostly undetectable concentrations while another subject at the low end of the %BSA range (22%) had a near-complete PK profile.

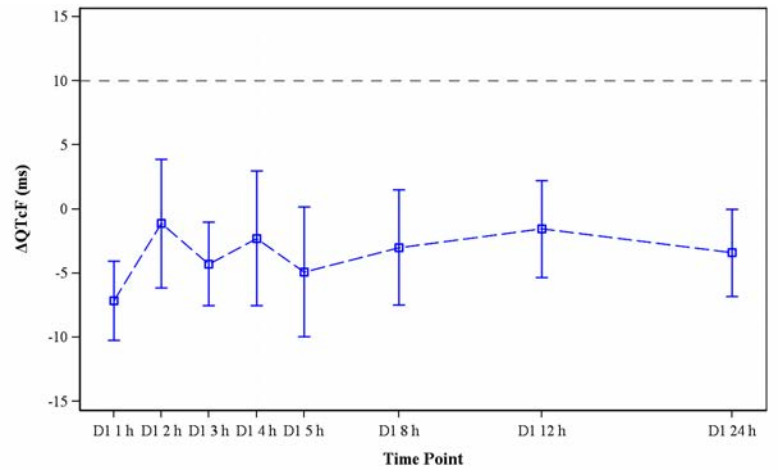
Figure 1. Individual Tapinarof Cmax Normalized by Baseline %BSA (cm2) Versus Study Visit (DMVT-505-2002)



Source: DMVT-505-2002 CSR, Listing 16.2.9.10

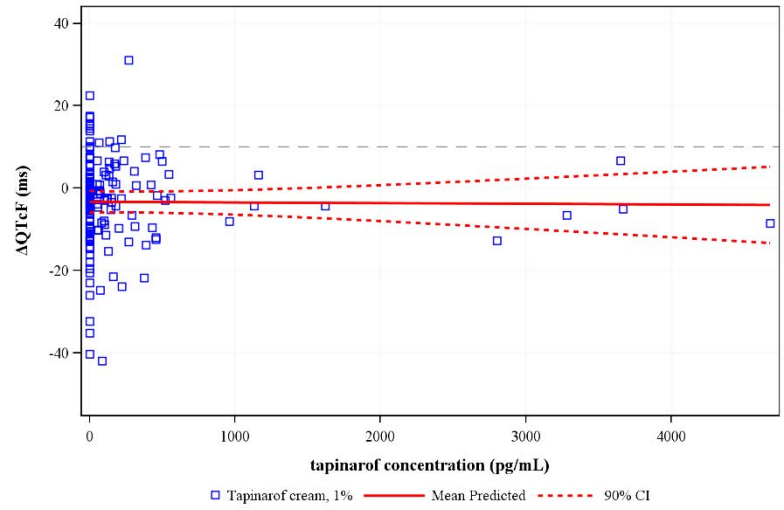
The effect of Tapinarof on ECG parameters was assessed by 2 statistical methods. Analyses were performed using Day 1 PK and ECG parameters since concentrations were highest on Day 1 compared to Day 29. In the by-time point analysis, Tapinarof did not have a clinically relevant effect on the QT interval. Mean change from baseline in QT interval using Fridericia's formula (ΔQTcF) after Tapinarof treatment was negative at all time points, ranging from −7.2 milliseconds (1 hour post-dose) to −1.1 milliseconds (2 hours post-dose) (Figure 2). The highest upper bound of the 90% confidence interval at any time point was 3.90 milliseconds (2 hours post-dose). A concentration-QTc analysis for Tapinarof also did not demonstrate a clinically relevant QT effect within the observed Tapinarof plasma concentration range (Figure 3). A QTcF effect (ΔQTcF) exceeding 10 milliseconds can be excluded within the observed range of Tapinarof plasma concentrations up to approximately 4600 pg/mL. Effects of Tapinarof on heart rate (mean ΔHR range: 2.6 beats per minute [3 hours post-dose] to 5.0 beats per minute [8 hours post-dose]) were minimal.

Figure 2. **ΔQTcF** Across Time Points (DMVT-505-2002)



Source: DMVT-505-2002 CSR, Appendix 16.2.5.2, Cardiac Safety Report

Figure 3. Scatter Plot of Observed Tapinarof Plasma Concentrations and **ΔQTcF** by Subject (DMVT-505-2002)



Source: DMVT-505-2002 CSR, Appendix 16.2.5.2, Cardiac Safety Report

Even with only 4 weeks of treatment, the majority of subjects had improvements in their psoriasis based on the Physician's Global Assessment (PGA), the Psoriasis Area and Severity Index (PASI), and %BSA of disease (see Section 8). Tapinarof was generally well tolerated in these subjects with extensive plaque psoriasis. Irrespective of causality, 12 subjects (57.1%) reported treatment-emergent adverse events (TEAEs) and 6 subjects (28.6%) reported TEAEs considered related to study drug. All TEAEs were Grade 3 or less, with the majority of TEAEs being Grade 1 (7 subjects [33.3%]). Four subjects (19.0%) each reported adverse event of special interest (AESIs) of folliculitis and headache. No subject had a TEAE leading to discontinuation or treatment interruption of study drug. Six subjects (29%) had TEAEs

considered related to study drug which were all Grade 1 or 2 in severity. The most common drug-related TEAEs were folliculitis (4 subjects [19.0%]) and headache (2 subjects [9.5%]). One subject had a serious adverse event (pancreatitis) reported as unrelated to study drug (for more details, see Section 8).

Overall Tapinarof plasma exposure was low with the majority of samples having concentrations that were BLQ (< 50 pg/mL). Plasma exposure declined over the course of the study with Day 29 concentration values approximately 10-fold lower than those on Day 1. Tapinarof, at the dose/concentrations studied, had no clinically relevant effects on QT interval or other ECG parameters. Tapinarof was generally well tolerated in subjects with extensive plaque psoriasis; the majority of TEAEs were mild and there were no treatment interruptions and no subject discontinued study drug due to TEAEs. Even with only 4 weeks of treatment, the majority of subjects had improvements in their psoriasis based on PGA, PASI, and %BSA of disease.

Skin Irritation Study in Healthy Japanese Subjects (200920): The purpose of this study was to assess skin irritation of GSK2894512 cream in healthy Japanese subjects. PK was assessed on Day 1 and Day 7 at pre-dose, 2 and 4 hours and on Days 3 and 5 before the morning application. All systemic levels were BLA (< 40 pg/mL).

Phase 3 Studies with Plaque Psoriasis (DMVT-505-3001 and DMVT-505-3002): The purpose of these studies was to assess efficacy, safety, tolerability, impact on daily activities, and PK of Tapinarof in subjects with plaque psoriasis. The study design for both studies were identical. Eligible subjects were randomized at a 2:1 ratio to receive QD treatment with Tapinarof cream, 1% or vehicle cream QD for 12 weeks. Subjects returned to the clinic at Weeks 2, 4, 8, and 12 for efficacy and safety assessments. Subjects were instructed to apply study drug QD to all affected areas, including newly appearing lesions and lesions/areas that improved during the study. Subjects applied sufficient study drug to cover completely each lesion with a thin layer and recorded the time of study drug application in a daily diary provided by the study site. Subjects were instructed to maintain the approximate dosing time chosen at the beginning of the study for their full study participation.
Formulation: To-be-marketed Formulation F.
PK assessments: PK samples were collected pre-dose at the Weeks 4 and 12 visits in a subset of subjects based upon whether the study center was designated as a PK collection site.
PK results: In Study DMVT-505-3001, 510 subjects (299 males/211 females) were enrolled. The PK subset included a total of 208 samples that were analyzed from 139 subjects (96 subjects on Tapinarof, 43 on vehicle). Only 9 samples had detectable concentrations of Tapinarof and the highest concentration was 357 pg/mL. No subjects receiving vehicle had a measurable value. A summary of plasma concentrations is shown in Table 5.

Table 5. Summary of Plasma Concentrations of Tapinarof in a Subset of Subjects (Study DMVT-505-3001)

	Tapinarof Cream, 1% QD (pg/mL) (n=96)	Vehicle Cream QD (pg/mL) (n=43)	Percent of tapinarof samples BQL (<50 pg/mL)
Week 4			
N	89	43	83/89 (93.3%)
Mean (SD)	8.64 (37.326)	0	
Median	0	0	
Minimum, maximum	0, 256	0, 0	
Week 12			
N	76	ND	73/76 (96.1%)
Mean (SD)	9.91 (51.516)		
Median	0		
Minimum, maximum	0, 357		

Source: DMVT-505-3001 CSR, Table 14.4.1.1 and Listing 16.2.5.5

In Study DMVT-505-3002, 515 subjects (290 males/225 females) were enrolled. The PK subset included a total of 296 samples that were analyzed from 186 subjects (120 subjects on Tapinarof, 66 on vehicle). Only 4 samples had detectable concentrations of Tapinarof, and the highest concentration was 418 pg/mL. No subjects receiving vehicle had a measurable value. A summary of plasma concentrations is shown in Table 6.

Table 6. Summary of Plasma Concentrations of Tapinarof in a Subset of Subjects (Study DMVT-505-3002)

	Tapinarof Cream, 1% QD (pg/mL) (n=120)	Vehicle Cream QD (pg/mL) (n=66)	Percent of tapinarof samples BQL (<50 pg/mL)
Week 4			
N	119	66	117/119 (98.3%)
Mean (SD)	2.36 (21.217)	0	
Median	0	0	
Minimum, maximum	0, 225	0, 0	
Week 12			
N	111	ND	109/111 (98.2%)
Mean (SD)	4.59 (40.545)		
Median	0		
Minimum, maximum	0, 418		

Source: DMVT-505-3002 CSR, Table 14.4.1.1 and Listing 16.2.5.5

Dose and Concentration Effect Relationships

The Applicant evaluated potential relationships between tapinarof plasma exposure and measures of efficacy and safety in subjects with psoriasis and AD. The exposure-response (ER) analysis for efficacy would be considered as exploratory as the drug is applied directly to the target site (skin) and systemic levels are used to assess systemic safety and not efficacy.

The analysis was conducted across 4 studies: two Phase 2 and two Phase 3 studies. The safety endpoints were the incidence of headache, folliculitis, and contact dermatitis, which were previously identified as AESIs in Phase 2 clinical trials. The efficacy endpoints were PGA and change from baseline in PASI. Demographic, PK, safety and efficacy data were graphically explored to identify any outliers and/or trends that can assist in model selection for the ER analysis. The minimum observed plasma concentration (C_{min}) and C_{max} were the only exposure parameters explored. Exploratory analysis yielded the following results:

- Approximately 63% of the total PK samples were BQL.
- Concentration-time plots showed no major trends between studies and dose.
- Since systemic exposure following topical administration of tapinarof was limited with a majority of PK samples (63%) being below the limit of quantitation, the ER analysis was conducted using imputed concentration values that assume a maximum exposure level that is approximately ½ of the LLOQ. This provided a maximum estimate of exposure levels following topical administration that can be used for assessing risk to the patients.
- PGA and PASI scores improved from Day 1 to Day 29, which was consistent with the overall results of the Phase 2 and 3 clinical trials.
- There was no trend between PASI/PGA score and C_{max} or C_{min} and this analysis is considered exploratory for the topical route of administration.
- No trend was observed between safety endpoints (incidence of headache, contact dermatitis and folliculitis) and age, weight, body mass index and associated concentration quintiles.
- Folliculitis developed in 12.8% (166 of 1293) of subjects in this analysis, with more cases in subjects with quantifiable C_{min} and C_{max} compared to subjects with non-quantifiable exposures. However, there was no trend observed between plasma concentrations and folliculitis.
- Only 3.7% (48 of 1293) of subjects in this analysis developed headache, with more cases in subjects with quantifiable C_{min} and C_{max} compared to subjects with non-quantifiable exposures. There was no trend seen between plasma concentrations and headache.
- Only 3.3% (43 of 1293) of subjects in this analysis developed contact dermatitis. No consistent dose dependence or meaningful covariate trends were observed, with more cases in subjects with quantifiable C_{min} and C_{max} compared to subjects with non-quantifiable exposures. There was no trend observed between plasma concentrations and contact dermatitis.

Drug metabolism: Tapinarof reaching the circulation is metabolized in the liver via multiple routes and primarily excreted in the feces (estimated 72-78%) and urine (estimated 11-17%). Due to the low systemic absorption following topical application, no radiolabeled mass balance study was conducted in humans. The interspecies (mouse, rat, rabbit, minipig and human) comparison of metabolism of Tapinarof was studied *in vitro*, in three separate studies, using liver microsomes (human only) and cryopreserved hepatocytes. These studies revealed that metabolism was extensive and the major biotransformation of Tapinarof in all of the species was generally attributed to Phase II enzymes, primarily glucuronidation or sulfation, alone or in

combination with oxidation. In general, metabolic profiles of the nonclinical species and human were qualitatively similar. All metabolites of [14C]-Tapinarof observed in human hepatocyte incubations were observed in at least one of the nonclinical species; therefore, there did not appear to be any unique human metabolites formed *in vitro*.

An *in vitro* study examined the human CYP enzymes responsible for the oxidative metabolism of Tapinarof in human liver and skin microsomes. Metabolism of [14C]-Tapinarof (5 μM final concentration) was primarily mediated by CYP1A2 and CYP3A4, with minor contributions from CYP2C9, CYP2C19, and CYP2D6. [^{14}C]-Tapinarof was also metabolized in the recombinant CYP systems by extrahepatic enzymes, primarily CYP1A1, with minor contribution from CYP1B1. In an investigation of the human uridine diphosphoglucuronosyl transferase (UGT) isoforms that catalyze the glucuronidation of Tapinarof, it was demonstrated that UGT1A9 isoform was the primary enzyme involved.

The sulfate metabolite was not detectable in any plasma samples collected from subjects in the maximal use study (DMVT-505-2002) where subjects with psoriasis applied drug to ≥ 20% BSA, even with a highly sensitive assay (LLOQ = 10 pg/mL or 0.03 nM).

Excretion: Preclinical studies with [^{14}C]-Tapinarof following subcutaneous dosing in mouse and rat demonstrated that the major route of elimination was primarily via the feces (approximately 72 to 78% of the dose) while urinary elimination accounted for approximately 11 to 17% of the administered dose. Further investigation demonstrated that biliary secretion accounted for 73% of the dose in bile-duct cannulated rats. Therefore, the major route of elimination following a parenteral dose appears to be via biliary excretion into feces. Following dermal dosing of [^{14}C]-Tapinarof cream in minipigs, less than 1% of the administered radiolabeled material was recovered in excreta (urine and feces) over the study period, suggesting very low absorption of the radioactive test material. Mean total recovery of the administered radioactivity was 88.7%. Blood and plasma concentrations of radioactivity were BLQ for all animals at all sampling times, with the exception of one blood sample, which was considered a potential result of contamination. The elimination half-life in humans can generally not be determined due to the lack of detectable Tapinarof concentrations in plasma samples in the elimination phase. In the maximal use study, half-life was estimated in 2 of 21 subjects on the first day of dosing with values of 6.41 and 6.90 hours. These estimates of half-life are not considered very reliable.

Drug Interactions: Tapinarof has been evaluated as a perpetrator of drug interactions. Against a panel of CYP enzymes, *in vitro* studies demonstrate that the IC_{50} for inhibition was > 100 nM. This concentration is approximately 500-fold above the highest plasma concentration observed following topical application in subjects. Against a panel of transporters, inhibition of up to 48.8% was observed for BCRP at the maximum Tapinarof concentration tested (0.1 μM). This concentration is approximately 500-fold above the highest plasma concentration observed ollowing topical application in subjects and thus is not clinically relevant. Tapinarof was not an inhibitor of P-gp, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K.

Tapinarof demonstrated the potential for induction through activation of AhR, which is related to its pharmacology. Tapinarof induced CYP1A1 mRNA in a target engagement model of human skin, as well as in minipig skin after a single dermal application of 1% cream (Formulation E, 10 mg/kg). Tapinarof was a potent inducer of CYP1A2 mRNA in human hepatocytes *in vitro*. However, there is low risk of a clinical drug interaction from CYP1A2 induction based on the regulatory guidance drug interaction risk assessment and since this drug is applied topically to the target site, there would be no impact of CYP inducers on the efficacy.

Overall, *in vitro* studies indicate minimal risk for a Tapinarof perpetrator DDI, either through induction of CYP1A2 or inhibition of CYPs.

As a victim (substrate) of drug interactions, CYP1A2 and CYP3A4 appear to be the major enzymes responsible for the oxidative metabolism of Tapinarof in hepatocytes, with minor contributions of CYP2C9, CYP2C19, and CYP2D6. Inhibition of any one of the CYPs is unlikely to lead to a significant increase in Tapinarof exposure as multiple CYP enzymes appear to be involved and direct glucuronidation and sulfation also play a notable role in Tapinarof metabolism, based on *in vitro* data from human hepatocytes. Tapinarof was also metabolized by the extrahepatic enzymes CYP1A1 and CYP1B1. Tapinarof was not a substrate for P-gp, BCRP, OATP1B1 or OATP1B3.

Overall, these data demonstrate a very low potential for CYP or transporter mediated drug interactions and therefore, no clinical DDI studies were conducted.

Effect of Intrinsic Factors on Tapinarof Pharmacokinetics

The effect of age was assessed in the Phase 3 studies based on a subset of subjects that had PK samples collected at Weeks 4 and 12. While < 10% of PK samples had measurable tapinarof concentrations, there were no clear differences in exposure between subjects below the age 65 and those who were 65 and older (Table 7). Subjects 65 years of age or older represented approximately 11 to 13% of the study population.

Table 7. Summary of Tapinarof Plasma Concentration by Age (DMVT-505-3001 and DMVT-505-3002)

	Tapinarof Concentration (pg/mL)			
	DMVT-505-3001 (N=96)		DMVT-505-3002 (N=120)	
	< 65 years	≥ 65 years	< 65 years	≥ 65 years
Week 4				
N	80	9	102	17
Mean (SD)	7.91 (36.586)	15.11 (45.333)	2.21 (22.278)	3.31 (13.631)
Median	0	0	0	0
Minimum, maximum	0, 256	0, 136	0, 225	0, 56.2
Week 12				
N	69	7	96	15
Mean (SD)	10.91 (54.000)	0 (0)	5.31 (43.584)	0 (0)
Median	0	0	0	0
Minimum, maximum	0, 357	0, 0	0, 418	0, 0

Source: DMVT-505-3001 CSR , Table 14.4.1.2 and DMVT-505-3002 CSR, Table 14.4.1.2

The effect of sex was assessed in the Phase 3 studies based on a subset of subjects that had PK samples collected at Weeks 4 and 12. While < 10% of PK samples had measurable tapinarof, there were no clear differences in exposure between male and female subjects (Table 8). Male and female subjects represented 59% and 41% of the study population, respectively, in DMVT-505-3001, and 56% and 44%, respectively, in DMVT-505-3002.

Table 8. Summary of Tapinarof Plasma Concentration by Sex (DMVT-505-3001 and DMVT-505-3002)

	Tapinarof Concentration (pg/mL)			
	DMVT-505-3001 (N=96)		DMVT-505-3002 (N=120)	
	Male	Female	Male	Female
Week 4				
N	44	45	69	50
Mean (SD)	6.46 (25.361)	10.76 (46.353)	4.08 (27.822)	0 (0)
Median	0	0	0	0
Minimum, maximum	0, 136	0, 256	0, 225	0, 0
Week 12				
N	40	36	62	49
Mean (SD)	14.33 (65.221)	5.00 (30.000)	6.74 (53.086)	1.88 (13.129)
Median	0	0	0	0
Minimum, maximum	0, 357	0, 180	0, 418	0, 91.9

Source: DMVT-505-3001 CSR, Table 14.4.1.3 and DMVT-505-3002 CSR, Table 14.4.1.3

The effect of race was assessed in the Phase 3 studies based on a subset of subjects that had PK samples collected at Weeks 4 and 12. While < 10% of PK samples had measurable tapinarof, there were no clear differences in exposure between White and non-White subjects (Table 9). White subjects represented 85% of the study population in both DMVT-505-3001 and DMVT-505-3002.

Table 9. Summary of Tapinarof Plasma Concentration by Race (DMVT-505-3001 and DMVT-505-3002)

	Tapinarof Concentration (pg/mL)			
	DMVT-505-3001 (N=96)		DMVT-505-3002 (N=120)	
	White	Non-White	White	Non-White
Week 4				
N	79	10	103	16
Mean (SD)	7.48 (34.556)	17.80 (56.289)	2.73 (22.798)	0 (0)
Median	0	0	0	0
Minimum, maximum	0, 256	0, 178	0, 225	0, 0
Week 12				
N	68	8	97	14
Mean (SD)	11.07 (54.385)	0 (0)	5.26 (43.360)	0 (0)
Median	0	0	0	0
Minimum, maximum	0, 357	0, 0	0, 418	0, 0

Source: DMVT-505-3001 CSR, Table 14.4.1.4 and DMVT-505-3002 CSR, Table 14.4.1.4

No studies were conducted in subjects with renal or hepatic impairment due to low systemic absorption, no circulating metabolites, and the lack of a relationship between plasma concentration and AEs.

Reviewer comments: Since very few subjects had quantifiable systemic concentrations in Phase 3 studies, it was not possible to conduct any analysis to assess the effect of intrinsic factors on the PKand the analyses conducted by the Applicant as shown above are only exploratory. Nonetheless, no dosage adjustment is necessary based on intrinsic factos due to the limited systemic exposure of Tapinarof following topical administration.

Effect of Age of Formulation on the Plasma Concentrations of Tapinarof

Based on the CMC review, the *in-vitro* release stability data showed that drug release rate doubled (from ~ 42 to ~ 80) for the aged products and the products under accelerated storage conditions. There were no significant changes observed for all other testing attributes, including appearance, viscosity, and (b) (4) globule size. It was not clear if the increase of release rate will not impact the *in vivo* release and performance of the drug product (both local and systemic). To further investigate if the age of the formulation had an impact of the plasma exposure of Tapinarof, an information request (IR) was sent to the Applicant to provide the age of the formulations used in subjects with quantifiable plasma concentrations in the Maximal use PK study and the Phase 3 studies.

Based on the data provided by the Applicant, this reviewer conducted analyses to evaluate the relationship (if any) between age of formulation and plasma concentrations.

As shown inFigure 4, the Applicant used formulation with age ranging between 30 to 35 months in the maximal use PK study. This range is rather narrow to make any concrete conclusions.

Figure 4. Relationship between Age of Formulation and Plasma Concentrations of Tapinarof in Maximal Use PK Study (Study DMVT-505-2002)

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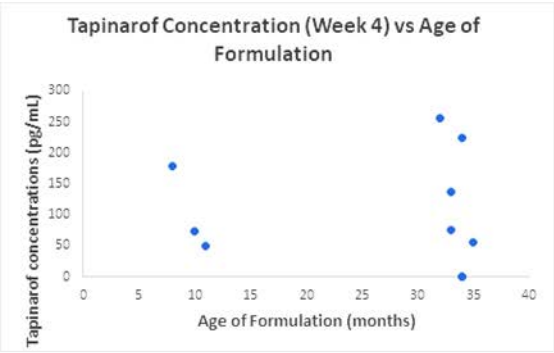
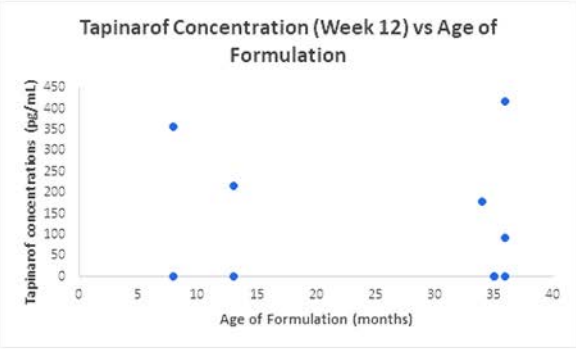
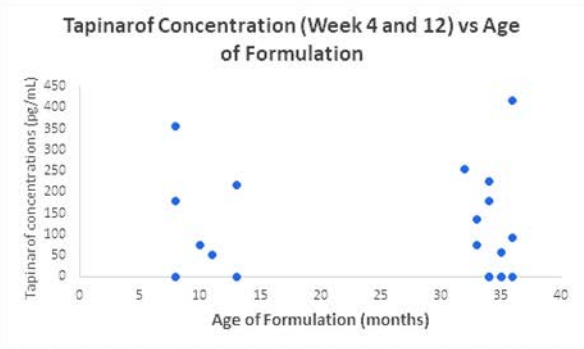
Source: Reviewer independent analyses

Figure 5shows the relationship between age of formulation and systemic concentrations in the Phase 3 studies. The analyses suggest that there does not appear to be any apparent relationship between the age of the formulation and systemic exposure of Tapinarof.

Figure 5. Relationship between Age of Formulation and Plasma Concentrations of Tapinarof in Phase 3 Studies (Studies DMVT-505-3001 and DMVT-505-3002)







Source: Reviewer independent analyses

Reviewer comments: The range of age of formulation used in the Maximal use PK study was rather narrow to make any concrete conclusions regarding the relationship between age of

formulation and systemic exposure of Tapinarof. However, limited data from the Phase 3 trials which used a wider age range of the formulation suggests that there does not appear to be any effect of the age of the formulation on the degree of systemic exposure.

Overall Reviewer Comments: Overall the exposures of Tapinarof were very low across studies and the variability was high. The high variability observed is not uncommon in topical products with factors such as skin integrity, percentage of BSA affected with disease, amount and technique of drug application all contributing to the variability. The Applicant has obtained EGC assessment in the maximal use PK trial and applicability of TQT assessment and ECG assessment to systemic safety is deferred to the Clinical reviewer. The observed QT changes were well below the regulatory threshold for concern (<10ms). The exposures post multiple doses were generally lower than those observed on Day 1. This can be attributed to healing of the skin which could have led to reduced drug absorption. Furthermore, the potential for CYP mediated drug-drug interactions for the parent drug appear to be very low.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The pivotal clinical pharmacology study was maximal use study that informs the systemic safety of Tapinarof Cream, 1% in subjects with psoriasis. Clinical pharmacology assessments do not provide evidence for efficacy.

Refer to clinical/statistical review for the efficacy and safety results from the phase 3 studies.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of Tapinarof cream, 1% to affected areas once daily appears reasonable. The proposed dosing regimen is based on the efficacy and safety results in Phase 3 studies in subjects with plaque psoriasis. See clinical/statistical review for the efficacy and safety results.

Pharmacokinetic results under maximal use conditions showed that systemic absorption is low following Tapinarof topical administration and tapinarof PK is not a significant factor driving efficacy for this topically applied product, rather it would inform the systemic safety.

In the two Phase 3 studies, tapinarof cream, 1% could not be detected in > 95% of PK samples from a subset of the study population even with a highly sensitive assay (< 50 pg/mL). No relationships have been identified between plasma concentrations and age, sex, race, or %BSA, however, it should be noted that the number of samples with quantifiable tapinarof levels was very low. Also there is no drug interaction potential with this product. Overall, there is no dose adjustment needed based on any intrinsic and extrinsic factors.
Based on the combined PK, efficacy, and safety data, tapinarof cream, 1% QD dosing is appropriate for the treatment of plaque psoriasis.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

An alternate dosing regimen for Tapinarof based on intrinsic patient factors is not needed. The intended site of tapinarof is the skin; therefore, the extent of systemic exposure does not relate with its efficacy. Furthermore, plasma concentration of tapinarof was below the quantifiable limits (BQL) of the assay in 68% of the PK samples in the maximal use PK study and in ≥95% of the PK samples in the Phase 3 studies suggesting low systemic absorption of tapinarof following topical administration.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The drug product is intended to be admisitered via topical route; therefore, the issue of a food-drug interaction is not relevant. *In vitro* drug-drug interaction data demonstrated a very low potential for CYP- or transporter mediated drug-drug interactions and therefore, no clinical DDI studies were conducted.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Formulation F of tapinarof cream is the proposed commercial (to be marketed) formulation. It was the formulation used in the Phase 1 dermal safety studies, dose-ranging Phase 2b studies, Phase 2 maximal use study, and Phase 3 studies.

Table 10. Listing of Clinical Studies Relevant to Assessment of Efficacy and Safety

Trial number	Objective/Endpoint	Study design	Test product; dosage; regimen	Number of subjects	Study subjects	Duration of treatment
Controlled Studies to Assess Efficacy and Safety						
DMVT-505-3001 Phase 3 Pivotal Study	Proportion of subjects who achieved a PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline (PGA Treatment Success) at Week 12	Randomized, double blind, vehicle controlled	Tapinarof cream, 1% or vehicle cream applied QD	Tapinarof: 340 Vehicle: 170 (2:1 PsO:vehicle randomization)	Adults with mild-severe PsO	84 days
DMVT-505-3002 Phase 3 Pivotal Study	Proportion of subjects who achieved a PGA score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline (PGA Treatment Success) at Week 12	Randomized, double blind, vehicle controlled	Tapinarof cream, 1% or vehicle cream applied QD	Tapinarof: 343 Vehicle: 172 (2:1 PsO:vehicle randomization)	Adults with mild-severe PsO	84 days
Studies to Support Safety						
DMVT-505-2002 Phase 2a Maximal Use Study	PK, QTc, safety, efficacy	Open label, multicenter	Tapinarof cream, 1% applied QD	21 subjects	Adults with mod-severe PsO, ≥20% BSA	29 days

DMVT-505-3003 LTE Study	Incidence, frequency, and nature of AEs and SAEs; change over time in clinical laboratory tests and vital signs; mean scores by visit from LTS	Open-label, multicenter	Tapinarof cream, 1% or vehicle cream applied QD and discontinue when PGA = 0. If PGA worsens to ≥ 2, then reapply.	Tapinarof: 508 Vehicle: 255 (2:1 PsO:vehicle randomization)	Adults with PsO; PGA 0 to ≥3	40 weeks

7.2. Review Strategy

Data Sources

The data sources used for the evaluation of the efficacy and safety of VTAMA Cream included the Applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. The submission was submitted in electronic common technical document format and was entirely electronic. Both Study Data Tabulation Model datasets and Analysis Data Model datasets were submitted. The analysis datasets used in this review are archived at:

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\\CDSESUB1\evsprod\NDA215272\0010

Data and Analysis Quality

The statistical and clinical teams evaluated the fitness of the data. In general, the data submitted by the Applicant to support the safety and efficacy of VTAMA Cream for the proposed indication appear to be adequate.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

The Applicant conducted two identically designed Phase 3 trials (DMVT-505-3001 and DMVT-505-3002). Both were randomized, multicenter, double-blind, vehicle-controlled, parallel-group trials to evaluate the safety and efficacy of tapinarof cream, 1% in subjects with plaque psoriasis. For enrollment, the protocols specified the following key 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 (BSA) involvement ≥ 3% and ≤ 20%; the protocols specified excluding the subject's scalp, palms, fingernails, toenails, and soles from the %BSA calculations
- Physician Global Assessment (PGA) score ≥ 2 (mild)

For each trial, approximately 500 subjects from about 50 to 60 centers (United States and Canada) were specified to be enrolled and randomized in a 2:1 to receive either tapinarof cream, 1% (N=333) or vehicle cream (N=167). The protocols specified stratifying the randomization by baseline PGA score. In addition, the protocols specified that subjects with mild disease (PGA=2) and severe disease (PGA=4) will be limited to approximately 10% each of the total population. Subjects were instructed to apply study product once daily to all affected areas for 12 weeks.

Subjects were scheduled to have the following study visits: screening (Day -34 to -1), baseline (Day 1), Weeks 2, 4, 8, and 12 (end of treatment). Subjects were also scheduled to be contacted by phone at Weeks 6 and 10 to assess AEs and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in trial. During the conduct of the trials, the Applicant allowed for alternative visits (i.e., modified in-clinic visits, phone visits, and virtual visits) as part of their mitigation strategy for the COVID-19 pandemic.

The protocol-specified primary efficacy endpoint was the proportion of subjects who achieve a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline at Week 12.

The protocols specified the following secondary efficacy endpoints:

- Proportion of subjects with ≥ 75% improvement in the Psoriasis Area and Severity Index (PASI-75) from baseline at Week 12
- Proportion of subjects with a PGA score of 0 (clear) or 1 (almost clear) at Week 12
- Mean change in percent of total BSA affected from baseline to Week 12
- Proportion of subjects with ≥ 90% improvement in the Psoriasis Area and Severity Index (PASI-90) from baseline at Week 12

Table 11. Physician Global Assessment (PGA)

Score/Grade		Description
0	Clear	No signs of psoriasis; postinflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable erythema; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

Source: page 72 of the protocol for Trial DMVT-505-3001

Table 12. Psoriasis Area and Severity Index (PASI)

Use the % Involvement for Each Region (0-100%) from the table above to convert each percentage to individual area scores (0 to 6; PASI Item 5) based on the following categories:

	Percentage of skin covered with psoriasis for each of the 4 areas						
Affected	0%	< 10%	10 - < 30%	30 - < 50%	50 - < 70%	70 - < 90%	≥ 90%
Score	0	1	2	3	4	5	6

Using the table below, for Items 1, 2, and 3, generate an average score for erythema, thickness, and scale for each of the 4 body areas using the following 5-point scale: 0=None; 1=Slight; 2=Mild; 3=Moderate; 4=Severe.

Item	Assessment		Body Area			
			Head/ Neck	Upper extremities (arms)	Trunk (to groin)	Lower extremities (leg to top of buttocks)
1	Erythema (redness)	(0-4)				
2	Induration (thickness)	(0-4)				
3	Scale (desquamation)	(0-4)				
4	**Sum of Items 1, 2, and 3**	**(0-12)**				
5	Area Score	(0-6)				
	Area Multiplier		0.1	0.2	0.3	0.4
6	Score of (Item 4) x (Item 5) x (Area Multiplier)		Item 4 x Item 5 x 0.1	Item 4 x Item 5 x 0.2	Item 4 x Item 5 x 0.3	Item 4 x Item 5 x 0.4
7	Sum of Item 6 for each column is the total **PASI** score	(0-72)				

Source: pages 73 and 74 of the protocol for Trial DMVT-505-3001

8.1.2. Statistical Methdologies

The protocol-specified primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocols and SAPs specified conducting supportive analyses using the per-protocol (PP). The SAP defined the PP population as all subjects in the ITT population who did not have any major protocol deviations or other events that may impact the interpretation of the primary efficacy endpoint. The SAP stated that the exclusion criteria for the PP population may include:

- Failure to meet the enrollment inclusion/exclusion criteria
- On-study use of oral corticosteroids for >3 days and/or at >10 mg dose
- Failure to have a Week 12 assessment that occurs ≤3 days post last dose and also between study day 78 to 91 (inclusive) for the primary efficacy endpoint
- Alternative days post dose and visit window may be used upon review of the actual blinded data before database lock
- Failure to be compliant with treatment regimen (i.e., compliance < 80%)

The protocols and SAPs specified analyzing the binary efficacy endpoints using the Cochran-Mantel-Haenszel (CMH) test stratified by baseline PGA score (i.e., the factor used to stratify the randomization). For the analysis of continuous efficacy endpoints, the protocols and SAPs specified using analysis of covariance (ANCOVA). The SAP specified including treatment group, baseline PGA score, and baseline value as factors in the ANCOVA model. The protocols and SAPs specified using a sequential gatekeeping approach to control the Type I error rate. The secondary efficacy endpoints were specified to be analyzed in the order listed in Section 8.1.1.

The protocol-specified primary method for handling missing data was the multiple imputation (MI) approach. The protocols and SAPs specified imputing the missing data 100 times using the

regression method. The Fully Conditional Specification (FCS) imputation model was specified to be used with treatment group, baseline value, post-baseline values, and baseline PGA score as factors in the model. The SAPs specified using last observation carried forward (LOCF), observed case (OC), and nonresponder imputation (only for binary endpoints) as sensitivity analyses for the handling of missing data. For LOCF, only post-baseline values were carried forwarded. In the Integrated Summary of Efficacy (ISE), the Applicant included tipping point analyses for the primary efficacy endpoint as sensitivity analyses for the handling of missing data.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial DMVT-505-3001 enrolled and randomized a total of 510 subjects (340 to tapinarof and 170 to vehicle) from 48 centers (40 in United States and 8 in Canada). Trial DMVT-505-3002 enrolled and randomized a total of 515 subjects (343 to tapinarof and 172 to vehicle) from 49 centers (41 in United States and 8 in Canada). Table 13 presents the disposition of subjects for Trials DMVT-505-3001 and DMVT-505-3002. The discontinuation rate was slightly higher in Trial DMVT-505-3001 compared to Trial DMVT-505-3002. In both trials, the rate of discontinuation due to adverse events was higher in the tapinarof group compared to the vehicle group. In addition, the rate of discontinuation due to subject request (i.e., withdrawal by subject) was higher in the vehicle group compared to the tapinarof group in both trials.

Table 13. Disposition of Subjects (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
Discontinued, n (%)	71 (21)	40 (24)	61 (18)	30 (17)
Adverse events	19 (6)	0	20 (6)	1 (1)
COVID-19[2]	2 (1)	2 (1)	3 (1)	1 (1)
Lost to follow-up	21 (6)	15 (9)	19 (6)	4 (2)
Physician decision	0	0	0	1 (1)
Pregnancy	0	1 (1)	1 (<1)	0
Progressive disease	2 (1)	1 (1)	1 (<1)	6 (3)
Protocol violation	5 (1)	1 (1)	2 (1)	0
Withdrawal by subject	22 (6)	19 (11)	14 (4)	17 (10)
Other	0	1 (1)	1 (<1)	0

[1] Intent-to-Treat (ITT) population: all randomized subjects.
[2] Discontinued due to reasons related to COVID-19. In both trials, no subjects discontinued due to a positive COVID-19 diagnosis.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

Table 14 presents the demographics and baseline disease characteristics for Trials DMVT-505-3001 and DMVT-505-3002. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were similar between the two trials.

Table 14. Demographics and Baseline Disease Characteristics (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
Age (years)				
Mean (SD)	50 (14)	49 (13)	50 (13)	50 (14)
Median	51	51	51	52
Min, Max	18, 75	21, 74	19, 75	18, 74
Categories, n (%)				
< 65	286 (84)	158 (93)	298 (87)	144 (84)
≥ 65	54 (16)	12 (7)	45 (13)	28 (16)
Sex, n (%)				
Male	213 (63)	86 (51)	188 (55)	102 (59)
Female	127 (37)	84 (49)	155 (45)	70 (41)
Race, n (%)				
White	286 (84)	146 (86)	300 (87)	138 (80)
Black or African American	18 (5)	11 (6)	12 (3)	6 (3)
Asian	21 (6)	4 (2)	25 (7)	21 (12)
Other	15 (4)	9 (5)	6 (2)	7 (4)
Ethnicity, n (%)				
Hispanic	53 (16)	34 (20)	43 (13)	23 (13)
Not Hispanic	284 (84)	135 (79)	300 (87)	148 (86)
Not Reported	3 (1)	1 (1)	0	1 (1)
Country, n (%)				
United States	248 (73)	129 (76)	266 (78)	133 (77)
Canada	92 (27)	41 (24)	77 (22)	39 (23)
PGA, n (%)				
2 – Mild	39 (11)	21 (12)	28 (8)	15 (9)
3 – Moderate	271 (80)	133 (78)	288 (84)	144 (84)
4 – Severe	30 (9)	16 (9)	27 (8)	13 (8)
PASI				
Mean (SD)	8.7 (4.0)	9.2 (4.4)	9.1 (3.7)	9.3 (4.0)
Median	8.1	8.0	8.4	8.8
Min, Max	2.0, 22.2	2.0, 21.9	1.5, 23.6	2.5, 25.0
Percent BSA				
Mean (SD)	7.8 (4.6)	8.2 (5.1)	7.8 (4.4)	7.3 (4.1)
Median	6.3	6.1	6.2	6.0
Min, Max	3.0, 20.0	3.0, 20.0	3.0, 20.0	3.0, 20.0

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt

8.1.4. Impact of COVID-19 Pandemic on Study Visits

Table 15 summarizes the impact of the COVID-19 pandemic on study visits. The proportion of subjects that had missing data due to the COVID-19 pandemic at the primary efficacy timepoint (i.e., Week 12) was less than 1% in each trial. Approximately 5% and 1% of the subjects had alternative visits (i.e., modified in-clinic visit, phone visit, or virtual visit) at Week 12 for Trials DMVT-505-3001 and DMVT-505-3002, respectively.

Table 15. Study Visits Impacted by COVID-19 Pandemic (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
Week 2, n (%)				
Missed due to COVID-19	1 (<1)	0	0	0
Modified in-clinic visit	0	0	0	0
Phone visit	0	0	0	0
Virtual visit	0	0	0	0
Week 4, n (%)				
Missed due to COVID-19	1 (<1)	0	1 (<1)	0
Modified in-clinic visit	1 (<1)	1 (<1)	0	0
Phone visit	0	0	0	0
Virtual visit	2 (1)	1 (1)	0	0
Week 8, n (%)				
Missed due to COVID-19	4 (1)	2 (1)	2 (1)	1 (1)
Modified in-clinic visit	0	1 (1)	0	1 (1)
Phone visit	4 (1)	1 (1)	0	0
Virtual visit	9 (3)	7 (4)	0	0
Week 12, n (%)				
Missed due to COVID-19	2 (1)	0	1 (<1)	1 (1)
Modified in-clinic visit	2 (1)	1 (1)	0	1 (1)
Phone visit	1 (<1)	1 (1)	1 (<1)	0
Virtual visit	10 (3)	8 (5)	2 (1)	2 (1)

[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADVE.xpt

8.1.5. Results of the Primary Efficacy Endpoint

Table 16 presents the results of the primary efficacy endpoint for both trials regardless of the type of study visit type. Table 17 presents the results of the primary efficacy endpoint for both trials when assessment based on the alternative visits are treated as missing and imputed using MI. The results were very similar between the two analyses as the proportion of subjects with alternative visits was small in each trial. For both analyses, tapinarof was statistically superior to vehicle in both trials (p-values < 0.001). The results for the PP population (not shown) were similar to the results for the ITT population.

Table 16. Results of the Primary Efficacy Endpoint (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
PGA Response[2] at Week 12				
Proportion[3]	35%	6%	40%	6%
Difference (95% CI)[3]	29% (23%, 36%)		34% (27%, 41%)	
Relative Risk (95% CI)[4]	5.8 (2.9, 11.5)		6.1 (3.3, 11.4)	
P-value[4]	<0.001		<0.001	

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Response is defined as a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline.
[3] Average over the 100 imputed datasets. The standard error for calculating the 95% CI was based on Rubin's rule (i.e., reflects both within and across the 100 imputed datasets).
[4] Relative risk, 95% CI, and p-value are based on a CMH test stratified by baseline PGA score (i.e., the factor used to stratify the randomization).
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt, ADPGA.xpt

Table 17. Results of the Primary Efficacy Endpoint when Assessments Based on Alternative Visits (Modified In-clinic Visits, Phone Visits, and Virtual Visits) are Treated as Missing (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
PGA Response[2] at Week 12				
Proportion[3]	36%	6%	40%	6%
Difference (95% CI)[3]	29% (22%, 36%)		34% (27%, 40%)	
Relative Risk (95% CI)[4]	5.5 (2.8, 11.0)		5.9 (3.2, 11.0)	
P-value[4]	<0.001		<0.001	

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Response is defined as a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline.
[3] Average over the 100 imputed datasets. The standard error for calculating the 95% CI was based on Rubin's rule (i.e., reflects both within and across the 100 imputed datasets).
[4] Relative risk, 95% CI, and p-value are based on a CMH test stratified by baseline PGA score (i.e., the factor used to stratify the randomization).
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

Table 18 presents the number of subjects with missing data and the number of subjects with alternative visit assessments for the primary efficacy endpoint. The table also presents the results of the primary efficacy endpoint across the various prespecified imputation methods for all visit types and when the alternative visits are treated as missing. The results were generally similar across the various methods and across the handling of the alternative visits. The Applicant also conducted tipping point analyses for the primary efficacy endpoint as a sensitivity analyses for the handling of missing data. Figure 6 presents the instances the results tip (i.e., no longer significant at the 0.05 level) for Trial DMVT-505-3001. The results tip for Trial DMVT-505-3001 when a very high proportion of the missing data for vehicle is imputed as successes and a very high proportion of the missing data for tapinarof is imputed as failures. For Trial DMVT-505-3002, there were no scenarios where the results tip (i.e., even under the worst-case scenario [all missing data for vehicle is imputed as successes and all missing data for tapinarof is imputed as failure] remained statistically significant).

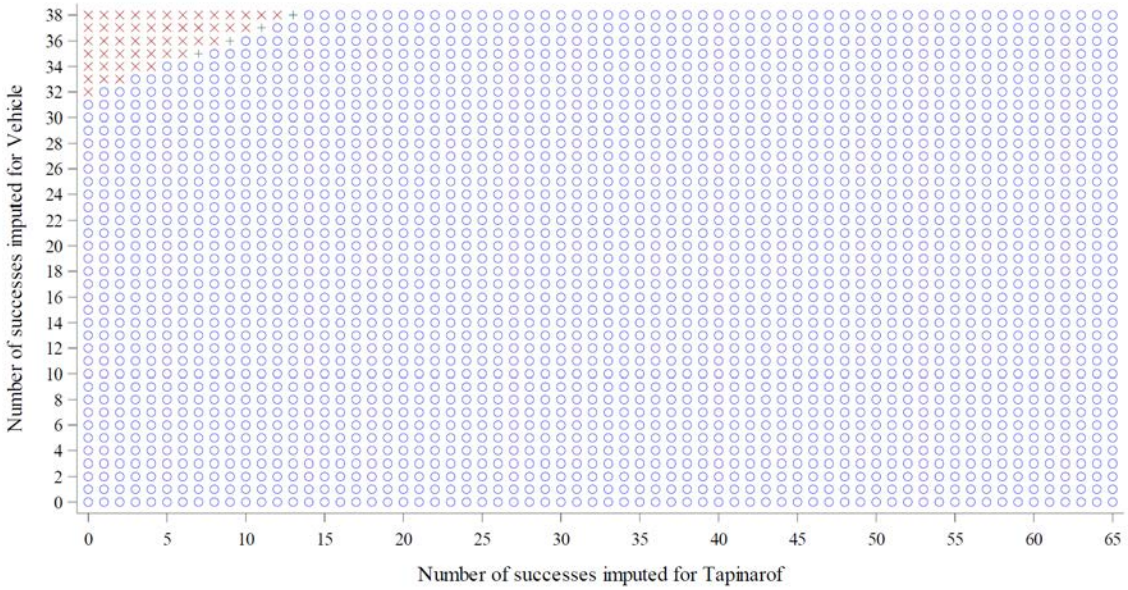
Table 18. Results of the Primary Efficacy Endpoint at Week 12 by Various Methods to Impute Missing Data

	Trial DMVT-505-3001			Trial DMVT-505-3002		
	Tapinarof (N=340)	**Vehicle (N=170)**	**Difference (P-value)[6]**	**Tapinarof (N=343)**	**Vehicle (N=172)**	**Difference (P-value)[6]**
Missing Data	65 (19%)	38 (22%)	-	54 (16%)	28 (16%)	-
Alternative Visits	13 (4%)	10 (6%)	-	3 (1%)	3 (2%)	-
All Visit Types						
MI (Primary)[1]	35%	6%	29% (<0.001)	40%	6%	34% (<0.001)
NRI[2]	31%	4%	27% (<0.001)	35%	5%	30% (<0.001)
LOCF[3]	32%	4%	28% (<0.001)	36%	5%	31% (<0.001)
OC[4]	39%	5%	33% (<0.001)	42%	6%	35% (<0.001)
Alternative Visits as Missing[5]						
MI (Primary)[1]	36%	6%	29% (<0.001)	40%	6%	34% (<0.001)
NRI[2]	30%	4%	26% (<0.001)	35%	5%	29% (<0.001)
LOCF[3]	31%	4%	27% (<0.001)	36%	5%	31% (<0.001)
OC[4]	37%	5%	32% (<0.001)	41%	6%	35% (<0.001)

[1] Missing data imputed using multiple imputation (MI). Rates displayed are the averages over the 100 imputed datasets.
[2] Missing data imputed using non-responder imputation (NRI).
[3] Missing data imputed using last observation carried forward (LOCF). For LOCF, only post-baseline values were carried forward.

[4] Missing data was not imputed. Rates displayed are based on only observed cases (OCs).
[5] PGA data obtained from alternative visits (i.e., modified In-clinic visits, phone visits, and virtual visits) are excluded/treated as missing.
[6] P-value are based on a CMH test stratified by baseline PGA score (i.e., the factor used to stratify the randomization).
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

Figure 6. Applicant's Tipping Point Analysis for Trial DMVT-505-3001 (ITT[1])



Plotting symbols: o = maximum CMH p-value < 0.05; x = minimum CMH p-value > 0.05; otherwise plotted as +.
[1] Intent-to-Treat (ITT) population: all randomized subjects.
Source: ISE Figure 6.2.1

8.1.6. Results of the Secondary Efficacy Endpoints

Table 19 presents the results of the secondary efficacy endpoints for both trials regardless of the study visit type. Table 20 presents the results of the secondary efficacy endpoints for both trials when assessment based on the alternative visits are treated as missing and imputed using MI. As with the primary efficacy endpoint, the results of the secondary efficacy endpoints were similar between the two analyses. For all secondary efficacy endpoints, tapinarof was statistically superior to vehicle in both trials (p-values < 0.001). The results for the PP population (not shown) were similar to the results for the ITT population.

Table 19. Results of the Secondary Efficacy Endpoints (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
PASI-75 at Week 12				
Proportion[2]	36%	10%	48%	7%
Difference (95% CI)[2]	26% (19%, 33%)		41% (34%, 47%)	
Relative Risk (95% CI)[3]	2.8 (1.7, 4.5)		6.5 (3.7, 11.5)	
P-value[3]	<0.001		<0.001	
PGA of 0 or 1 at Week 12				
Proportion[2]	38%	10%	44%	8%
Difference (95% CI)[2]	28% (21%, 35%)		35% (28%, 42%)	
Relative Risk (95% CI)[3]	2.7 (1.6, 4.4)		4.6 (2.7, 7.7)	
P-value[3]	<0.001		<0.001	

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
Change in Percent BSA from Baseline to Week 12				
Mean[4]	-3.5	-0.4	-4.3	0.3
LS Mean[5]	-3.5	-0.2	-4.2	0.1
Difference (95% CI)[5]	-3.3 (-4.4, -2.1)		-4.3 (-5.2, -3.5)	
P-value[5]	<0.001		<0.001	
PASI-90 at Week 12				
Proportion[2]	19%	2%	21%	2%
Difference (95% CI)[2]	17% (13%, 22%)		18% (13%, 23%)	
Relative Risk (95% CI)[3]	8.5 (2.6, 28.3)		7.3 (2.9, 18.4)	
P-value[3]	<0.001		<0.001	

[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation (MI).
[2] Average over the 100 imputed datasets. The standard error for calculating the 95% CI was based on Rubin's rule (i.e., reflects both within and across the 100 imputed datasets).
[3] Relative risk, 95% CI, and p-value are based on a CMH test stratified by baseline PGA score (i.e., the factor used to stratify the randomization).
[4] Average over the 100 imputed datasets.
[5] LS means, difference, 95% CI, and p-value are based on ANCOVA with treatment group, baseline PGA score, and baseline percent BSA score as factors in the model.
Source: Statistical Reviewer's Analysis (same results as Applicant's Analysis); ADSL.xpt, ADPGA.xpt

Table 20. Results of the Secondary Efficacy Endpoints when Assessments Based on Alternative Visits (Modified In-clinic Visits, Phone Visits, and Virtual Visits) are Treated as Missing (ITT[1])

	Trial DMVT-505-3001		Trial DMVT-505-3002	
	Tapinarof (N=340)	**Vehicle (N=170)**	**Tapinarof (N=343)**	**Vehicle (N=172)**
PASI-75 at Week 12				
Proportion[2]	35%	10%	48%	6%
Difference (95% CI)[2]	25% (18%, 32%)		41% (35%, 48%)	
Relative Risk (95% CI)[3]	2.7 (1.6, 4.4)		7.1 (3.9, 12.9)	
P-value[3]	<0.001		<0.001	
PGA of 0 or 1 at Week 12				
Proportion[2]	38%	10%	44%	8%
Difference (95% CI)[2]	28% (20%, 35%)		35% (28%, 42%)	
Relative Risk (95% CI)[3]	2.7 (1.6, 4.4)		4.6 (2.7, 7.7)	
P-value[3]	<0.001		<0.001	
Change in Percent BSA from Baseline to Week 12				
Mean[4]	-3.5	-0.3	-4.3	0.3
LS Mean[5]	-3.5	-0.2	-4.2	0.1
Difference (95% CI)[5]	-3.4 (-4.5, -2.2)		-4.3 (-5.2, -3.5)	
P-value[5]	<0.001		<0.001	
PASI-90 at Week 12				
Proportion[2]	19%	2%	21%	2%
Difference (95% CI)[2]	17% (12%, 22%)		18% (13%, 23%)	
Relative Risk (95% CI)[3]	8.0 (2.4, 26.5)		7.2 (2.8, 18.3)	
P-value[3]	<0.001		<0.001	

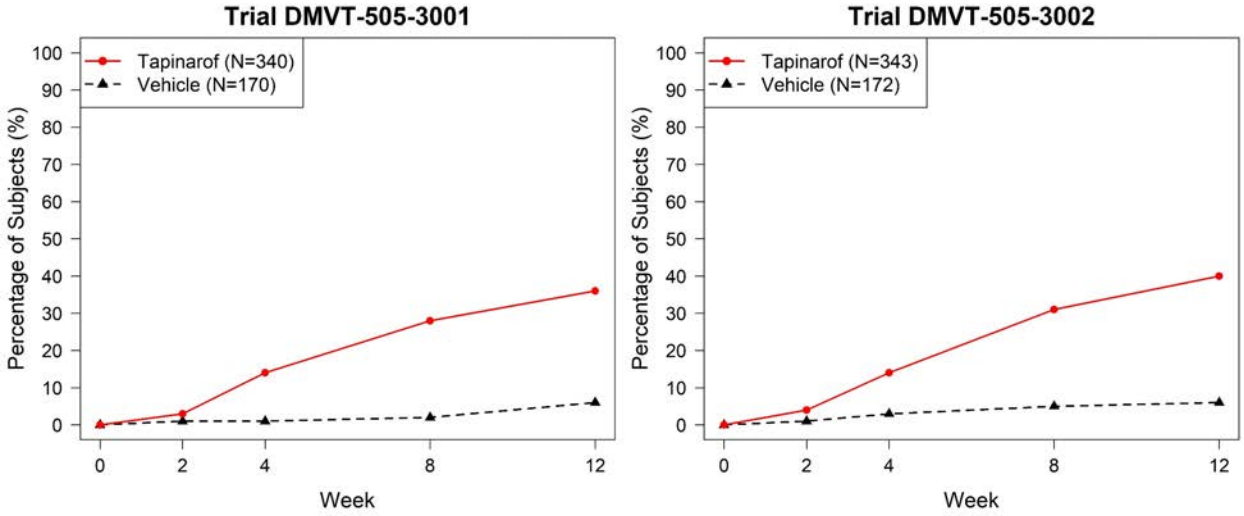
[1] Intent-to-Treat (ITT) population: all randomized subjects. Missing data were imputed using multiple imputation.
[2] Average over the 100 imputed datasets. The standard error for calculating the 95% CI was based on Rubin's rule (i.e., reflects both within and across the 100 imputed datasets).
[3] Relative risk, 95% CI, and p-value are based on a CMH test stratified by baseline PGA score (i.e., the factor used to stratify the randomization).
[4] Average over the 100 imputed datasets.

[5] LS means, difference, 95% CI, and p-value are based on ANCOVA with treatment group, baseline PGA score, and baseline percent BSA score as factors in the model.
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

8.1.7. Efficacy Over Time

Figure 7 presents the results for PGA response over time for Trials DMVT-505-3001 and DMVT-505-3002.

Figure 7. Results of PGA Response[1] Over Time (ITT[2])



[1] Response is defined as a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. PGA data obtained from alternative visits (i.e., modified In-clinic visits, phone visits, and virtual visits) are excluded/treated as missing. Missing data were imputed using multiple imputation (MI). Rates displayed are the averages over the 100 imputed datasets.
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

A total of 73 subjects who were treated with tapinarof in Trials DMVT-505-3001 and DMVT-505-3002 achieved a PGA score of 0 (clear) at Week 12 and enrolled into the long-term extension study (DMVT-505-3003). These subjects were withdrawn from treatment and followed for up to 40 additional weeks. The median time to first worsening (i.e., PGA score ≥ 2 [mild]) was 114 days (95% CI: 85, 142).

8.1.8. Findings in Special/Subgroup Populations

Table 21 and Table 22 present the results of PGA response at Week 12 (i.e., primary efficacy endpoint) by age, sex, race, ethnicity, country, and baseline PGA score for Trials DMVT-505-3001 and DMVT-505-3002, respectively. In both trials, the response rate was consistently higher for tapinarof compared to vehicle across these subgroups; however, there was some variability in the treatment effect for the smaller subgroups (e.g., race). The treatment effect was smaller in the subgroup of subjects with a PGA score of 2 (mild) compared to the subgroups of subjects with a PGA score of 3 (moderate) and PGA score of 4 (severe) in both trials.

Table 21. PGA Response[1] at Week 12 by Age, Sex, Race, Ethnicity, Country, and Baseline PGA Score (ITT[2]) for Trial DMVT-505-3001

	Tapinarof (N=340)	Vehicle (N=170)	Difference (95% CI)
Age (years)			
< 65 (286, 158)	34%	6%	27% (20%, 35%)
≥ 65 (54, 12)	46%	9%	37% (16%, 59%)
Sex			
Male (213, 86)	36%	6%	30% (21%, 39%)
Female (127, 84)	35%	7%	28% (17%, 39%)
Race			
White (286, 146)	36%	7%	29% (22%, 37%)
Black (18, 11)	20%	1%	19% (-3%, 40%)
Asian (21, 4)	48%	5%	43% (7%, 79%)
Other (15, 9)	25%	3%	22% (-6%, 50%)
Ethnicity			
Hispanic (53, 34)	30%	2%	28% (13%, 42%)
Not Hispanic (284, 135)	37%	7%	29% (21%, 37%)
Not Reported (3, 1)	33%	0%	-
Country			
United States (248, 129)	33%	5%	28% (21%, 36%)
Canada (92, 41)	41%	10%	31% (17%, 46%)
Baseline PGA Score			
2 – Mild (39, 21)	17%	5%	12% (-3%, 28%)
3 – Moderate (271, 133)	37%	6%	31% (23%, 39%)
4 – Severe (30, 16)	42%	9%	33% (9%, 57%)

[1] Response is defined as a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. PGA data obtained from alternative visits (i.e., modified In-clinic visits, phone visits, and virtual visits) are excluded/treated as missing. Missing data were imputed using multiple imputation (MI). Rates displayed are the averages over the 100 imputed datasets.
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

Table 22. PGA Response[1] at Week 12 by Age, Sex, Race, Ethnicity, Country, and Baseline PGA Score (ITT[2]) for Trial DMVT-505-3002

	Tapinarof (N=343)	Vehicle (N=172)	Difference (95% CI)
Age (years)			
< 65 (298, 144)	39%	6%	33% (26%, 41%)
≥ 65 (45, 28)	46%	10%	36% (17%, 56%)
Sex			
Male (188, 102)	42%	5%	37% (28%, 46%)
Female (155, 70)	38%	8%	30% (19%, 40%)
Race			
White (300, 138)	41%	6%	35% (28%, 42%)
Black (12, 6)	27%	17%	11% (-29%, 50%)
Asian (25, 21)	34%	7%	28% (4%, 51%)
Other (6, 7)	33%	3%	30% (-11%, 72%)
Ethnicity			
Hispanic (43, 23)	37%	6%	31% (12%, 50%)
Not Hispanic (300, 148)	41%	7%	34% (27%, 41%)
Not Reported (0, 1)	-	0%	-
Country			
United States (266, 133)	39%	7%	32% (24%, 39%)
Canada (77, 39)	45%	4%	41% (27%, 54%)
Baseline PGA Score			

	Tapinarof (N=343)	Vehicle (N=172)	Difference (95% CI)
2 – Mild (28, 15)	24%	7%	17% (-4%, 38%)
3 – Moderate (288, 144)	43%	7%	36% (28%, 43%)
4 – Severe (27, 13)	31%	1%	30% (11%, 50%)

[1] Response is defined as a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline.
[2] Intent-to-Treat (ITT) population: all randomized subjects. PGA data obtained from alternative visits (i.e., modified In-clinic visits, phone visits, and virtual visits) are excluded/treated as missing. Missing data were imputed using multiple imputation (MI). Rates displayed are the averages over the 100 imputed datasets.
Source: Statistical Reviewer's Analysis; ADSL.xpt, ADVE.xpt, ADPGA.xpt

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety for tapinarof cream 1%, for the topical treatment of plaque psoriasis focuses on data from two Phase 3 studies, DMVT-505-3001 (Study 3001) and DMVT-505-3002 (Study 3002). Studies 3001 and 3002 were identical in design and were randomized, multicenter, investigator-blind, parallel-group studies in adult subjects with stable plaque psoriasis. For a detailed description of the study designs, refer to Section 7.1, Table of Clinical Studies.

To determine the safety profile of tapinarof cream 1%, the review team analyzed the following types of data: exposure, demographics, baseline characteristics, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory results, vital signs, and local tolerability.

The Phase 3 vehicle-controlled study population included 1025 subjects ≥18 years of age with mild-to-severe plaque psoriasis, defined as a PGA score of 2 (mild), 3 (moderate), or 4 (severe); and BSA of 3 to 20% (excluding scalp, palms, soles, and nails). Subjects with mild (PGA 2) and severe (PGA 4) were limited to approximately 10% each of the total randomized population. Subjects were randomized 2:1 to treatment with tapinarof cream 1%, or vehicle cream.

During the Phase 3 vehicle-controlled studies, subjects applied the study drug in a thin layer to cover all affected areas (including newly appearing lesions and lesions that are improving) once daily for 12 weeks. Subjects were allowed, but not required, to treat fingernails, toenails, palms, soles, and scalp lesions. Investigators conducted safety assessments at Baseline followed by Weeks 2, 4, 8, and 12, with additional investigator phone calls to assess AEs at Weeks 6 and 10.

In addition, data from two open-label studies were submitted by the Applicant. Interpretation of data from these studies is inherently more challenging due to the lack of a placebo arm.

Because plaque psoriasis is a chronic condition, it is expected that patients will continue to treat with tapinarof cream, 1% as needed for a period greater than 12 weeks. The Applicant submitted the data from an open-label, long-term extension (LTE) study (Study DMVT-505-

3003, hereafter referred to as LTE Study 3003) of 763 subjects who rolled over from the Phase 3 vehicle-controlled studies 3001 and 3002. The subjects previously randomized to tapinarof during the 12-week studies continued use of tapinarof cream, 1% for up to an additional 40 weeks, while those who were initially randomized to vehicle cream switched to tapinarof cream for the 40-week LTE study.

Subjects were treated based on their PGA score from the Week 12 visit in the double-blind, Phase 3 vehicle-controlled studies(Study 3001 or 3002) as follows:

- Subjects entering with a PGA ≥ 1 received treatment with tapinarof cream, 1% once daily until they achieved a PGA = 0, at which time treatment was discontinued and subjects were monitored for durability of response (remittive response). If and when disease worsening occurred, as evidenced by a PGA ≥ 2, treatment was re-initiated and continued until a PGA = 0 was achieved.
- Subjects entering with a PGA = 0 had treatment discontinued and were monitored for duration of remittive response. If and when disease worsening occurred, as evidenced by a PGA ≥ 2, treatment was re-initiated and continued until a PGA = 0 was achieved.
- This treatment and re-treatment pattern of use was continued until the end of the LTE study.

Subjects were followed for an additional 4 weeks after they discontinued treatment. Safety assessments included AEs, vital signs, physical examinations, laboratory tests, and local tolerability scale (LTS). The results of LTE Study 3003 will be integrated with the analyses of the Phase 3 pivotal trials where applicable.

To assess the safety and PK of tapinarof cream, 1%, the Applicant conducted Study DMVT-505-2002 (hereafter referred to as Study 2002), a Phase 2, open-label PK/maximal use study (MuST) with 21 subjects with moderate to severe plaque psoriasis (PGA ≥3 and BSA ≥ 20%). Subjects applied tapinarof cream, 1%, for 29 days, and were assessed for adverse events and PK. Investigators also assessed for local tolerability (erythema, peeling, dryness) on Days 1, 15, and 29. Analysis of this study is presented in Section 8.2.8.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database includes all subjects from Studies, 3001, 3002, 3003 and PK study 2002. The safety population was defined to include all subjects who received at least one dose of the study drug and had at least one post-baseline safety assessment.

The number of subjects exposed to the to-be-marketed formulation of tapinarof cream, 1% in these studies is presented below:

Table 23. Overall Exposure to tapinarof cream, 1% (Phase 2 and Phase 3 trials)

Exposure to Drug	Number of Subjects (Studies 2002, 3001, 3002, 3003)			
	Study 2002 N = 60	Studies 3001-3002 N = 683	Study 3003[a] N = 763	Total N = 1085
≥ 4 weeks	57	634	344[b]	1035
≥ 8 weeks	--	597	328[b]	925
≥ 12 weeks	--	420	300[b]	720
≥ 26 weeks	--	--	548	548
≥ 52 weeks	--	--	139	139

Source: Reviewer
Note: Total number of days exposed is calculated as date of last dose – date of first dose + 1.
Note: If subject did not return dose diary or returned the diary with missing dosing record, the number of doses administered and the days exposed during that period was assumed to be 0.
[a] Calculation of total number of days of drug exposure for subjects from Studies 3001-3002 who were previously on tapinarof include the number of days exposed during those studies plus the additional days exposed during Study 3003.
[b] Subjects from Studies 3001-3002 who were previously on placebo and subjects previously on tapinarof who had not been exposed for this duration during the Phase 3 trials

Relevant Characteristics of the Safety Population

In the safety population for the Phase 3 studies, the majority of subjects applying tapinarof were white (85.6%), male (58.7%), with a mean age of 49.9 years. A total of 99 (14.5%) subjects were over 65 years of age. The demographic characteristics of the two treatment groups were comparable. Most subjects were non-Hispanic or Latino (85.5%). See Table 24.

Table 24. Demographics, Phase 3 Pivotal Trials 3001 and 3002

Characteristic, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Age		
Mean (SD)	49.9 (13.4)	49.6 (13.5)
Median	51	51
Range	18-75	18-74
Age range		
18-65 years	584 (85.5)	302 (88.3)
≥65 years	99 (14.5)	40 (11.7)
Sex		
Male	401 (58.7)	188 (55)
Female	282 (41.3)	154 (45)
Race		
White	586 (85.6)	284 (83)
Black or African American	30 (4.4)	17 (5)
Asian	46 (6.7)	25 (7.3)
American Indian or Alaska native	2 (0.3)	2 (0.6)
Multiple	5 (0.7)	4 (1.2)

Other	9 (1.3)	7 (2.1)
Not reported	5 (0.7)	3 (0.9)
Ethnicity		
Hispanic or Latino	96 (14.1)	57 (16.7)
Not Hispanic or Latino	584 (85.5)	283 (82.7)
Not reported	3 (0.4)	2 (0.6)
Country		
USA	514 (75.3)	262 (76.6)
Canada	169 (24.7)	80 (23.4)

Relevant Characteristics of the LTE Study 3003

The demographic characteristics of subjects in the LTE Study 3003 were similar to the safety population for the Phase 3 studies 3001 and 3002, as the subjects from Studies 3001 and 3002 rolled over to the LTE Study 3003.

Table 25. Demographics, LTE Study 3003 Population

Characteristic, n (%)	Tapinarof cream, 1% (Pivotal) N = 508	Vehicle cream (Pivotal) N = 255	Overall N = 763
Age			
Mean (SD)	50.5 (12.9)	51 (12.9)	50.7 (12.9)
Median	52	53	52
Range	18-75	18-74	18-75
Age range			
18-65 years	454 (89.4)	231 (90.6)	685 (89.8)
≥66 years	54 (10.6)	24 (9.4)	78 (10.2)
Sex			
Male	304 (59.8)	144 (56.5)	448 (58.7)
Female	204 (40.2)	111 (43.5)	315 (41.3)
Race			
White	433 (85.2)	210 (82.4)	643 (84.3)
Black or African American	24 (4.7)	15 (5.9)	39 (5.1)
Asian	32 (6.3)	19 (7.5)	51 (6.7)
American Indian or Alaska native	2 (0.4)	2 (0.8)	4 (0.5)
Multiple	5 (1)	4 (1.6)	9 (1.2)
Other	6 (1.2)	3 (1.2)	9 (1.2)
Not reported	5 (1)	1 (0.4)	6 (0.8)
Ethnicity			
Hispanic or Latino	77 (15.2)	40 (15.7)	117 (15.3)
Not Hispanic or Latino	428 (84.3)	213 (83.5)	641 (84)
Not reported	3 (0.6)	2 (0.8)	5 (0.7)
Country			
USA	385 (75.8)	193 (75.7)	578 (75.8)
Canada	123 (24.2)	62 (24.3)	185 (24.2)

Source: Reviewer

Adequacy of the Safety Database

The total subject exposure to tapinarof cream, 1%, applied once daily for up to 12 weeks and the extension period for an additional 40 weeks provides adequate data for the evaluation of safety. The demographics of the Phase 3 vehicle-controlled studies population are sufficiently representative of the target population. Therefore, the safety database submitted by the Applicant is sufficient to characterize the safety profile of tapinarof cream, 1%, for the topical treatment of plaque psoriasis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted for the Phase 3 vehicle-controlled studies (3001 and 3002) is adequate to characterize the safety and efficacy of tapinarof cream, 1%, for the topical treatment of plaque psoriasis in adults. There were no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant. For LTE Study 3003, there was incomplete/missing exposure data for 43 subjects (5.6%).

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as "any untoward medical occurrence in a subject temporally associated with the use of a medicinal product, whether considered causally related or not related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product." An AE occurring after the date of the first dose was considered a treatment-emergent adverse event (TEAE).

AEs were categorized by system-organ class and preferred term using the Medical Dictionary for Regulatory Activities version 22.0. The coding of AEs in the NDA submission appeared adequate and allowed for accurate estimation of AE risk.

The following AEs were identified and reported by the Applicant as AEs of significant importance (AESIs):

- Contact dermatitis
- Folliculitis
- Headache

Investigators conducted an active assessment for local skin tolerability at all visits during the Phase 3 studies. Using a local tolerability scale (LTS), the investigator assessed LSRs included perilesional dryness, erythema, peeling, burning/stinging, and itching, using a 5-point tolerability scale to average severity across all application sites.

An SAE was defined as an AE that met any of the following criteria:

- Resulted in death.
- Was life-threatening.
- Required hospitalization or a prolongation of an existing hospitalization.
- Resulted in disability/incapacity (sustantial disruption of a person's ability to conduct normal life functions).
- Resulted in a congenital anomaly or birth defect.
- Was considered by the investigator as an important medical event that was not immediately life-threatening or resulting in death or hospitalization but could have jeopardized the subject or required medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

AEs were collected from the time of signed informed consent until the final visit. Investigators assessed for AEs at each visit during the trial by nondirective questioning of the subjects, signs and symptoms detected during examinations, observations of study personnel, and spontaneous reports from subjects. Investigators recorded all AE/SAEs in the electronic case report form, including a description of the AE, relationship to study product administration, start and stop dates, seriousness, severity, action taken and outcome.

Investigators categorized the severity of the AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), v 5.0, 2017. For terms not specified in the CTCAE, the criteria to determine the grade severity was as follows:

- Grade 1 – Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- Grade 2 – Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3 – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4 – Life-threatening consequences; urgent intervention indicated
- Grade 5 – Death related to adverse event

The Principal Investigator was responsible for making the causality assessment.
the relationship of the AE to treatment with the study drug. The following definitions are to be used for the relationship of the adverse event to study drug:

- Related – A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship plausible, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge), although information on drug withdrawal may be lacking or unclear.
- Not related – A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable

and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

Any AEs/SAEs assessed as related to study participation (eg, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study drug were recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

When an Investigator determined that an AE meets the protocol definition of an SAE during the study, he/she notified the Sponsor using an SAE Report Form within 24 hours of the study site personnel's knowledge of the event, regardless of the Investigator assessment of the relationship of the event to study drug.

After the initial AE/SAE report, the Investigator was required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs were to be followed until resolution, until the condition stabilized, until the event was otherwise explained, or until the subject was lost to follow-up.

The Investigator will assess the outcome of each AE using the following criteria:

- Recovered/Resolved – The event has improved or subject recuperated.
- Recovered/Resolved with sequelae – The subject has recuperated but retained pathological conditions resulting from the prior disease or injury.
- Recovering/Resolving – The event is improving.
- Not recovered/Not resolved – The event has not improved or subject recuperated.
- Unknown – The outcome of the event is not known, not observed, not recorded, or refused.
- Fatal – Termination of life as an outcome of the AE.

The Applicant presented standard AE analyses. The definition of AE and SAE are acceptable. The classification system used by investigators to describe the severity of AEs as well as the causal relationship between AEs and study product are also acceptable.

Routine Clinical Tests

During the Phase 3 vehicle-controlled studies, investigators conducted safety assessments at screening and baseline (Day 1) followed by Weeks 2, 4, 8, 12, and 16 (end-of-study 4-week follow-up). In addition, telephone visits were conducted at Weeks 6 and 10 to assess for AEs as well as compliance with treatment. At screening and baseline, subjects were assessed with a brief physical examination and vital signs. ECG and laboratory tests (including serum chemistry and hematology) were conducted at screening but not repeated at the baseline visit. At the Week 2 visit, the safety evaluation included vital signs and assessment for AEs. The evaluation of safety at subsequent in-person study visits included vital signs, brief physical examination, and assessment for AEs. Pregnancy testing was conducted at Baseline and Weeks 4, 8, 12, and 16. Investigators conducted clinical laboratory testing at Baseline and Weeks 4, 12, and 16. Laboratory assessments included serum hematology, biochemistry, and urinalysis. When

possible, subjects discontinuing the study or study drug early had an end-of-study (EOS) visit 4 weeks after last dosing.

Overall, safety monitoring performed during the conduct of studies supporting this NDA was appropriate and adequate for evaluation of the safety of tapinarof cream, 1%.

8.2.4. Safety Results

Deaths

One death was reported in the LTE Study 3003, a myocardial infarction, considered unrelated to tapinarof cream, 1%.

- Subject (b) (6) was a 73 yo white male with a history of plaque psoriasis, 4 coronary arterial stents, hypertension, and former heavy smoker (16 years, average of 40 cigarettes/day). He had 87 days of exposure to tapinarof cream, 1% during Study 3001 and rolled over to Study 3003. He had a myocardial infarction on Day 22 of Study 3003, with a total exposure to tapinarof cream, 1%, for 109 days.

Reviewer's comment: This reviewer agrees with the Applicant's assessment that the death of this subject was not related to tapinarof cream, 1%.Taking into consideration subject's history of coronary artery disease and low systemic exposure of tapinarof cream, it is reasonable to conclude that this AE was not likely related to the study drug administration.

Serious Adverse Events

Phase 3 Studies 3001 and 3002

During the Phase 3 vehicle-controlled studies, a total of 19 SAEs were reported in 17 subjects in Studies 3001 and 3002; all subjects using tapinarof cream, 1%. There were no SAEs reported in subjects using the vehicle cream. The investigators assessed all SAEs as not treatment-related.

Table 26. Serious Adverse Events, Trials 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Total SAEs	19	0
Subjects with at least 1 SAE	17 (2.5)	0
Pancreatitis/acute pancreatitis	2 (0.2)	0
Hypertensive crisis/urgency	2 (0.2)	0
Aortic arteriosclerosis*	1 (0.1)	0
Appendicitis	1 (0.1)	0
Cardiac failure congestive	1 (0.1)	0
Cellulitis	1 (0.1)	0
Cholelithiasis	1 (0.1)	0
Coronary artery disease*	1 (0.1)	0

Coronary artery stenosis	1 (0.1)	0
Headache	1 (0.1)	0
Laryngospasm	1 (0.1)	0
Laryngeal squamous cell carcinoma	1 (0.1)	0
Nephrolithiasis	1 (0.1)	0
Nerve compression	1 (0.1)	0
Oesophageal obstruction	1 (0.1)	0
Pericardial effusion*	1 (0.1)	0
Stab wound	1 (0.1)	0

Source: Reviewer
* These AEs were all in the same subject.

Information for the SAEs of headache and cellulitis are presented below:

- Headache – Subject DMVT-3002-(b) (6), tapinarof arm, is a 39 yo white male who was hospitalized for a Grade 3 acute, nontractable headache on (b) (6) (Day 115) of the study. The last exposure to treatment was on (b) (6) (Day 85). It is not known what therapeutic measures were taken during the hospitalization to treat the headache. The date of resolution of the headache was (b) (6) (Day 117). The action taken with the study drug was "Not applicable". The subject was discontinued from the study on 7 (b) (6) (Day 120) for "Protocol violation" and "Week 12 PGA OOW" due to missed visits on Weeks 10 and 12 and use of topical corticosteroids.

- Cellulitis – Subject DMVT-505-3001-(b) (6), tapinarof arm, is a 53 yo female with a history of chronic right leg cellulitis, venous stasis on her bilateral lower legs, and plaque psoriasis on her upper and lower extremities. She was hospitalized for a Grade 3 cellulitis on the right leg on (b) (6) (Day 82) of the study. The last exposure to treatment was on (b) (6) (Day 84). The subject was treated with ceftriaxone, vancomycin, enoxaparin (deep vein thrombosis prophylaxis), fentanyl, norco, acetaminophen, and tylenol 3 while hospitalized. The date of resolution of the cellulitis was (b) (6) (Day 97). The action taken with the study drug was "Permanently discontinued". The subject was discontinued from the study on (b) (6) (Day 114) for "Adverse Event".

<u>Reviewer's Comment:</u> This reviewer agrees with the investigator assessment that the Headache AE was not related to the study drug considering the duration of time between the last exposure to the study drug and the onset of the headache.

Regarding AE of cellulitis, there is insufficient information to definitively conclude whether this AE is treatment-related, as the locations of the psoriasis plaques and application of the study drug on the lower extremities were not stated. Also, the subject had a history of lower extremity venous stasis, which is associated with increased risk of skin ulcerations and skin infections.

LTE Study 3003

Table 27. Serious Adverse Events, LTE Study 3003

Preferred Term, n (%)	Overall N = 763
Total SAEs	23
Subjects with at least 1 SAE	21 (2.8)
Pancreatitis	2 (0.3)
Melanoma	2 (0.3)
Road traffic accident	2 (0.3)
Ankle fracture	1 (0.1)
Appendicitis	1 (0.1)
Arrhythmia*	1 (0.1)
Cerebrovascular accident	1 (0.1)
Diverticulitis	1 (0.1)
Dyspnea†	1 (0.1)
Head injury	1 (0.1)
Intracranial aneurysm	1 (0.1)
Myocardial infarction	1 (0.1)
Nephrolithiasis	1 (0.1)
Osteoarthritis	1 (0.1)
Patella fracture	1 (0.1)
Pelvic inflammatory disease	1 (0.1)
Pelvi-ureteric obstruction*	1 (0.1)
Pericardial effusion†	1 (0.1)
Pneumonia	1 (0.1)
Tooth abscess	1 (0.1)

Source: Reviewer
* These AEs were in the same subject.
† These AEs were in the same subject.

During the LTE Study 3003, there were a total of 23 SAEs experienced by 21 (2.8%) subjects. None of these SAEs were considered by the Applicant to be related to tapinarof cream, 1%.

Reviewer's comment: This reviewer agrees with the investigator's assessments that the SAEs in LTE Study 3003 were not related to the study drug. Each SAE was reported in one or two subjects. There is an absence of a clear safety signal. However, the absence of a vehicle arm in Study 3003 does not allow for comparison of incidence rates with an untreated group of subjects.

With respect to the entire development program (Studies 2002, 3001, 3002, and 3003), there were a total of 9 cases of pancreatic-related conditions reported by the Applicant – 1 case of pancreatic tear and 8 cases of pancreatitis. The median onset of pancreatitis was study Day 18, with 3 of these cases occurring between Study Days 6-8. The median duration of pancreatitis was 5 days. Five cases of pancreatitis required hospitalized, but all recovered/resolved. In all but 1 case of pancreatitis, the dose of tapinarof was unchanged during treatment; the other one had

a drug interruption. Two subjects ultimately withdrew from their respective study. The number of cases of pancreatitis in this development program is notable, particularly as no subjects on vehicle had an AE of pancreatitis. However, a clear relationship cannot be established between tapinarof use and pancreatitis, especially with the early median onset, short duration of exposure, complete resolution of the pancreatitis while maintaining treatment with tapinarof, and undetactable or very low systemic exposure to the study drug.

Dropouts and/or Discontinuations Due to Adverse Effects

Phase 3 Studies 3001 and 3002

The incidence of TEAEs that led to study discontinuation was 59/683 (8.6%) in the tapinarof cream group, compared to 5/342 (1.5%) in the vehicle cream group. See Table 28.

Table 28. Summary of Subject Disposition, Phase 3 Vehicle-Controlled Studies 3001 and 3002

	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Study Status		
Completed Study	551 (80.7)	272 (79.5)
Discontinued Study	132 (19.3)	70 (20.5)
Reasons for Discontinuation		
Adverse Event	59 (8.6)	5 (1.5)
Lost to Follow-Up	30 (4.4)	17 (5)
Withdrawal of Subject	26 (3.8)	34 (9.9)
Protocol Violation	7 (1)	1 (0.3)
COVID-19	5 (0.7)	3 (0.9)
Progressive Disease	3 (0.4)	7 (2)
Pregnancy	1 (0.1)	1 (0.3)
Physician Decision	0 (0)	1 (0.3)
Other	1 (0.1)	1 (0.3)

Source: Reviewer

The most common TEAEs that led to discontinuation in the tapinarof cream, 1% arm was folliculitis (2.5% vs 0% in vehicle) and contact dermatitis (2% vs 0.3% in vehicle). See Table 29.

Table 29. TEAEs Leading to Study Discontinuation, Phase 3 Vehicle-Controlled Studies 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
AE leading to study discontinuation	59 (8.6)	5 (1.5)
Folliculitis	17 (2.5)	0 (0)
Contact dermatitis[a]	14 (2)	1 (0.3)
Psoriasis exacerbation[b]	5 (0.7)	0 (0)
Headache[c]	5 (0.7)	0 (0)

Application site reaction[d]	4 (0.6)	3 (0.9)
Vascular disease[e]	3 (0.4)	0 (0)
Musculoskeletal pain[f]	2 (0.3)	1 (0.3)
Urticaria	1 (0.1)	0 (0)
Ankle/tibial fractures	1 (0.1)	0 (0)
Asteatosis	1 (0.1)	0 (0)
Cholelithiasis	1 (0.1)	0 (0)
Hypertension	1 (0.1)	0 (0)
Impetigo	1 (0.1)	0 (0)
Stab wound	1 (0.1)	0 (0)
Sunburn	1 (0.1)	0 (0)
Transaminitis	1 (0.1)	0 (0)

Source: Reviewer
[a] Contact dermatitis includes contact dermatitis, atopic dermatitis, dermatitis, and rash
[b] Psoriasis exacerbation includes erythrodermic psoriasis and worsening psoriasis
[c] Headache includes headache and migraine
[d] Application skin reaction includes pruritus, application site pruritus, burning sensation, skin swelling, and worsening pruritus
[e] Vascular disease includes coronary artery occlusion, aortic arteriosclerosis, and arterial stenosis
[f] Musculoskeletal pain includes arthralgia and lower back pain

Reviewer's comment: The proportion of subjects who completed and discontinued Studies 3001 and 3002 were similar in the tapinarof cream, 1% compared to the vehicle cream group. However, a significantly higher proportion of subjects in the tapinarof cream, 1% group discontinued the study due to adverse events than in the vehicle group.

LTE Study 3003

The proportion of subjects that discontinued for any reason over the 40-week study duration was 30.5%. The incidence of TEAEs that led to study discontinuation in 3003 was 65 out of 763 (8.5%) subjects. This rate was similar to that of subjects using tapinarof cream, 1% in Studies 3001 and 3002. See Table 30.

Table 30. Summary of Subject Disposition, LTE Study 3003

	Tapinarof cream, 1% N = 763
Study Status	
Completed Study	531 (69.5)
Discontinued Study	232 (30.5)
Reasons for Discontinuation	
Adverse Event	65 (8.5)
Lost to Follow-Up	64 (8.4)
Withdrawal of Subject	52 (6.8)
COVID-19	17 (2.2)
Progressive Disease	11 (1.4)
Protocol Violation	6 (0.8)

Physician Decision	3 (0.4)
Pregnancy	2 (0.3)
Other	11 (1.4)

Source: Reviewer

The most common TEAEs leading to discontinuation in the LTE Study 3003 were contact dermatitis (2.6%) and folliculitis (2.2%). Discontinuation due to psoriasis exacerbation was slightly higher over the longer 40-week study.

Table 31. TEAEs Leading to Study Discontinuation, LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
AE leading to study discontinuation	65
Contact dermatitis[a]	20 (2.6)
Folliculitis	17 (2.2)
Psoriasis	8 (1)
Drug eruption	4 (0.5)
Nasopharyngitis	3 (0.4)
Motor vehicle accident	3 (0.4)
Pruritus	2 (0.3)
Squamous cell cancer	2 (0.3)
Urticaria	1 (0.1)
Stasis dermatitis	1 (0.1)
Abscess neck	1 (0.1)
Pancreatitis	1 (0.1)
Esophagitis	1 (0.1)
Facial bone fracture	1 (0.1)

Source: Reviewer
[a] Contact dermatitis includes contact dermatitis, atopic dermatitis, and rash

Significant Adverse Events

Phase 3 Studies 3001 and 3002

The applicant evaluated AEs by severity grade (Grade 1-4). The majority of TEAEs were of mild or moderate (Grade 1 and 2) severity.

Table 32. TEAEs by Grade Severity, Phase 3 Studies 3001 and 3002

	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Subjects with any AE	358 (52.4)	83 (24.3)
Total TEAEs	694	129
Severity, n TEAEs		
Grade 1	382	64
Grade 2	283	65
Grade 3	25	0

Grade 4	4	0

Source: Reviewer

The majority of the Grade 3 and Grade 4 TEAEs were also SAEs (see Tables 33 and 34) and not treatment-related. Three of the Grade 3 AEs – 1 each of folliculitis, headache, and contact dermatitis – were treatment-related and resulted in study drug discontinuation or study withdrawal.

Table 33. Grade 3 TEAEs, Phase 3 Vehicle-Controlled Studies 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683
Subjects with Grade 3 TEAEs	18 (2.6)
Total Grade 3 TEAEs	25
Nerve compression	2 (0.3)
Pericardial effusion	2 (0.3)
Pancreatitis (including acute)	2 (0.3)
Hypertensive crisis/urgency	2 (0.3)
Anemia postoperative	1 (0.1)
Arterial stenosis	1 (0.1)
Back pain	1 (0.1)
Cardiac failure congestive	1 (0.1)
Cellulitis	1 (0.1)
Cholelithiasis	1 (0.1)
Coronary artery occlusion	1 (0.1)
Coronary artery disease	1 (0.1)
Dermatitis contact	1 (0.1)
Erythrodermic psoriasis	1 (0.1)
Folliculitis	1 (0.1)
Headache	1 (0.1)
Influenza	1 (0.1)
Laryngeal squamous cell cancer	1 (0.1)
Laryngospasm	1 (0.1)
Stab wound	1 (0.1)
Tooth infection	1 (0.1)

Source: Reviewer

Table 34. Grade 4 TEAEs, Phase 3 Vehicle-Controlled Studies 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683
Subjects with Grade 4 TEAEs	3 (0.4)
Total Grade 4 TEAEs	4
Aortic arteriosclerosis	1 (0.1)
Appendicitis	1 (0.1)
Esophageal obstruction	1 (0.1)

Pericardial effusion	1 (0.1)

Source: Reviewer

LTE Study 3003

Table 35. TEAEs by Grade Severity, LTE Study 3003

	Tapinarof cream, 1% N = 763
Subjects with Any TEAE	474 (62.1)
Total TEAEs	1190
Severity, n of TEAEs	
Grade 1	599
Grade 2	545
Grade 3	42
Grade 4	3
Grade 5	1

Source: Reviewer

During the LTE Study 3003, most TEAEs were of mild or moderate severity. According to the Applicant, none of the Grade 3, 4, or 5 TEAEs in the LTE Study 3003 were considered treatment-related.

Table 36. Grade 3 TEAEs, LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
Subjects with Grade 3 TEAEs	24 (3.1)
Total Grade 3 TEAEs	42
Cataract	3 (0.4)
Nephrolithiasis	2 (0.3)
Pericardial effusion	2 (0.3)
Pancreatitis	2 (0.3)
Dyspnea	2 (0.3)
Pain in extremity	1 (0.1)
Peripheral swelling	1 (0.1)
Angle closure glaucoma	1 (0.1)
Ankle fracture	1 (0.1)
Appendicitis	1 (0.1)
Arrhythmia	1 (0.1)
Blood loss anemia	1 (0.1)
Cardiac failure congestive	1 (0.1)
Cellulitis	1 (0.1)
Corona virus infection	1 (0.1)
Diverticulitis	1 (0.1)
Drug hypersensitivity	1 (0.1)
Fall	1 (0.1)

Head injury	1 (0.1)
Hypoxia	1 (0.1)
Nerve compression	1 (0.1)
Patella fracture	1 (0.1)
Pelvic inflammatory disease	1 (0.1)
Pelvi-ureteric obstruction	1 (0.1)
Pericardial hemorrhage	1 (0.1)
Pleural effusion	1 (0.1)
Pneumonia	1 (0.1)
Procedural pain	1 (0.1)
Road traffic accident	1 (0.1)
Shock	1 (0.1)
Stasis dermatitis	1 (0.1)
Tooth abscess	1 (0.1)
Urticaria	1 (0.1)

Source: Reviewer

Table 37. Grades 4 and 5 TEAEs, LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
Subjects with Grade 4 TEAEs	3 (0.4)
Total Grade 4 TEAEs	3
Cerebrovascular accident	1 (0.1)
Intracranial aneurysm	1 (0.1)
Road traffic accident	1 (0.1)
Subjects with Grade 5 TEAEs	1 (0.1)
Myocardial infection	1 (0.1)

Source: Reviewer

Reviewer's comment: With the exception of one case of urticaria, I concur that none of the Grade 3, 4, or 5 AEs are treatment-related. For the Grade 3 TEAE of urticaria, relatedness to tapinarof is not clear. See below for additional information.

- *Subject* (b) (6) *is a 52-yo, white, non-Hispanic female who used the vehicle cream during the Phase 3 pivotal trial 3001 before rolling over to LTE Study 3003. Ongoing prior medical history included anxiety, arthritis, seasonal allergy, headache, rubber sensitivity, and oral herpes. At the start of the study, the subject was on ethinylestradiol/ levonorgestrel, venlafaxine hydrochloride, and budesonide inhaler. On Day 166 of LTE Study 3003 (Day 81 of tapinarof use), the subject experienced a Grade 3 TEAE of urticaria (whole body). The subject's tapinarof dose was not changed. Between Study Days 196-198 of LTE 3003, the subject started the following medications: hydroxyzine, clotrimazole, topical hydrocortisone, bilastine, and topical desonide. The subject completed the study (Study 3003 Day 287, Day 202 of tapinarof use). The TEAE of urticaria was ongoing at the completion of the study. On Study Day 303 (after treatment completion), the subject was started on omalizumab. The Applicant called this event "Not related" to tapinarof and cited "Concomitant Medication"*

as other action, but it is not clear if they attribute the urticaria to another medication (not listed above) or if that notation refers to the additional medications that were used to treat the urticaria/alleviate symptoms.

Treatment Emergent Adverse Events

Phase 3 Studies 3001 and 3002

A total of 1025 subjects (683 tapinarof cream, 1% and 342 vehicle cream) from the Phase 3 studies 3001 and 3002 were included in the analysis. At Week 12, there were twice as many subjects with TEAEs (52.4%) in tapinarof cream treatment arm compared to subjects in the vehicle treatment arm (24.3%). The TEAEs are summarized in Table 38.

Table 38. Summary of TEAEs occurring in **≥1%** of Subjects in Phase 3 Trials 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
TEAEs, total	694	129
Subjects with any TEAE	358 (52.4)	83 (24.3)
Folliculitis [a]	140 (20.5)	3 (0.9)
Nasopharyngitis[b]	73 (10.7)	31 (9.1)
Contact dermatitis[c]	45 (6.6)	2 (0.6)
Headache[d]	26 (3.8)	5 (1.5)
Pruritus[e]	20 (2.9)	2 (0.6)
Influenza[f]	14 (2)	2 (0.6)
Diarrhea	8 (1.2)	0 (0)

Source: Reviewer
[a] Folliculitis includes application site folliculitis and folliculitis
[b] Nasopharyngitis includes nasopharygitis, nasal congestion, pharyngitis, respiratory tract infection (RTI) viral, rhinorrhea, sinus congestion, upper RTI, and viral upper RTI
[c] Contact dermatitis includes dermatitis, dermatitis contact, hand dermatitis, and rash
[d] Headache includes headache, migraine, and tension headache
[e] Pruritus includes application site pruritus, pruritus, pruritus generalized, and pruritus genital
[f] Influenza includes influenza and influenza-like illness

LTE Study 3003

In the LTE Study 3003, the most common TEAEs were similar to those seen in the shorter Phase 3 vehicle-controlled studies: folliculitis, nasopharyngitis, contact dermatitis, pruritus, and headache. With the extended length of the study, other notable AEs emerged including drug eruptions (2.1%, including urticaria and drug hypersensitivity, approximately half of which were treatment-related or possibly related), coronavirus infection or positivity (2%), squamous cell carcinoma of the skin (1.6%) and hyperlipidemia (1.6%). The TEAEs with ≥1% incidence are summarized in Table 39.

Table 39. Summary of TEAEs occurring in **≥1%** of Subjects in LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
TEAEs, total	1145
Subjects with any TEAE	469 (61.5)
Folliculitis[a]	187 (24.5)
Nasopharyngitis[b]	71 (9.3)
Contact dermatitis[c]	66 (8.7)
Pruritus[d]	23 (3)
Headache[e]	18 (2.4)
Drug eruption[f]	16 (2.1)
Acne	15 (2)
Corona virus infection[g]	15 (2)
Back pain	14 (1.8)
Hypertension	13 (1.7)
Urinary tract infection	13 (1.7)
Squamous cell carcinoma (SCC)[h]	12 (1.6)
Bronchitis	12 (1.6)
Hyperlipidemia[i]	12 (1.6)
Cough	10 (1.3)
Gastroenteritis	9 (1.2)
Influenza[j]	8 (1)
Actinic keratosis	8 (1)
Arthralgia	8 (1)
Diarrhea	8 (1)
Pain in extremity	8 (1)
Sinusitis	8 (1)

Source: Reviewer
[a] Folliculitis includes application site folliculitis, folliculitis, milia, and keratosis pilaris
[b] Nasopharyngitis includes nasopharygitis, nasal congestion, pharyngitis, rhinitis, sinus congestion, upper respiratory tract infection (URTI), viral pharyngitis, and viral URTI
[c] Contact dermatitis includes application site dermatitis, dermatitis, dermatitis contact, hand dermatitis, eczema, neurodermatitis, rash, rash papular, and rash pruritic
[d] Pruritus includes application site pruritus and pruritus
[e] Headache includes headache, migraine, migraine with aura, and tension headache
[f] Drug eruption includes drug eruption, urticaria, drug hypersensitivity, and rash maculo-papular
[g] Corona virus infection includes corona virus infection and coronavirus test positive
[h] Squamous cell carcinoma (SCC) of the skin includes SCC and Bowen's disease
[I] Hyperlipidemia includes hyperlipidemia, hypercholesterolemia, blood cholesterol increased, blood triglycerides increased, and hypertriglyceridemia
[J] Influenza includes influenza and influenza-like illness

Adverse Reactions (ARs)

Phase 3 Studies 3001 and 3002

The most common treatment-related TEAEs (adverse reactions, ARs) for the Phase 3 studies (3001, 3002, and 3003) were folliculitis, contact dermatitis, and pruritus, with a much larger

percentage of tapinarof subjects experiencing the adverse reactions as compared to the vehicle group (24.5% vs 2.9%). The ARs are summarized in Tables 40 and 41.

Table 40. Summary of Adverse Reactions (ARs) Occurring in **≥1%** of Subjects in Studies 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
ARs, total	212	14
Subjects with any AR	167 (24.5)	10 (2.9)
Folliculitis[a]	126 (18.5)	3 (0.9)
Contact dermatitis[b]	36 (5.3)	1 (0.3)
Pruritus[c]	10 (1.5)	0 (0)

Source: Reviewer
[a] Folliculitis includes application site folliculitis and folliculitis
[b] Contact dermatitis includes dermatitis, dermatitis allergic, dermatitis contact, hand dermatitis, and rash
[c] Pruritus includes application site pruritus, pruritus, pruritus generalized, and pruritus genital

LTE Study 3003

The incidence rate and type of of adverse reactions in the LTE Study 3003 were similar to those reported in Studies 3001 and 3002.

Table 41. Summary of Adverse Reactions (ARs) Occurring in **≥1%** of Subjects in LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
ARs, total	290
Subjects with any AR	209 (27.4)
Folliculitis[a]	162 (21.2)
Contact dermatitis[b]	37 (4.8)
Pruritus[c]	11 (1.4)

Source: Reviewer
[a] Folliculitis includes application site folliculitis, folliculitis, milia, and keratosis pilaris
[b] Contact dermatitis includes application site dermatitis, dermatitis, dermatitis contact, hand dermatitis, eczema, rash papular
[c] Pruritus includes application site pruritus and pruritus

Adverse Events of Special Interest (AESIs)

Based on the incidence of adverse events in early studies, the Applicant designated contact dermatitis, folliculitis, and headache as AESIs. In addition, the reviewer examined the AE of pruritus as an AESI because it is reported as an AR of tapinarof.

Contact dermatitis
Phase 3 Studies 3001 and 3002

Table 42. AESI Summary of Contact Dermatitis, Phase 3 Studies 3001 and 3002

Parameter	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Total TEAEs of contact dermatitis, n	54	2
Subjects with TEAE of contact dermatitis, n	45 (6.6)	2 (0.6)
Drug Discontinuations due to AE, n (%)	20 (2.9)	0 (0)
Preferred Term, n subjects (%)		
Dermatitis	6 (0.9)	1 (50)
Dermatitis contact	33 (4.8)	1 (50)
Hand dermatitis	1 (0.1)	0 (0)
Rash	6 (0.9)	0 (0)
Causality, n subjects (%)		
Related	35 (5.1)	1 (50)
Not related	10 (1.5)	1 (50)
Maximum CTCAE Grade, n subjects (%)		
Grade 1	17 (2.5)	1 (50)
Grade 2	27 (4)	1 (50)
Grade 3	1 (0.1)	0 (0)
Maximum Action Taken with Study Drug, n subjects (%)		
Dose Not Changed	11 (1.6)	1 (50)
Dose Reduced	2 (0.3)	0 (0)
Dose Interrupted	11 (1.6)	1 (50)
Dose Withdrawn	20 (2.9)	0 (0)
Not applicable	1 (0.1)	0 (0)
Worst Outcome, n subjects (%)		
Recovered/resolved	29 (4.2)	2 (100)
Not recovered/Not resolved	16 (2.3)	0 (0)

Source: Reviewer

The Applicant described this contact dermatitis as an irritant (as opposed to allergic) contact dermatitis, as subjects were able to discontinue the drug to allow for resolution and if tapinarof application was resumed, the dermatitis did not consistently recur.

Contact dermatitis occurred more frequently in the tapinarof cream group (6.6%) compared to the vehicle group (0.6%). Most were Grade 1 or 2; however, 20 (2.9%) subjects treated with tapinarof subjects withdrew due to contact dermatitis. Of the subjects taking tapinarof, 1.6% had drug interruptions due to contact dermatitis. This points that tapinarof is mildly ot moderately irritating.

LTE Study 3003

Table 43. AESI Summary of Contact Dermatitis, LTE Study 3003

Parameter	Tapinarof cream, 1% N = 763
Total TEAEs of contact dermatitis, n	79
Subjects with TEAE of contact dermatitis, n	66 (8.7)
Drug Discontinuations due to AE, n (%)	18 (2.4)
Preferred Term, n subjects (%)	
Dermatitis contact	41 (5.4)
Dermatitis	9 (1.2)
Eczema	7 (0.9)
Neurodermatitis	4 (0.5)
Application site dermatitis	2 (0.3)
Rash	2 (0.3)
Hand dermatitis	2 (0.3)
Rash papular	2 (0.3)
Rash pruritic	1 (0.1)
Causality, n subjects (%)	
Related	37 (4.9)
Not related	29 (3.8)
Maximum CTCAE Grade, n subjects (%)	
Grade 1	23 (3)
Grade 2	43 (5.6)
Maximum Action Taken with Study Drug, n subjects (%)	
Dose Not Changed	23 (3)
Dose Reduced	1 (0.1)
Dose Interrupted	21 (2.8)
Dose Withdrawn	17 (2.2)
Not applicable	4 (0.5)
Worst Outcome, n subjects (%)	
Recovered/resolved	40 (5.2)
Not recovered/Not resolved	25 (3.3)
Unknown	1 (0.1)

Source: Reviewer

In the 40-week LTE study, there was a slightly lower incidence of contact dermatitis (8.7%) compared to the Phase 3 studies 3001 and 3002. However, the number of subjects that discontinued the study due to the AE of contact dermatitis was similar.

Folliculitis

Phase 3 Studies 3001 and 3002

Table 44. AESI Summary of Folliculitis, Phase 3 Studies 3001 and 3002

Parameter	Tapinarof cream, 1% N = 683	Vehicle cream N = 342

Total TEAEs of folliculitis, n	153	5
Subjects with TEAE of folliculitis, n	143 (20.9)	4 (1.2)
Drug Discontinuations due to AE, n (%)	19 (2.8)	0 (0)
Preferred Term, n subjects (%)		
Folliculitis	138 (20.2)	3 (0.9)
Application site folliculitis	2 (0.3)	0
Keratosis pilaris	4 (0.6)	1 (0.3)
Causality, n subjects (%)		
Related	126 (18.4)	3 (0.9)
Not related	17 (2.6)	1 (0.3)
Maximum CTCAE Grade, n subjects (%)		
Grade 1	97 (14.2)	2 (0.6)
Grade 2	45 (6.6)	2 (0.6)
Grade 3	1 (0.1)	0 (0)
Maximum Action Taken with Study Drug, n subjects (%)		
Dose Not Changed	91 (13.3)	4 (1.2)
Dose Reduced	4 (0.6)	0 (0)
Dose Interrupted	29 (4.2)	0 (0)
Dose Withdrawn	19 (2.8)	0 (0)
Worst Outcome, n subjects (%)		
Recovered/resolved	50 (7.3)	2 (0.6)
Not recovered/Not resolved	89 (13)	2 (0.6)
Unknown	4 (0.6)	0 (0)

Source: Reviewer

The Applicant described the folliculitis resulting from tapinarof application as "increased follicular cornification with subsequent follicular plugging resulting in mild to moderate, non-infectious papules" similar in morphology to keratosis pilaris (KP), a common perifollicular skin condition that results in trapped "coiled hairs". Per the Applicant, the mechanism of action of tapinarof results in upregulation of components of the stratum corneum, including filaggrin, hornerin, and involucrin, the same proteins implicated in KP.

In the Phase 3 studies 3001 and 3002, 20.9% of subjects using tapinarof had an AE of folliculitis. Although the majority of the AEs were Grade 1 or 2, 7.6% of subjects using tapinarof required dose modification due to folliculitis and 2.8% resulted in drug withdrawal. Moreover, 13% of tapinarof subjects had an unresolved or persistent folliculitis at the end of the 12-week trial.

LTE Study 3003

Table 45. AESI Summary of Folliculitis, LTE Study 3003

Parameter	Tapinarof cream, 1% N = 763
Total TEAEs of folliculitis, n	227
Subjects with TEAE of folliculitis, n	187 (24.5)

Drug Discontinuations due to AE, n (%)	9 (1.2)
Preferred Term, n subjects (%)	
Folliculitis	172 (22.5)
Application site folliculitis	8 (1)
Keratosis pilaris	6 (0.8)
Milia	3 (0.4)
Causality, n subjects (%)	
Related	162 (21.2)
Not related	25 (3.3)
Maximum CTCAE Grade, n subjects (%)	
Grade 1	124 (16.3)
Grade 2	63 (8.3)
Maximum Action Taken with Study Drug, n subjects (%)	
Dose Not Changed	139 (18.2)
Dose Reduced	1 (0.1)
Dose Interrupted	35 (4.6)
Dose Withdrawn	9 (1.2)
Not applicable	3 (0.4)
Worst Outcome, n subjects (%)	
Recovered/resolved	102 (13.4)
Not recovered/Not resolved	84 (11)
Unknown	1 (0.1)

Source: Reviewer

During the LTE Study 3003, folliculitis continued to be a common AE. Over the 40-week study, there was a lower rate of discontinuations due to folliculitis, and, a greater percentage of subjects (13.4%) recovered/resolved.

Headache

Phase 3 Studies 3001 and 3002

Table 46. AESI Summary of Headache, Phase 3 Studies 3001 and 3002

Parameter	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Total TEAEs of headache, n	28	9
Subjects with TEAE of headache, n	26 (3.8)	5 (1.5)
Drug Discontinuations due to AE, n (%)	3 (0.4)	0 (0)
Preferred Term, n (%)		
Headache	23 (3.4)	4 (1.2)
Migraine	2 (0.3)	1 (0.3)
Tension headache	1 (0.1)	0 (0)
Causality, n subjects (%)		
Related	7 (1)	1 (0.3)
Not related	19 (2.8)	4 (1.2)

Maximum CTCAE Grade, n subjects (%)		
Grade 1	21 (3.1)	2 (0.6)
Grade 2	4 (0.6)	3 (0.9)
Grade 3	1 (0.1)	0 (0)
Maximum Action Taken with Study Drug, n subjects (%)		
Dose Not Changed	18 (2.6)	5 (1.5)
Dose Interrupted	4 (0.6)	0 (0)
Dose Withdrawn	3 (0.4)	0 (0)
Not applicable	1 (0.1)	0 (0)
Worst Outcome, n subjects (%)		
Recovered/resolved	24 (3.5)	5 (1.5)
Not recovered/Not resolved	2 (0.3)	0 (0)

Source: Reviewer

The AE of headache occurred more frequently in the tapinarof cream group (7.6%) than the vehicle group (1.5%). Most were Grade 1 or 2; however, in the majority of cases for the tapinarof and vehicle, the dose was unchanged. The investigators assessed that the majority of the headaches in tapinarof subjects were not related to the treatment. Of the subjects treated with tapinarof, 3 subjects (0.4%) withdrew due to headache.

LTE Study 3003

Table 47. AESI Summary of Headache, LTE Study 3003

Parameter	Tapinarof cream, 1% N = 763
Total TEAEs of headache, n	18
Subjects with TEAE of headache, n	16 (2.1)
Drug Discontinuations due to AE, n (%)	0 (0)
Preferred Term, n subjects (%)	
Headache	11 (1.4)
Migraine	2 (0.3)
Migraine with aura	1 (0.1)
Tension headache	2 (0.3)
Causality, n subjects (%)	
Related	3 (0.4)
Not related	13 (1.7)
Maximum CTCAE Grade, n subjects (%)	
Grade 1	9 (1.2)
Grade 2	7 (0.9)
Maximum Action Taken with Study Drug, n subjects (%)	
Dose Not Changed	15 (2)
Dose Interrupted	1 (0.1)
Worst Outcome, n subjects (%)	
Recovered/resolved	12 (1.6)
Not recovered/Not resolved	4 (0.5)

Source: Reviewer

In the LTE Study 3003, there was a lower rate of headaches (2.1%) compared to the Phase 3 studies. All were Grade 1 or 2 and for all but one subject, the dose was unchanged.

Reviewer Comment: I concur with the Applicant's assessment that there is no obvious mechanism of action in tapinarof that would trigger a headache, as there is little systemic absorption with tapinarof and in general, no changes in dose were necessary for the headaches to resolve.

Pruritus
Phase 3 Studies 3001 and 3002

Table 48. AESI Summary of Pruritus, Phase 3 Studies 3001 and 3002

Parameter	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Total TEAEs of pruritus, n	27	2
Subjects with TEAE of pruritus, n	20 (2.9)	2 (0.6)
Drug Discontinuations due to AE, n (%)	4 (0.6)	0 (0)
Preferred Term, n subjects (%)		
Pruritus	15 (2.2)	2 (0.6)
Application site pruritus	5 (0.7)	0 (0)
Pruritus generalized	1 (0.1)	0 (0)
Pruritus genital	1 (0.1)	0 (0)
Causality, n subjects (%)		
Related	10 (1.5)	0 (0)
Not related	10 (1.5)	2 (0.6)
Maximum CTCAE Grade, n subjects (%)		
Grade 1	11 (1.6)	1 (0.3)
Grade 2	9 (1.3)	1 (0.3)
Maximum Action Taken with Study Drug, n subjects (%)		
Dose Not Changed	12 (1.8)	1 (0.3)
Dose Reduced	1 (0.1)	0 (0)
Dose Interrupted	3 (0.4)	0 (0)
Dose Withdrawn	4 (0.6)	1 (0.3)
Worst Outcome, n subjects (%)		
Recovered/resolved	11 (1.6)	0 (0)
Not recovered/Not resolved	9 (1.3)	2 (0.6)

Source: Reviewer

Although pruritus was not selected by the Applicant as an AESI, pruritus was a common adverse reaction of tapinarof. There were 2.9% of tapinarof subjects affected by pruritus (compared to 0.6% of vehicle subjects). Although investigators assessed that over half of the affected subjects' pruritus was unrelated to treatment with tapinarof , 8 out of 20 subjects using

tapinarof required a dose reduction, interruption, or withdrawal, and almost half had not resolved by the end of the 12-week study.

LTE Study 3003

Table 49. AESI Summary of Pruritus, LTE Study 3003

Parameter	Tapinarof cream, 1% N = 763
Total TEAEs of pruritus, n	23
Subjects with TEAE of pruritus, n (%)	20 (2.6)
Drug Discontinuations due to AE, n (%)	2 (0.3)
Preferred Term, n subjects (%)	
Pruritus	4 (0.5)
Application site pruritus	16 (2.1)
Causality, n subjects (%)	
Related	11 (1.4)
Not related	9 (1.2)
Maximum CTCAE Grade, n subjects (%)	
Grade 1	15 (2)
Grade 2	5 (0.7)
Maximum Action Taken with Study Drug, n subjects (%)	
Dose Not Changed	13 (1.7)
Dose Reduced	1 (0.1)
Dose Interrupted	4 (0.5)
Dose Withdrawn	2 (0.3)
Worst Outcome, n subjects (%)	
Recovered/resolved	13 (1.7)
Not recovered/Not resolved	7 (0.9)

Source: Reviewer

During the LTE Study 3003, the proportion of subjects affected by pruritus was 2.6%. Although over half resolved, the high rate of unresolved cases and those requiring dose modification (0.9% for both categories) suggests that pruritus can be a mild to moderate, but persistent, AE for some subjects while using tapinarof.

Reviewer Comment: Pruritus is a common symptom associated with folliculitis and irritant contact dermatitis and therefore not unexpected.

Laboratory Findings

The investigators conducted clinical laboratory testing at Screening, Weeks 4 and 12, and Week 16 (at the 4-week follow-up visit). The laboratory assessments included serum hematology and biochemistry. The serum hematology and biochemistry parameters assessed in the Phase 3 trials included hemoglobin, hemocrit, WBC, AST, ALT, alkaline phosphatase,

and BUN/creatinine. The mean changes from Screening to Weeks 4 and 12 were small and comparable between the treatment groups. Table 50 shows the TEAEs associated with abnormal laboratory parameters.

Table 50. Lab test abnormalities, Phase 3 Studies 3001 and 3002

Preferred Term, n (%)	Tapinarof cream, 1% N = 683	Vehicle cream N = 342
Lab test abnormality, total	18	4
Subjects with any lab test abnormality	16 (2.3)	4 (1.2)
Hyperlipidemia [a]	4 (0.6)	2 (0.6)
Liver function test increased[b]	4 (0.6)	0 (0)
Anemia	3 (0.4)	0 (0)
Glucose tolerance impaired	2 (0.3)	2 (0.6)
Hematuria	1 (0.2)	0 (0)
Hyperkalemia	1 (0.2)	0 (0)
Blood sodium decreased	1 (0.2)	0 (0)
International normalized ratio increased	1 (0.2)	0 (0)
Vitamin D deficiency	1 (0.2)	0 (0)

Source: Reviewer

[a] Hyperlipidemia includes blood cholesterol increased, hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia

[b] Liver function test increased includes alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, hypertransaminasemia

There were no clinically significant, treatment-related abnormalities in laboratory tests or between treatment arms in the Phase 3 trials 3001 and 3002.

LTE study 3003

Table 51. Lab abnormalities, LTE Study 3003

Preferred Term, n (%)	Tapinarof cream, 1% N = 763
Lab test abnormality, total	47
Subjects with any lab test abnormality	37 (4.9)
Hyperlipidemia [a]	12 (1.6)
Blood glucose increased[b]	8 (1.2)
Anemia[c]	4 (0.6)
Liver function test increased[d]	3 (0.4)
Hematuria	2 (0.3)
Hyponatremia	2 (0.3)
Blood potassium increased	2 (0.3)
Blood creatinine increased	1 (0.2)
Eosinophil count increased	1 (0.2)
Hyperthyroidism	1 (0.2)

Hyperuricemia	1 (0.2)
Hypothyroidism	1 (0.2)
Lipase increased	1 (0.2)
Platelet count increased	1 (0.2)
Urine analysis abnormal	1 (0.2)
Vitamin D decreased	1 (0.2)
Leukocytosis	1 (0.2)
Lymphopenia	1 (0.2)
Monoclonal B-cell lymphocytosis	1 (0.2)

Source: Reviewer
[a] Hyperlipidemia includes blood cholesterol increased, hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia
[b] Blood glucose increased included blood glucose increased and hyperglycemia
[c] Anemia includes anemia, blood loss anemia, and blood iron decreased
[d] Liver function test increased includes alanine aminotransferase increased and liver function test increased

Reviewer comment: During the vehicle controlled studies, 6 subjects were diagnosed with hyperlipidemia. An additional 8 subjects were diagnosed with hyperlipidemia during the long-term extension Study 3003. However, it is not clear how these diagnoses were made because a lipid panel was not a per-protocol laboratory assessment for any of the Phase 3 studies. It is also not clear how blood samples for these laboratory tests were taken (e.g., whether subjects were fasting). Also, the Applicant did not provide actual laboratory values to support these diagnoses. Still, with intermittent treatment with tapinarof during the OLE study 3003, the unknown timing of laboratory evaluations in relation to dosing with tapinarof, and the overall low systemic exposure, it is unlikely that these diagnoses can be attributed to treatment with tapinarof.

Vital Signs

Per the Applicant, no clinically relevant changes in the vital sign values from Baseline to Week 12 were observed.

Electrocardiograms (ECGs)

In DMVT-505-2002, the Applicant collected and submitted data on Holter monitor recordings from 21 subjects on Days -1, 1, 2, 29, and 30. Digital 12-lead ECGs were extracted from the continuous recording that corresponded with time points on Days 1 and 29. Day 1 was selected as the study day for ECG analysis because the highest mean C_{max} was observed on Day 1 (vs Day 29). Tapinarof had no clinically relevant effect on heart rate or on the QT interval. There was also no clinically relevant effect on cardiac conduction, i.e., the PR and QRS intervals. ECGs were conducted only at baseline during the pivotal studies.

QT

In a consult review dated November 22, 2021, the Interdisciplinary Review Team (IRT) for Cardiac Safety Studies determined that no significant QTcF prolongation effect of tapinarof cream, 1%, *w/w* was detected in this QT assessment.

Immunogenicity

Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Malignancies

8.2.5.1.1. Squamous cell carcinoma (SCC)

According to the Applicant, in the Phase 3 studies evaluating tapinarof cream, 1% for plaque psoriasis (Studies 3001, 3002, and 3003), a total of 12 subjects reported 20 TEAEs of SCC of skin or SCC in situ (SCCIS or Bowen's disease). In the 2 vehicle-controlled studies (Studies 3001 and 3002), 5 subjects (0.7%) in the tapinarof cream, 1% group developed 8 TEAEs of SCC or SCCIS of skin. All 5 of those subjects completed the 12-week studies and enrolled in the LTE study 3003, where monitoring of these AEs continued. In the LTE study, 10 subjects (1.3%) developed 12 new skin cancers. Of these, 3 subjects were originally diagnosed with SCC in Studies 3001 and 3002 and then developed 3 additional TEAEs of SCC of skin in Study 3003. The remaining 7 subjects diagnosed with SCC in LTE 3003, developed 9 SCC of. Six of those 7 subjects were treated with tapinarof cream, 1% in the 12-week study and 1 subject was treated with vehicle cream. Overall, 2 subjects each had 3 events, 4 subjects each had 2 events, and 6 subjects each had 1 event. All 20 TEAEs of SCC in the 3 studies have been considered not related to treatment by the investigators.

Table 52. TEAEs of SCC in Phase 3 Studies 3001, 3002, and 3003

Subject Identifier	SCCs in Trial 3001	SCCs in Trial 3002	SCCs in Study 3003
(b) (6) [a]	2	-	
[a,c]	2	-	1
[a,c]	-	2	1
[a,c]	-	1	
[a,c]	-	1	1
[a,c]	-	-	2
[a,c]	-	-	1
[a]	-	-	1
[a,c]	-	-	1
[b,c]	-	-	1
[a]	-	-	1
[a,c]	-	-	2

Source: Reviewer
[a] In tapinarof arm during 12-week study
[b] In vehicle arm during 12-week study
[c] Past medical history of actinic keratoses or non-melanoma skin cancer prior to study enrollment

The Applicant provided additional information regarding the AE of squamous cell cancer of the skin/Bowen's disease (12 subjects, 20 events). The subjects ranged in age from 57 to 73 years. All 12 subjects were Caucasian, with one subject of mixed Caucasian/American or Alaskan Indian. Of these 12 subjects, 9 had a prior history of actinic keratosis and 6 had a prior history of basal cell carcinoma, squamous cell carcinoma, or melanoma in situ. For the 3 subjects that had no prior history of actinic keratoses or skin cancer, they were not applying tapinarof in the areas where the squamous cell was diagnosed.

These subjects had multiple pre-existing risk factors for developing new squamous cell cancers, independent of tapinarof use. People with a prior history of skin cancer or actinic keratoses, particularly Caucasians (Fitzpatrick Skin Types I-III), are at a higher risk of developing new primary skin cancers. In addition, compared to the general population, subjects with psoriasis are at slightly higher risk for developing non-melanoma skin cancer: RR 1.72 compared to non-psoriasis patients; RR 1.82 for moderate to severe psoriasis; RR 1.61 for mild psoriasis; and RR 2.08 for SCC in particular (Wang, et al., 2020). Given the pre-existing increased risk factors for developing new skin cancers in these subjects, this reviewer agrees with the Applicant's assessment that the squamous cell cancers reported in Phase 3 studies are unlikely to be related to the treatment with tapinarof cream.

8.2.5.1.2. Melanoma

Two subjects were diagnosed with malignant melanoma during the Phase 3 studies, both during the LTE Study 3003. One melanoma was definitively diagnosed as malignant melanoma in situ. In both cases, the subjects were older (ages 59 and 73) Caucasians. Both had significant risk factors – one with a PMH including tanning bed use and multiple sunburns, the other with a history of SCC. Both melanomas were diagnosed in areas in which tapinarof was not applied. The use of tapinarof was not changed during the study and the melanomas were resolved with wide local excision only. This reviewer agrees with the investigators' assessments that the melanomas were not likely to be related to treatment with tapinarof cream.

8.2.5.1.3. Laryngeal SCC

During Study 3002, Subject (b) (6), a 63 yo white male with plaque psoriasis, developed a left glottic squamous cell cancer. He had a PMH including acid reflux, diabetes, leukoplakia, and stroke. On Day 17 of tapinarof use, he was diagnosed with a CTCAE 3 laryngeal squamous cell carcinoma, assessed by the investigator as unrelated to the study drug. He was given radiation therapy from (b) (6) to (b) (6); however, he continued use of tapinarof. While the SCC was not considered resolved by the end of the study, he did complete Study 3002 and enrolled in Study 3003. This reviewer agrees that it is unlikely that tapinarof contributed to the development of this SCC, particularly because it was diagnosed very early in the study.

8.2.6. Local Tolerability

Local tolerability scales (LTS) were used to assess the presence and overall degree of irritation during the Phase 3 trials 3001 and 3002 and LTE Study 3003. During the Phase 3 vehicle-controlled studies, local tolerability was assessed at Weeks 2, 4, 8, and 12. Using the scale in Table 52, investigators used dryness, erythema, and peeling at the application sites, with the score ideally representing an "average" across all sites.

Table 53. Investigator Local Tolerability Scale

Local Tolerability – Dryness, Erythema, and Peeling

Score	Severity	Description
0	No irritation	No evidence of local irritation/intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but does not require treatment modification
3	Severe	Erythema, edema glazing with fissures, few vesicles or papules
4	Very Severe	Strong reaction spreading beyond the treated area, bullous reaction, erosions

Source: Applicant ISS, Table 10.

Similarly, burning/stinging and itching was assessed by subjects using the scale in Table 53.

Table 54. Subject Local Tolerability Scale

Local Tolerability – Burning/Stinging and Itching

Score	Severity	Description
0	None	Normal, no discomfort
1	Slight	An awareness, but no discomfort and no intervention required
2	Mild	A noticeable discomfort that causes intermittent awareness
3	Moderate	A noticeable discomfort that causes intermittent awareness and interferes occasionally with normal daily activities
4	Strong/Severe	A definite continuous discomfort that interferes with normal daily activities

Source: Applicant ISS, Table 11.

Phase 3 Studies 3001 and 3002

Table 55. Investigator Assessment of Dryness, Erythema, and Peeling, Phase 3 Studies 3001 and 3002

Visit	Tapinarof Cream, 1% QD (N = 683)						Vehicle Cream QD (N = 342)					
	n	None	Mild	Moderate	Severe	Very Severe	N	None	Mild	Moderate	Severe	Very Severe
Week 2	658	553 (84.0)	67 (10.2)	33 (5.0)	4 (0.6)	1 (0.2)	328	285 (86.9)	18 (5.5)	23 (7.0)	2 (0.6)	0
Week 4	638	540 (84.6)	73 (11.4)	22 (3.4)	2 (0.3)	1 (0.2)	316	288 (91.1)	18 (5.7)	10 (3.2)	0	0
Week 8	596	524 (87.9)	44 (7.4)	21 (3.5)	6 (1.0)	1 (0.2)	293	274 (93.5)	8 (2.7)	9 (3.1)	2 (0.7)	0
Week 12	564	501 (88.8)	44 (7.8)	14 (2.5)	4 (0.7)	1 (0.2)	276	256 (92.8)	15 (5.4)	4 (1.4)	1 (0.4)	0
Week 16	49	43 (87.8)	6 (12.2)	0	0	0	17	16 (94.1)	0	1 (5.9)	0	0

Source: ISS Table 3.10.2.
QD = once daily.

Table 56. Subjects with Dryness, Erythema, and Peeling, Phase 3 Studies 3001 and 3002

Subjects with any LTS signs, (Tapinarof/Vehicle)	Tapinarof cream, 1% QD n (%)	Vehicle cream QD n (%)
Week 2 (N= 658/328)	105 (16)	43 (13.1)
Week 4 (N=638/316)	98 (15.4)	28 (8.9)
Week 8 (N=596/293)	72 (12.1)	19 (6.5)
Week 12 (N=564/276)	63 (11.2)	20 (7.3)

Source: Reviewer

Based on investigator assessments of dryness, erythema, and peeling, the majority were of mild or moderate severity. The percentage of subjects with dryness, erythema, and peeling was fairly consistent over the duration of the studies, ranging from 11.2-16%.

Table 57. Subject Assessment of Burning/Stinging and Itching, Phase 3 Studies 3001 and 3002

	Tapinarof Cream, 1% QD (N = 683)						Vehicle Cream QD (N = 342)					
Visit	n	None	Slight	Mild	Moderate	Strong/ Severe	n	None	Slight	Mild	Moderate	Strong/ Severe
Week 2	658	139 (21.1)	156 (23.7)	203 (30.9)	129 (19.6)	31 (4.7)	327	65 (19.9)	69 (21.1)	91 (27.8)	63 (19.3)	39 (11.9)
Week 4	638	155 (24.3)	222 (34.8)	163 (25.5)	78 (12.2)	20 (3.1)	315	59 (18.7)	72 (22.9)	86 (27.3)	69 (21.9)	29 (9.2)
Week 8	596	182 (30.5)	189 (31.7)	128 (21.5)	70 (11.7)	27 (4.5)	291	57 (19.6)	74 (25.4)	76 (26.1)	62 (21.3)	22 (7.6)
Week 12	560	204 (36.4)	161 (28.8)	116 (20.7)	54 (9.6)	25 (4.5)	276	53 (19.2)	71 (25.7)	66 (23.9)	61 (22.1)	25 (9.1)
Week 16	50	18 (36.0)	13 (26.0)	11 (22.0)	4 (8.0)	4 (8.0)	17	5 (29.4)	5 (29.4)	5 (29.4)	2 (11.8)	0

Source: ISS Table 3.11.2.
QD = once daily

Table 58. Subjects with Burning/Stinging and Itching, Phase 3 Studies 3001 and 3002

Subjects with any LTS signs, (Tapinarof/Vehicle)	Tapinarof cream, 1% QD n (%)	Vehicle cream QD n (%)
Week 2 (N= 658/327)	519 (78.9)	262 (80.1)
Week 4 (N=638/315)	483 (75.7)	256 (81.3)
Week 8 (N=596/291)	414 (69.5)	234 (80.4)
Week 12 (N=560/276)	356 (63.6)	223 (80.8)

Source: Reviewer

In contrast, a high percentage of subjects reported some degree of irritation using tapinarof or the vehicle cream. The proportion of vehicle treated subjects reporting irritation was fairly consistent over the course of the 12-week study, while there was a slight decrease in tapinarof subjects reporting irritation from Week 2 to 12.

LTE Study 3003

Table 59. Investigator Assessment of Dryness, Erythema, and Peeling, LTE Study 3003

	Tapinarof Cream, 1% QD																	
	Tapinarof Cream, 1% QD (N = 508) n (%)						Vehicle Cream QD (N = 255) n (%)						All 3003 Patients (All Treated) (N=763) n (%)					
Visit	n	None	Mild	Moderate	Severe	Very Severe	n	None	Mild	Moderate	Severe	Very Severe	n	None	Mild	Moderate	Severe	Very Severe
Week 4	400	359 (89.8)	34 (8.5)	6 (1.5)	1 (0.3)	0	225	207 (92.0)	14 (6.2)	3 (1.3)	0	1 (0.4)	625	566 (90.6)	48 (7.7)	9 (1.4)	1 (0.2)	1 (0.2)
Week 8	371	336 (90.6)	26 (7.0)	7 (1.9)	1 (0.3)	1 (0.3)	213	198 (93.0)	9 (4.2)	3 (1.4)	1 (0.5)	2 (0.9)	584	534 (91.4)	35 (6.0)	10 (1.7)	2 (0.3)	3 (0.5)
Week 12	334	308 (92.2)	21 (6.3)	5 (1.5)	0	0	197	182 (92.4)	11 (5.6)	3 (1.5)	1 (0.5)	0	531	490 (92.3)	32 (6.0)	8 (1.5)	1 (0.2)	0
Week 16	319	291 (91.2)	23 (7.2)	3 (0.9)	2 (0.6)	0	179	166 (92.7)	12 (6.7)	1 (0.6)	0	0	498	457 (91.8)	35 (7.0)	4 (0.8)	2 (0.4)	0
Week 20	304	289 (95.1)	11 (3.6)	2 (0.7)	2 (0.7)	0	168	153 (91.1)	13 (7.7)	1 (0.6)	1 (0.6)	0	472	442 (93.6)	24 (5.1)	3 (0.6)	3 (0.6)	0
Week 24	296	279 (94.3)	17 (5.7)	0	0	0	159	151 (95.0)	5 (3.1)	3 (1.9)	0	0	455	430 (94.5)	22 (4.8)	3 (0.7)	0	0
Week 28	297	282 (94.9)	8 (2.7)	6 (2.0)	1 (0.3)	0	146	138 (94.5)	5 (3.4)	3 (2.1)	0	0	443	420 (94.8)	13 (2.9)	9 (2.0)	1 (0.2)	0
Week 32	260	249 (95.8)	9 (3.5)	2 (0.8)	0	0	130	123 (94.6)	5 (3.8)	1 (0.8)	0	1 (0.8)	390	372 (95.4)	14 (3.6)	3 (0.8)	0	1 (0.3)
Week 36	222	214 (96.4)	6 (2.7)	2 (0.9)	0	0	111	106 (95.5)	3 (2.7)	2 (1.8)	0	0	333	320 (96.1)	9 (2.7)	4 (1.2)	0	0
Week 40	191	183 (95.8)	2 (1.0)	6 (3.1)	0	0	92	89 (96.7)	2 (2.2)	1 (1.1)	0	0	283	272 (96.1)	4 (1.4)	7 (2.5)	0	0

Source: ISS Table 3.10.3.
QD = once daily.

Table 60. Subjects with Dryness, Erythema, and Peeling, LTE Study 3003

Subjects with any LTS signs, (Tapinarof/Vehicle)	All Subjects, LTE Study 3003 n (%)
Week 4 (N=400/225/625)	59 (9.4)
Week 8 (N=371/213/584)	50 (8.6)
Week 12 (N=334/197/531)	41 (7.7)
Week 16 (N=319/179/498)	41 (8.2)
Week 20 (N=304/168/472)	30 (6.4)
Week 24 (N=296/159/455)	25 (5.5)
Week 28 (N=297/146/443)	23 (5.2)
Week 32 (N=260/130/390)	18 (4.6)
Week 36 (N=222/111/333)	13 (3.9)
Week 40 (N=191/92/283)	11 (3.9)

Source: Reviewer

Overall, the rates of dryness, erythema, and peeling were less than those assessed during the 12-week study. However, recognizing the LTE Study is continuation of the Phase 3 vehicle-controlled studies, the decline in incidence rate is more likely an indication of subjects' discontinuation due to irritation and to a lesser extent, possible resolution of these signs.

Table 61. Subject Assessment of Burning/Stinging and Itching, LTE Study 3003

	Tapinarof Cream, 1% QD																	
	Tapinarof Cream, 1% QD (N = 508) n (%)						Vehicle Cream QD (N = 255) n (%)						All 3003 Patients (All Treated) (N=763) n (%)					
Visit	n	None	Slight	Mild	Moderate	Strong/ Severe	n	None	Slight	Mild	Moderate	Strong/ Severe	n	None	Slight	Mild	Moderate	Strong/ Severe
Week 4	399	153 (38.3)	122 (30.6)	83 (20.8)	33 (8.3)	8 (2.0)	226	55 (24.3)	87 (38.5)	51 (22.6)	23 (10.2)	10 (4.4)	625	208 (33.3)	209 (33.4)	134 (21.4)	56 (9.0)	18 (2.9)
Week 8	371	155 (41.8)	106 (28.6)	71 (19.1)	33 (8.9)	6 (1.6)	215	83 (38.6)	75 (34.9)	29 (13.5)	23 (10.7)	5 (2.3)	586	238 (40.6)	181 (30.9)	100 (17.1)	56 (9.6)	11 (1.9)
Week 12	335	141 (42.1)	96 (28.7)	57 (17.0)	30 (9.0)	11 (3.3)	194	81 (41.8)	59 (30.4)	23 (11.9)	24 (12.4)	7 (3.6)	529	222 (42.0)	155 (29.3)	80 (15.1)	54 (10.2)	18 (3.4)
Week 16	317	134 (42.3)	94 (29.7)	54 (17.0)	28 (8.8)	7 (2.2)	177	73 (41.2)	49 (27.7)	32 (18.1)	16 (9.0)	7 (4.0)	494	207 (41.9)	143 (28.9)	86 (17.4)	44 (8.9)	14 (2.8)
Week 20	306	139 (45.4)	80 (26.1)	66 (21.6)	16 (5.2)	5 (1.6)	166	71 (42.8)	53 (31.9)	26 (15.7)	11 (6.6)	5 (3.0)	472	210 (44.5)	133 (28.2)	92 (19.5)	27 (5.7)	10 (2.1)
Week 24	294	137 (46.6)	81 (27.6)	57 (19.4)	17 (5.8)	2 (0.7)	155	68 (43.9)	46 (29.7)	25 (16.1)	10 (6.5)	6 (3.9)	449	205 (45.7)	127 (28.3)	82 (18.3)	27 (6.0)	8 (1.8)
Week 28	291	133 (45.7)	82 (28.2)	57 (19.6)	17 (5.8)	2 (0.7)	145	63 (43.4)	44 (30.3)	21 (14.5)	14 (9.7)	3 (2.1)	436	196 (45.0)	126 (28.9)	78 (17.9)	31 (7.1)	5 (1.1)
Week 32	256	122 (47.7)	70 (27.3)	48 (18.8)	15 (5.9)	1 (0.4)	127	56 (44.1)	36 (28.3)	21 (16.5)	11 (8.7)	3 (2.4)	383	178 (46.5)	106 (27.7)	69 (18.0)	26 (6.8)	4 (1.0)
Week 36	221	88 (39.8)	68 (30.8)	49 (22.2)	14 (6.3)	2 (0.9)	110	63 (57.3)	28 (25.5)	13 (11.8)	5 (4.5)	1 (0.9)	331	151 (45.6)	96 (29.0)	62 (18.7)	19 (5.7)	3 (0.9)
Week 40	192	83 (43.2)	62 (32.3)	30 (15.6)	14 (7.3)	3 (1.6)	91	55 (60.4)	21 (23.1)	4 (4.4)	8 (8.8)	3 (3.3)	283	138 (48.8)	83 (29.3)	34 (12.0)	22 (7.8)	6 (2.1)

Source: ISS Table 3.11.3.
QD = once daily.

Table 62. Subjects with Burning/Stinging and Itching, LTE Study 3003

Subjects with any LTS signs, (Tapinarof/Vehicle)	All Subjects, LTE Study 3003 n (%)
Week 4 (N=399/226/625)	417 (66.7)
Week 8 (N=371/215/586)	348 (59.4)
Week 12 (N=335/194/529)	307 (58)
Week 16 (N=317/177/494)	287 (58.1)
Week 20 (N=306/166/472)	262 (55.5)
Week 24 (N=294/155/449)	244 (54.3)
Week 28 (N=291/145/436)	240 (55)
Week 32 (N=256/127/383)	205 (53.5)
Week 36 (N=221/110/331)	180 (54.4)
Week 40 (N=192/91/283)	145 (51.2)

Source: Reviewer

Similar to what was seen in the 12-week studies, subjects experienced a high rate of irritation over the course of the LTE study 3003, consistently above 50%.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.8. Safety Analyses by Demographic Subgroups

Additional analyses to evaluate the safety profile of tapinarof cream, 1%, in several demographic subgroups was conducted. Because the safety database consists of two Phase 3 trials and a long-term extension study of limited size, the data should be interpreted with caution (particularly with respect to race due to very small numbers of subjects). Adverse events by age group, sex, and race are presented in the following tables.

Phase 3 Studies 3001 and 3002

Table 63. TEAEs by Age Group, Tapinarof Subjects, Phase 3 Studies 3001 and 3002

Preferred Term, n (%)	Ages 18-65 N = 584	Ages **≥66** N = 99
Folliculitis[a]	131 (22.4)	12 (12.1)
Nasopharyngitis[b]	72 (12.3)	6 (6.1)
Contact dermatitis[c]	36 (6.2)	9 (9.1)
Headache[d]	24 (4.1)	2 (2)
Pruritus[e]	21 (3.6)	5 (5.1)

Source: Reviewer
[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinusitis, sinus congestion, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, dermatitis allergic, hand dermatitis, neurodermatitis, rash
[d] Headache includes headache, migraine, tension headache
[e] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, genital burning sensation, pruritus generalized, pruritus genital, skin burning sensation, pain of skin

Of the most common TEAEs, folliculitis, nasopharyngitis, and headache occurred more frequently in subjects ages 18 to 65 during the Phase 3 trials 3001 and 3002. Subjects aged 66 and older were more likely to experience contact dermatitis (9.1%) and pruritus (5.1%) than younger subjects (6.2% and 3.6% respectively).

Table 64. TEAEs by Sex, Tapinarof Subjects, Phase 3 Studies 3001 and 3002

Preferred Term, n (%)	Males N = 401	Females N = 282
Folliculitis[a]	101 (25.2)	42 (14.9)
Nasopharyngitis[b]	42 (10.5)	36 (12.8)
Contact dermatitis[c]	24 (6)	21 (7.4)
Pruritus[d]	19 (4.7)	7 (2.5)
Headache[e]	14 (3.5)	12 (4.3)

Source: Reviewer
[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinusitis, sinus congestion, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, dermatitis allergic, hand dermatitis, neurodermatitis, rash
[d] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, genital burning sensation, pruritus generalized, pruritus genital, skin burning sensation, pain of skin
[e] Headache includes headache, migraine, tension headache

Folliculitis was more likely to occur in males (25.2%) compared to females (14.9%), which might be explained by the greater density and caliber of hairs on the trunk and extremities of men (where the cream is most likely to be applied). Pruritus was also more common in males (4.7%) than females (2.5%). Nasopharyngitis, contact dermatitis, and headache were slightly more common in females.

Table 65. Adverse Reactions by Race, Tapinarof Subjects, Phase 3 Studies 3001 and 3002

Preferred Term, n (%)	White N = 586	African-American N = 30	Asian N = 46
Folliculitis[a]	119 (20.3)	6 (20)	14 (30.4)
Nasopharyngitis[b]	70 (11.9)	3 (10)	2 (4.3)
Contact dermatitis[c]	45 (7.7)	0 (0)	0 (0)
Headache[d]	24 (4.1)	1 (3.3)	1 (2.2)
Pruritus[e]	21 (3.6)	0 (0)	5 (10.9)

Source: Reviewer
[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinusitis, sinus congestion, upper respiratory tract infection, viral sinusitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, dermatitis allergic, hand dermatitis, neurodermatitis, rash
[d] Headache includes headache, migraine, tension headache
[e] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, genital burning sensation, pruritus generalized, pruritus genital, skin burning sensation, pain of skin

Asians were also more likely to develop folliculitis (30.4%) and pruritus (10.9%) than whites (20.3% and 3.6% respectively) and blacks (20% and 0% respectively). However, the comparative samples of non-white subjects were relatively small, therefore no definitive conclusions can be drawn.

LTE Study 3003

Table 66. Adverse Reactions by Age Group, LTE Study 3003

Preferred Term, n (%)	Ages 18-65 N = 685	Ages **≥66** N = 78
Folliculitis[a]	174 (25.4)	11 (14.1)
Nasopharyngitis[b]	68 (9.9)	3 (3.8)
Contact dermatitis[c]	52 (7.6)	6 (7.7)
Pruritus[d]	21 (3.1)	3 (3.8)
Headache[e]	15 (2.2)	1 (1.3)

Source: Reviewer

[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinus congestion, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, application site dermatitis, hand dermatitis, neurodermatitis, rash, rash popular, rash pruritic
[d] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, skin irritation
[e] Headache includes headache, migraine, migraine with aura, tension headache

Similar to the Studies 3001 and 3002, during the LTE Study 3003, subjects ages 18 to 65 were more likely to experience folliculitis, nasopharyngitis, and headache. There were similar rates of contact dermatitis (7.6% in subjects 65 and under, 7.7% in subjects 66 and over). Pruritus was more common in subjects 66 and over (3.8%).

Table 67. Adverse Reactions by Sex, LTE Study 3003

Preferred Term, n (%)	Males N = 448	Females N = 315
Folliculitis[a]	135 (30.1)	50 (15.9)
Nasopharyngitis[b]	33 (7.4)	38 (12.1)
Contact dermatitis[c]	36 (8)	22 (7.0)
Pruritus[d]	16 (3.6)	8 (2.5)
Headache[e]	9 (2)	7 (2.2)

Source: Reviewer
[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinus congestion, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, application site dermatitis, hand dermatitis, neurodermatitis, rash, rash popular, rash pruritic
[d] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, skin irritation
[e] Headache includes headache, migraine, migraine with aura, tension headache

During the LTE Study 3003, folliculitis continued to be more common TEAE in males (30.1%) occurring almost twice the incidence of females. Contact dermatitis (8%) and pruritus (3.6%) and was also more common in males (compared to 7% and 2.5% respectively in females), and nasopharyngitis was more in females (12.1% compared to 7.4% in males).

Table 68. Adverse Reactions by Race, LTE Study 3003

Preferred Term, n (%)	White N = 643	African-American N = 39	Asian N = 51
Folliculitis[a]	153 (23.8)	7 (17.9)	16 (31.4)
Nasopharyngitis[b]	66 (10.3)	3 (7.7)	1 (2)
Contact dermatitis[c]	52 (8.1)	0 (0)	6 (11.8)
Headache[d]	16 (2.5)	0 (0)	0 (0)
Pruritus[e]	15 (2.3)	1 (2.6)	7 (13.9)

Source: Reviewer
[a] Folliculitis includes folliculitis, application site folliculitis, keratosis pilaris
[b] Nasopharyngitis includes nasopharyngitis, nasal congestion, pharyngitis, respiratory tract infection viral, rhinorrhea, sinus congestion, upper respiratory tract infection, viral pharyngitis, viral upper respiratory tract infection
[c] Contact dermatitis includes dermatitis, dermatitis contact, application site dermatitis, hand dermatitis, neurodermatitis, rash, rash popular, rash pruritic

[d] Headache includes headache, migraine, migraine with aura, tension headache
[e] Pruritus includes application site irritation/pain/pruritus, burning sensation, pruritus, skin irritation

Asian subjects experienced folliculitis (31.4%) and pruritus (13.9%) more frequently than white subjects (23.8% and 2.3% respectively) or African-American subjects (17.9% and 2.6% respectively).

Due to small number of African-American and Asian subjects included in the clinical studies for tapinarof, the conclusions regarding safety of tapinarof cream in these subgroups could not be made with any certainty.

8.2.9. Specific Safety Studies/Clinical Trials

Maximal Use Study (MuST) – DMVT-505-2002

The Applicant conducted a Phase 2a, open-label, maximal use study to evaluate the safety and systemic exposure of tapinarof cream, 1%, applied once daily in adults with extensive plaque psoriasis (PGA ≥3, BSA ≥20%). Twenty-one subjects were evaluated. Besides assessment for adverse events, subjects were assessed at Day 1, Day 15, and Day 29 for local tolerability with an investigator assessment (dryness, erythema, and peeling).

No subjects had a TEAE leading to study or drug discontinuation. There was one unrelated SAE of pancreatitis. Twelve (57.1%) subjects reported TEAEs, including 4 AESI of folliculitis (19%) and 4 AESI of headache (19%). All AEs of folliculitis and 2 AEs of headache were considered treatment-related. There were no cases of contact dermatitis. Although 1/3 of subjects experienced some degree of irritation upon initial application, the skin tolerability improved over the course of the month.

Table 69. Local Tolerability Scale Assessments (Dryness, Erythema, Peeling), MuST

	Day 1	Day 15	Day 29
Subjects, n	21	20	19
No irritation	14 (66.7%)	14 (70%)	17% (89.5%)
Mild	5 (23.8%)	5 (25%)	2 (10.5)
Moderate	1 (4.8%)	1 (5%)	0
Severe	1 (4.8%)	0	0
Very Severe	0	0	0

Source: Derived from Applicant Table 14.3.5.2.1, Study 2002

8.2.10. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct a clinical trial specifically to evaluate human carcinogenicity or tumor development. During the development program, the trial designs did not include

specific assessments of carcinogenicity or safety signals related to malignancy. For a discussion of the malignancy events that occurred during the Phase 3 studies, refer to Section 8.2.5.1.

Human Reproduction and Pregnancy

During the development program for tapinarof, the Applicant required females of reproductive potential to have a negative pregnancy test at Screening and to use at least one form of effective contraception. For hormonal contraceptives, subjects of child-bearing potential must have been on a stable dose for at least 4 weeks prior to the baseline visit. During the studies, urine pregnancy tests (UPTs) were performed on all females of child-bearing potential at Baseline and every 4 weeks (Weeks 4, 8, 12, and 16). This was also the case for Study 2002 (MuST) and the Study 3003 (LTE).

Table 70. Pregnancies, Tapinarof Subjects in the Study 3001, Study 3002 and LTE Study 3003

Study/Subj ID	Subj Age	Duration of exposure (days)	Date of last dose	Date preg'y reported	Outcome of pregnancy
3002/ (b) (6)	27	58	(b) (6)	(b) (6)	Not available at datalock
3003/ (b) (6)	28	320 [88 (3001) + 232 (3003)]	(b) (6)	(b) (6)	Lost to follow-up
3003/ (b) (6)	35	56	(b) (6)	(b) (6)	Full-term, healthy female
3003/ (b) (6)	39	68	(b) (6)	(b) (6)	Elective termination

Source: Reviewer

Several pregnancies occurred during the development program for tapinarof cream, 1%. There were no pregnancies reported in Study 2002, and only one pregnancy occurred in Study 3001 in a subject using the vehicle cream. Of the four reported pregnancies in tapinarof treated subjects, there was only one definitive outcome of a full-term healthy female baby.

In their review dated March 2, 2022, the Division of Pediatric and Maternal Health (DPMH) reviewed the Pharmacovigilance Database (PV) and found 5 subjects and 1 subject partner that became pregnant during the clinical trials. One additional subject had a positive urine pregnancy test but was confirmed to be not pregnant by a negative serum pregnancy test. As of November 25, 2020, 1 pregnancy was ongoing. Of the remaining 5 pregnancies, the outcomes were 4 healthy babies and 1 elective abortion. The DPMH reviewer felt these reports were insufficient to evaluate drug-associated risks, including major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Pediatrics and Assessment of Effects on Growth

Clinical studies were conducted only in adults. Because tapinarof cream, 1% is a new molecular entity, this NDA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). See Sections 10 (Pediatrics) and 13 (Postmarketing Requirements/Commitments).

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Tapinarof cream, 1%, has not been marketed in any jurisdiction. Therefore, no postmarketing safety data is available.

Expectations on Safety in the Postmarket Setting

Analysis of safety data did not identify any safety signals. There are no safety concerns that are expected to change the favorable benefits/risk assessment or lead to increased risk for tapinarof cream in the postmarket setting. However, additional safety data is required to characterize the safety profile of tapinarof cream in the pediatric population. Thus, the review team is recommending a PMR to assess the safety in pediatric subjects ages 2 to 17 (see Section 13). At the time of this review, the following study is ongoing:

Study ID (Location)	Study Title	Study Design	Treatment and Duration	Study Population	FSFV[a]	Planned Enrollment	Subject Exposure[b]
ONGOING							
DMVT-505-3004 (US, Canada)	A Phase 3 Study of Tapinarof for the Treatment of Plaque Psoriasis in Pediatric Subjects	Open-label, multicenter study to evaluate tapinarof cream, 1% in pediatric subjects with plaque psoriasis consisting of a 12-week primary treatment phase and an optional 40-week LTE. Subjects who choose to participate in the optional LTE will be treated based on their PGA score from the Week 12 visit.	Tapinarof cream, 1% is applied once daily for 12 weeks. For subjects who choose to participate in the optional LTE, treatment will continue to receive tapinarof cream, 1% QD until they achieve a PGA score of 0.	Male and female subjects ages 2 to 17 years old with a clinical diagnosis of chronic plaque psoriasis and stable disease for at least 3 months before the baseline visit	–[c]	100	–[c]

Source: Applicant Annual Report, IND 104601, December 17, 2021

This reviewer considers this pediatric study planned by the Applicant sufficient for long term safety evaluation.

8.2.12. Integrated Assessment of Safety

The safety database included 683 subjects from the Studies 3001 and 3002 treated with tapinarof cream, 1%, once daily for 12 weeks. In addition, the Applicant submitted the data from an open-label, long-term extension (LTE) study (Study 3003) of 763 subjects who rolled over from the Phase 3 vehicle-controlled studies 3001 and 3002. The subjects previously randomized to tapinarof during the 12-week studies continued use of tapinarof cream, 1% for up to an additional 40 weeks, while those who were initially randomized to vehicle cream switched to tapinarof cream for the 40-week LTE study.

The treatment with tapinarof cream, 1%, was not associated with an increased risk of mortality. One death due to myocardial infarction was reported during the LTE study 3003. This AE was considered unrelated to the study drug administration.

During the vehicle-controlled studies 3001 and 3002, SAEs were reported in 2.5% of subjects treated with tapinarof cream, 1% and none of subjects treated with vehicle cream. During the LTE Study 3003, 2.8% of subjects reported SAEs. None of the SAEs in the Phase 3 studies were considered related to treatment with tapinarof cream.

During the Phase 3 vehicle-controlled studies, adverse reactions occurred in 25% of tapinarof subjects compared to 3% of subjects treated with vehicle. The most frequently reported ARs were: folliculitis (19%), contact dermatitis (5%), and pruritus (2%). These trends continued in the LTE Study 3003: folliculitis (21%), contact dermatitis (5%), and pruritus (1%) being most common.

The Applicant also conducted active assessments of local tolerability. The majority of subjects treated with tapinarof cream, 1%, reported symptoms of burning/stinging and itching during the conduct of Studies 3001, 3002 and 3003.

The available data from the Phase 3 studies demonstrated that tapinarof cream, 1%, was safe in the treatment of adults with plaque psoriasis. This reviewer recommends no additional risk management assessments postmarketing. A pediatric PMR will be issued for tapinarof cream, 1%.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were generally consistent across trials and endpoints. There were no substantial differences in efficacy among subgroups. For handling of missing data, the results were similar across the various methods investigated to impute the missing data (see Table 18).

8.3.2. Conclusions and Recommendations

To establish the efficacy of tapinarof cream, 1% in the treatment of plaque psoriasis, the Applicant submitted the data from two adequate and well-controlled Phase 3 studies (DMVT-505-3001, and DMVT-505-3002). The studies enrolled subjects 18 years of age and older with plaque psoriasis with body surface area (BSA) involvement of 3% to 20% and a Physician's Global Assessment (PGA) score of 2 (mild), 3 (moderate), or 4 (severe). The studies assessed the primary endpoint of "treatment success" at Week 12. Treatment success was defined as a PGA score of 0 ("clear") or 1 ("almost clear") and a minimum two-point decrease from Baseline (i.e., PGA score of 0 or 1 if moderate disease at Baseline or PGA score of 0 if mild disease at Baseline).
In both studies, tapinarof cream, 1%, was superior to vehicle cream ($p<0.001$, difference [95% confidence interval (CI)]) for the primary endpoint of treatment success at Week 12. Efficacy data submitted by the Applicant demonstrates that tapinarof cream, 1%, is effective for its intended use in the target population.

The Applicant conducted a comprehensive assessment of the safety of tapinarof cream, 1% in the target population. The size of the safety database and the safety evaluations were adequate to characterize the safety profile of tapinarof cream, 1%.

To support the safety of tapinarof cream, the Applicant submitted the data from 683 subjects who took part in two vehicle-controlled studies 3001 and 3002 and the data from 763 subjects who took part in an open-label LTE Study 3003. In studies 3001 and 3002 the most frequently reported ARs were: folliculitis (19%); contact dermatitis (5%); and pruritus (2%). The safety results from Study 3003 were consistent to those reported in studies 3001 and 3002. The most frequently reported ARs were: folliculitis (21%); contact dermatitis (5%); and pruritus (1%).

This reviewer recommends to Division and Office leadership that tapinarof cream, 1% be approved for the treatment of adults with plaque psoriasis.

9 Advisory Committee Meeting and Other External Consultations

The Agency did not convene an Advisory Committee Meeting regarding this application because the no efficacy or safety issues were identified that required imput from Advisory Committee.

10 Pediatrics

Because tapinarof cream, 1% is a new molecular entity, it triggers the requirement under the PREA (21 USC 355c) for an assessment of its safety and effectiveness for the topical treatment of plaque psoriasis in pediatric patients unless said requirement is waived, deferred, or inapplicable. The Applicant submitted an initial Pediatric Study Plan (iPSP) on March 10, 2017 for the indications of atopic dermatitis and plaque psoriasis on March 10, 2017. Regarding the indication of treatment of plaque psoriasis in the iPSP, the Applicant requested a deferral of a 12-week open label safety and efficacy study in pediatric subjects 2 to 17 years of age and a maximal use PK (MUPK) study in pediatric subjects 2 to 17 years of age. They also requested a partial waiver of clinical studies in pediatric subjects ≤ 23 months of age.

After the change of sponsorship in 2018 to Dermavant, the Sponsor submitted an amended Agreed iPSP on March 28, 2019. In the Agreed iPSP, the Applicant requested a partial waiver for clinical studies in preterm newborn infants, term newborn infants, infants and toddlers ≤ 23 months of age due to studies being impossible or highly impractical, and a deferral for completion of a 12-week open label study in children and adolescents 2 to 17 years of age with collection of PK data, including additional sampling in a subset of subjects with high % BSA. The safety and PK data from the adult MuST (DMVT-505-2002) will be used to extrapolate systemic exposures and inform the PK sampling scheme for the pediatric study. At the September 10, 2019 meeting, the PeRC concurred with the Sponsor's requests for partial waiver and deferral of studies in pediatrics as described. A formal agreement letter was sent to the Sponsor on September 18, 2019.

The protocol for the 12-week safety, PK, and tolerability study in pediatric subjects with plaque psoriasis, DMVT-505-3004, was submitted to IND 104601 (SDN 121) on September 11, 2020. Based on the Agency's feedback, the Sponsor amended their protocol to enroll 100 pediatric subjects ages 2 to 11 with plaque psoriasis, with an optional 40-week extension study. There will be a PK maximal use sub-study of subjects ages 12 to 17 with BSA ≥10% and ages 2 to 11 with BSA ≥3%. During the course of this review, the Applicant reported that the DMVT-505-3004 study is ongoing.

On April 19, 2022, this information was presented to the PeRC. During this meeting, the PeRC reiterated their agreement with the Division's recommendation to grant a partial waiver to subjects under 2 years of age. They also agreed with the Division's recommendation for the following PMR:

Conduct an open-label, long-term safety and pharmacokinetic (PK) study in at least 100 pediatric subjects with plaque psoriasis ages 2 to <18 years. Subjects should be exposed to tapinarof cream, 1%, for a minimum of 52 weeks.

For PK evaluation under maximal use conditions, include at least 16 evaluable subjects ages 12 to <18 years with involved BSA ≥ 10%, and at least 8 subjects ages 2 to <12 years with involved

BSA ≥ 3% exposed to tapinarof cream, 1%, for a minimum of 12 weeks, with the option of continuing for a total of 52 weeks.

Study Completion: September 2024
Final Report Submission: March 2025

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI), patient package insert (PPI), instructions for use, and carton/container labels for VTAMA cream. The review team provided recommendations regarding PI, which are provided throughout this review. Madhuri R. Patel, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) reviewed the proposed PI, PPI, container labels, and carton labeling. DMEPA stated that, "The proposed Prescribing Information (PI) and Patient Package Instert (PPI) are acceptable from a medication error perspective. However, the proposed container labels and carton labeling can be improved" to "prevent wrong strength errors and deteriorated drug errors and to facilitate product identification." Dr. Patel made specific recommendations to address these concerns (refer to the review dated October 27, 2021).

The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the proposed PI, PPI, and carton/container labeling and label. Refer to the OPDP review by Laurie Buonaccorsi, PharmD, dated January 22, 2022. These comments are reflected in the final labeling. Table 58 provides the location in this review of the discussion of each section of the product labeling.

Table 71. Locations of Discussion of Significant High-Level Labeling Changes

Section	**Location of Reviewer Comments on Proposed Labeling**
1 Indications and Usage	Section 1.1
2 Dosage and Administration	Sections 1.1, 6.2.2
3 Dosage Forms and Strengths	Section 4.2
6 Adverse Reactions	Sections 8.2.4
8 Use in Specific Populations	Sections 6.3, 8.2.7, 8.2.9, 10, 13
11 Description	Section 4.2
12 Clinical Pharmacology	Section 6
13 Nonclinical Toxicology	Section 5
14 Clinical Studies	Section 8.1
16 How Supplied/Storage and Handling	Section 4.2 (and IQA Review)
17 Patient Counseling Information	Reflects the data in other sections of Labeling Sections 2 and 8

11.2. Patient Labeling

The Division of Medical Policy and OPDP reviewed and provided comments regarding the PPI and instructions for use for VTAMA Cream. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Jessica Chung, PharmD, MS and Laurie Buonaccorsi, PharmD, dated January 27, 2022.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and standard postmarketing surveillance are not warranted at this time.

13 Postmarketing Requirements and Commitment

The following PMR will be issued:

Conduct an open-label, long-term safety and pharmacokinetic (PK) study in at least 100 pediatric subjects with plaque psoriasis ages 2 to <18 years. Subjects should be exposed to tapinarof cream, 1%, for a minimum of 52 weeks.

For PK evaluation under maximal use conditions, include at least 16 evaluable subjects ages 12 to <18 years with involved BSA ≥ 10%, and at least 8 subjects ages 2 to <12 years with involved BSA ≥ 3% exposed to tapinarof cream, 1%, for a minimum of 12 weeks, with the option of continuing for a total of 52 weeks.

Study Completion: September 2024
Final Report Submission: March 2025

14 Division Director (DPT-II) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (Clinical) Comments

I concur with the review team's recommendation for approval.

Tapinarof is a small molecule aryl hydrocarbon receptor agonist and new molecular entity. The proposed indication is topical treatment of plaque psoriasis in patients 18 years of age and older. The proposed dosing regimen is to apply a thin layer to affected areas once daily. Tapinarof cream, 1% will be packaged and dispensed as a 60 g tube.

To support efficacy, the Applicant submitted two identically designed, randomized, double-blind, vehicle-controlled phase 3 trials (3001 and 3002); the primary endpoint in both trials was treatment success at Week 12 (defined as Physician Global Assessment [PGA] of clear/almost clear with at least two point reduction from baseline). In both trials, tapinarof cream, 1%, was superior to vehicle cream ($p<0.001$) for the primary endpoint, demonstrating effectiveness. Results of subgroup analyses and secondary endpoints were consistent with results of the primary endpoint.

The safety profile of tapinarof cream, 1% appears to have been adequately characterized. The clinical safety database included 683 subjects from the 12-week controlled trials (3001 and 3002) and 763 subjects from an open-label, long-term extension (3003) . The most commonly reported adverse reactions were folliculitis, contact dermatitis and pruritus.

The Applicant also conducted active assessments of local tolerability. In considering both investigator and subject assessment, the majority of subjects treated with tapinarof cream, 1%, reported symptoms of burning/stinging and itching during the conduct of Studies 3001, 3002 and 3003.

I concur with issuance of a PMR for an open-label, long-term safety and pharmacokinetic (PK) study, including PK evaluation under maximal use conditions, in pediatric subjects with plaque psoriasis ages 2 to <18 years.

17 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to approve NDA 215272 for tapinarof cream, 1% for the treatment of adults with plaque psoriasis. Tapinarof cream is a new molecular entity; it is an aryl hydrocarbon receptor (AhR) modulating agent, exerting its therapeutic effects via binding to AhR, thereby down-regulating several pro-inflammatory cytokines. Tapinarof cream, 1% is applied as a thin layer to affected areas once daily.

The efficacy of tapinarof cream, 1% was demonstrated in two identically designed randomized, vehicle-controlled clinical trials conducted in adult subjects with plaque psoriasis and body surface involvement of 3-20%. At baseline, the majority of subjects had moderate disease as assessed by Physician Global Assessment (PGA) score. In both trials, tapinarof cream, 1% was superior to vehicle for the primary endpoint of the proportion of subjects who achieve a PGA score of 0 (clear) or 1 (almost clear) with a ≥2-grade improvement from baseline at Week 12.

Tapinarof cream, 1% was generally well tolerated. In the 12-week vehicle-controlled trials, the most frequently reported adverse reactions on tapinarof cream, 1% were: folliculitis (19%), contact dermatitis (5%), and pruritus (2%). These reactions were also the most commonly reported reactions with long-term use of the drug. Product labeling will adequately describe these findings. A postmarketing trial will be required to assess the pharmacokinetics and long-term safety of tapinarof cream, 1% in pediatric subjects with plaque psoriasis ages 2 to <18 years.

18 Appendices

18.1. References

Armstrong, April W., et al. "Psoriasis Prevalence in Adults in the United States." *JAMA Dermatology* (Chicago, Ill.), vol. 157, no. 8, American Medical Association, 2021, pp. 940–46, https://doi.org/10.1001/jamadermatol.2021.2007.

Kim HO, Kang SY, Kim JC, Park CW, Chung BY. Pediatric Psoriasis: From New Insights into Pathogenesis to Updates on Treatment. *Biomedicines.* 2021 Aug 2;9(8):940. doi: 10.3390/biomedicines9080940. PMID: 34440145; PMCID: PMC8393839.

Lin, I. Chun, et al. "Psoriasis Severity and Cardiometabolic Risk Factors in a Representative US National Study." *American Journal of Clinical Dermatology*, vol. 22, no. 5, Springer International Publishing, 2021, pp. 719–30, https://doi.org/10.1007/s40257-021-00600-z.

Merola JF, Li T, Li W -Q., Cho E, Qureshi AA. Prevalence of psoriasis phenotypes among men and women in the USA. *Clinical & Experimental Dermatology*. 2016;41(5):486-489. doi:10.1111/ced.12805.

Parisi R, Iskandar IYK, Kontopantelis E, et al. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ*. 2020;369:m1590. Published 2020 May 28. doi:10.1136/bmj.m1590.

Takeshita, Junko, et al. "Psoriasis in the US Medicare Population: Prevalence, Treatment, and Factors Associated with Biologic Use." *Journal of Investigative Dermatology*, vol. 135, no. 12, Elsevier Inc, 2015, pp. 2955–63, https://doi.org/10.1038/jid.2015.296.

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Wang, Xiujuan et al. "Risk of non-melanoma skin cancer in patients with psoriasis: An updated evidence from systematic review with meta-analysis." *Journal of Cancer* vol. 11,5 1047-1055. 1 Jan. 2020, doi:10.7150/jca.37015

18.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and subinvestigators who participated in the covered clinical studies for VTAMA cream, 1%. Prior to study initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were the Phase 3 vehicle-controlled studies DMVT-505-3001 and DMVT-505-3002 which provided the primary data to establish effectiveness and safety of this product. The LTE Study DMVT-505-3003, which is not considered a covered clinical study, is included for completeness. Refer to Section 8.1.1 for the study designs.

The Applicant reported 2 investigators, 1 each in DMVT-505-3001 and DMVT-505-3002; both also participated in DMVT-505-3003. In response to an information request, the Applicant provided the following information:

- Both had significant payment of other sorts (SPOOS) for consulting services above $25,000 in the two-year period from April 2019 – December 2021.
    - Investigator 1 - The largest single payment was $6,375 for serving the Chair of the Advisory Board during a Company Town Hall Meeting Presentation. The other payments ranged from $350 to $3000 on 11 other occasions from (b) (6) .
    - Investigator 2 – This investigator had 2 payments of $6,375, one for the Internal Advisory Program for a Company Town Hall Meeting Presentation and for Advisory Panel Consulting, Medical Affairs. The other payments ranged from $750 to $4,125 on 6 other occasions from (b) (6) .
- Minimization of Potential Bias
    - Investigator 1 enrolled (b) (6) subjects out of 510 ((b) (6) %) in Trial 3001. Two of these subjects rolled over to Study 3003, which had 763 subjects ((b) (6) %).
    - Investigator 2 enrolled (b) (6) subjects out of 515 ((b) (6) %) in Trial 3002. All (b) (6) subjects rolled over to Study 3003, for a total of (b) (6) % of subjects.

Reviewer Comment: There appears to be minimal potential for trial/study bias from these investigators as a result of their financial arrangements.

Covered Clinical Study (Name and/or Number): DMVT-505-3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 47		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): DMVT-505-3002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 50		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): DMVT-505-3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 97		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

18.3. Nonclinical Pharmacology/Toxicology

18.3.1. Calculations for multiples of exposures

The following table summarizes the multiples of exposure based on AUC comparisons between the NOAEL from nonclinical studies and the maximum recommended human dose (MRHD) from clinical studies. (b) (4) .

Table 72. Summary of the multiples of exposure based on AUC comparisons between the NOAEL from nonclinical studies and the maximum recommended human dose (MRHD) from clinical studies

Study Type	Dose of Interest (NOAEL or Toxicity Dose)	Estimated AUC_{0-t} (ng·hr/mL)	Multiples of exposure
Human	1%	8*	---
28 day Subcutaneous Rat	1 mg/kg/day	54 (male) 48 (female)	7 6
	6 mg/kg/day	543 (male) 358 (female)	68 45
	30 mg/kg/day	3060 (male) 2140 (female)	383 268
26 Week Subcutaneous Rat	1 mg/kg/day	66 (male) 60 (female)	8 8
	6 mg/kg/day	677 (male) 401 (female)	85 50
	30 mg/kg/day	3830 (male) 2730 (female)	479 341

39 Week Dermal Minipig	NOAEL: 3%	4.7 (male) 5.6 (female)	0.6 0.7
Fertility Subcutaneous Injection Female Rats	NOAEL: 30 mg/kg/day	2140**	268
Embryofetal Subcutaneous Injection Female Rats	NOAEL: 34 mg/kg/day+	2140**	268
Embryofetal Subcutaneous Injection Female Rabbits	NOAEL: 1.0 mg/kg/day 3.0 mg/kg/day	128 239	16 30
Embryofetal Subcutaneous infusion Female Rabbits	NOAEL: 3.0 mg/kg/day	159	20
Prenatal and postnatal development	NOAEL: 1.0 mg/kg/day	48**	6
Juvenile Rat	NOAEL: 1/1.5 mg/kg/day Renal pelvis dilatation: 10/15 mg/kg/day	86.4 (combined) 1320 (combined)	11 165
Carcinogenicity (Rats)	NOAEL: 1.0 mg/kg/day	73.1 (male) 63.9 (female)	9 8
Carcinogenicity (Mice)	NOAEL: 3%	259 (male) 444 (female) Average: 351	32 56 44

Source: Reviewer

*: The systemic exposure observed in the psoriasis maximal use study (505-2002) following once daily application of VTAMA cream, 1% to up to 46% BSA (range:21% to 46% BSA) for 29 Days are at mean C_{max} of 0.9 ng/mL and mean AUC_{0-24} of 8 ng.h/mL. For the multiple of exposure calculations, it is more appropriate to use the mean AUC_{0-t} of 8 ng.h/mL instead of using the (b) (4) AUC_{0-t} value of (b) (4) ng.h/mL which was proposed by the applicant.

** For the reproductive and development study in rats, the sponsor did not conduct any toxicokinetic analysis and therefore there were no AUC data available. The AUC_{0-t} values for these studies were extrapolated from the 28-day rat subcutaneous study.

+Skeletal variations only were seen at this dose.

18.3.2. Nonclinical labeling

Recommended changes to the applicant's proposed wording for the nonclinical and related sections of 8.1, 8.2, 8.3, 12.1, and 13.1 of the label are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted. Although the applicant provided nonclinical data to factually support statements made in section 12.1, several portions are of unclear relevance to the mechanism of action and should be removed.

In addition, the average AUC_{0-t} of 8 ng.h/mL in the maximal use PK study is used for the AUC comparisons instead of using the (b) (4) AUC_{0-t} value of (b) (4) ng.h/mL as proposed by the applicant.

(b) (4)

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18.3.3. Review of Carcinogenicity Studies Conducted with Tapinarof

Study Title: GSK2894512A: A 2-Year Carcinogenicity Study by Subcutaneous Injection in the Wistar Han Rat

Study no.:	DMVT-505-9002
Study report location:	SDN 1, Module 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Tapinarof (GSK2894512A), lot # 2894C502, purity 100%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	MTD

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings: Subcutaneous administration of the cyclodextrin vehicle was associated with the development of subcutaneous sarcomas (primarily pleomorphic fibrosarcomas and fibrosarcomas) at the subcutaneous injection sites that resulted in all males being terminated early during week 60 and all females being terminated early during weeks 82-83. The formation of subcutaneous sarcomas due to cyclodextrin vehicle administration in this study is not clinically relevant since the clinical use will be topical administration of the tapinarof cream.

No tapinarof treatment related tumor findings were noted in this study.

Methods

Doses:	0 (saline control), 0 (vehicle control), 0.1, 0.3 and 1 mg/kg/day tapinarof
Frequency of dosing:	Once daily
Number/Sex/Group:	60 for main study; 9 for all toxicokinetic groups; additional 6 females/group for tapinorof toxicokinetic groups using 10% cyclodextrin vehicle
Dose volume:	3 mL/kg
Formulation/Vehicle:	30% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol) in sterile water 10% (w/v) aqueous sulfobutyl ether 7-β-cyclodextrin (Captisol) in sterile water (beginning day 372)
Route of administration:	SUBCUTANEOUS
Species:	RAT
Strain:	WISTAR HAN
Age:	6 weeks at initiation of treatment.
Comment on Study Design and Conduct:	Due to the presence of injection site tumors in vehicle control animals, dosing was discontinued for males on day 342 and restarted on day 372 with a lower concentration (10%) of cyclodextrin in the vehicle. Females were also dosed with a lower concentration (10%) of cyclodextrin in the vehicle beginning on day 372.
Dosing Comments (Dose Adjustments or Early Termination):	All male groups were terminated during week 60 when the number of surviving vehicle control males reached 20 males. All female groups were terminated during weeks 82/83 when the number of surviving vehicle control females reached 20 females. The termination criteria for male and female rats in this study received ECAC concurrence.
Dosing Solution Analysis:	Adequate. The concentrations of all doses were within ± 10% of their nominal values.

Observations and Results

Mortality

The male groups were terminated during week 60 when the number of surviving vehicle control males reached 20 males. The female groups were terminated during week 82/83 when the number of surviving vehicle control females reached 20 females. The mortality data is provided in the following table. The termination criteria received ECAC concurrence.

Table 73. Number of Surviving Animals in the Subcutaneous Rat Carcinogenicity Study

Number of Surviving Animals at 0, 6, 12, and 18 Months, and at Termination										
Sex	**Male**					**Female**				
Group	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Dose (mg/kg/day)	**0 (Saline)**	**0 (Vehicle)**	**0.1**	**0.3**	**1**	**0 (Saline)**	**0 (Vehicle)**	**0.1**	**0.3**	**1**
No. of Animals at Intverval (months):										
0	60	60	60	60	60	60	60	60	60	60
6 (Week 26)	60	60	60	59	60	59	60	59	60	60
12 (Week 52)	59	32	34	33	36	57	57	52	54	56
14 (Week 60)[a]	59	14	23	20	20					
18 (Week 78)	-	-	-	-	-	53	27	20	20	30
20/21 (Week 82/83)[a]	-	-	-	-	-	49	20	16	20	21

- = not applicable.
[a] Termination = beginning Week 60 for males; Weeks 82-83 for females.

Clinical Signs
An increase in palpable masses around the administration site was noted in vehicle control and all tapinarof dose group animals. No other treatment related effects on clinical signs were noted in this study.

Body Weights
No treatment related effects on body weight were noted in this study.

Feed Consumption
No treatment related effects on mean food consumption were noted in this study.

Ophthalmoscopy
No treatment related effects on ophthalmic findings were noted in this study

Gross Pathology
No tapinarof treatment related effects on gross pathology were noted in this study.

Gross pathology findings related to the cyclodextrin vehicle include: Masses at the injection site, discoloration and enlargement of the kidney, enlargement of the liver and enlargement of the spleen. The incidence of these findings was similar for vehicle control and low, mid and high dose groups.

Histopathology
Peer Review Conducted: Yes
Historical Control Provided for Tumor Incidence: Yes

Histopathology was performed on a standard list of tissues, plus any gross lesions, from all animals including both premature decedents and animals killed at terminal sacrifice.

Neoplastic
No statistically significant differences in tapinarof-related tumor incidence were observed in rats of either sex in this study, according to the statistical criteria used by the ECAC.

Subcutaneous administration of cyclodextrin elicited sarcomas in the subcutaneous tissue at the administration site in vehicle control and all tapinarof dose groups. Considering the similar incidence values among the groups administered the cyclodextrin alone and the groups administered all dose levels of tapinarof in combination with cyclodextrin, all neoplastic findings were attributed to the cyclodextrin vehicle. The cyclodextrin excipient is not contained in the to-be-marketed tapinarof cream formulation.

The Agency statistical reviewer, Dr. Feng Zhou, listed thyroid follicular cell adenoma in female rats as a tumor type that showed a dose response increase in incidence based on trend analysis. However, the pairwise comparison of the high dose incidence to the vehicle control incidence was not statistically significant. Therefore, this tumor finding is not considered treatment related. Refer to table below copied from Dr. Zhou's statistical review.

Table 74. Possible Statistically Significant Tumor Types in Rats

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Vehicle Control in Rats

SEX	Organ name	Tumor name	0 mg/kg/day Vehicle C P – Trend	0.1 mg/kg/day Low (L) P - VC vs. L	0.3 mg/kg/day Mid (M) P - VC vs. M	1 mg/kg/day High (H) P - VC vs. H	0 mg/kg/day Saline C (SC) P - VC vs. SC
Female Rats	Gland, Thyroid	Follicular Cell Adenoma	0/60 (21) 0.0055 *	0/60 (19) NS	0/60 (20) NS	4/60 (24) 0.0713	0/60 (27) NS

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.

Also, Dr. Zhou listed multiple tumor types at the injection site (i.e., fibrosarcoma, pleomorphic fibrosarcoma, myxosarcoma and fibroma) as statistically significant tumors based on pairwise comparison of saline control versus vehicle control. However, these tumor types are not clinically relevant for the topical administration of tapinarof cream.

Non Neoplastic
No tapinarof treatment related effects on non-neoplastic findings were noted in this study.

Cyclodextrin treatment related effects on non-neoplastic findings included cytoplasmic vacuolation of several tissues (kidney, parathyroid gland, prostate, and subcutaneous macrophages at injection sites) as well as secondary changes resulting from tissue damage associated with the expanding neoplasms at the injection sites. These findings were seen at a similar incidence and severity in cyclodextrin treated animals compared to low, mid and high dose animals. Therefore, all non-neoplastic findings were attributed to the cyclodextrin vehicle.

Toxicokinetics
Toxicokinetic data was obtained during the first 26 weeks of the study. Plasma samples were collected on Days 28 and 182 from all dose group toxicokinetic animals. Also, plasma samples were collected after 28 days of dosing an additional cohort of female animals with 0.1, 0.3 or 1 mg/kg/day tapinarof using the 10% cyclodextrin vehicle.

The systemic exposure increased in a dose dependent manner on days 28 and 182. There was no apparent difference in systemic exposure between male and female rats. The systemic exposure was similar on days 28 and 182.

There was no marked difference in systemic exposure between female rats using either the 30% cyclodextrin or 10% cyclodextrin vehicle.

The toxicokinetic parameters are summarized in the following tables.

Table 75. Toxicokinetic Parameters for Tapinarof (GSK2894512) on Days 28 and 182 in Male and Female Rats Dosed with the Vehicle Containing 30% Cyclodextrin (Captisol)

Parameter	Period	Males		
		Dose of GSK2894512 (mg/kg/day)		
		0.1	0.3	1
AUC_{0-t} (ng·h/mL)	Day 28	3.83	14.0	49.3
	Day 182	4.38	21.0	73.1
C_{max} (ng/mL)	Day 28	2.98	10.1	31.9
	Day 182	3.13	9.56	37.7
T_{max} (h)	Day 28	0.500	1.00	0.500
	Day 182	0.500	1.00	0.500
		Females		
AUC_{0-t} (ng·h/mL)	Day 28	2.52	9.46	39.8
	Day 182	3.90	18.9	63.9
C_{max} (ng/mL)	Day 28	2.08	8.05	30.4
	Day 182	3.19	11.5	39.7
T_{max} (h)	Day 28	0.500	0.500	0.500
	Day 182	0.500	0.500	0.500

Table 76. Toxicokinetic Parameters on Day 28 for Tapinarof (GSK2894512) in Female Rats Dosed with the Vehicle Containing 10% Cyclodextrin (Captisol)

Parameter	Female		
	Dose of GSK2894512 (mg/kg/day)		
	0.1	0.3	1
AUC_{0-t} (ng·h/mL)	NC	6.97	37.4
C_{max} (ng/mL)	2.11	6.70	35.6
T_{max} (h)	0.500	0.500	0.500

NC: Not calculated.

Study Title+: GSK2894512A: A 2-Year Dermal Carcinogenicity Study in the Mouse

Study no.: 20097894
Study report location: SDN 1, Module 4.2.3.4.1
Conducting laboratory and location: (b) (4)
GLP compliance: Yes
Drug, lot #, and % purity: Tapinarof cream 0.5%, batch # 162398059 and 162401291, purity 99.9%
Tapinarof cream 1.5%, batch # 162398069 and 162401296, purity 99.9%
Tapinarof cream 3.0%, batch # 162398073 and 162401348, purity 99.9%
Prior Exec CAC Dose Concurrence: Y
Basis for Dose Selection: MFD

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative
ECAC Carcinogenicity Conclusion (negative/ positive): Negative

Tumor Findings: No tapinarof cream treatment related tumor findings were noted in this study.

Methods

Doses:	0 (untreated control), 0 (vehicle cream control), 0.5%, 1.5%, and 3%
Frequency of dosing:	Once daily
Number/Sex/Group:	60 for main study; 30 for treated toxicokinetic animals; 6 for untreated and vehicle control toxicokinetic animals
Dose volume:	0.2 ml/day
Formulation/Vehicle:	Cream/ (b) (4) sodium citrate dihydrate, (b) (4) %, citric acid, (b) (4) %, EDTA disodium, (b) (4) triglycerides, (b) (4) , polysorbate 80, (b) (4) %, BHT, (b) (4) %, benzoic acid, (b) (4) %, propylene glycol, (b) (4) %, diethylene glycol monoethyl ether, (b) (4) % and water, (b) (4) %.
Route of administration:	TOPICAL
Species:	MOUSE
Strain:	CD1(ICR)
Age:	7 weeks at initiation of treatment
Comment on Study Design and Conduct:	Test article was applied daily to a clipped treatment area equivalent to 10% BSA. The treatment site was not occluded. The treatment site was wiped with gauze soaked in water prior to each daily treatment.
Dosing Comments (Dose Adjustments or Early Termination):	All female groups were terminated during week 98 when the number of surviving vehicle control females reached 20 females. All male groups were terminated during weeks 100 – 102 when the number of surviving mid dose males reached 15 males. The termination criteria for male and female mice in this study received ECAC concurrence.
Dosing Solution Analysis:	Adequate. The concentrations of all doses were within ± 10% of their nominal values.

Observations and Results

Mortality

There were no tapinarof cream related effects on survival. The number of surviving females in the vehicle control group declined to 20 in week 98. Therefore, all females were terminated in week 98. The number of surviving males in the mid dose group declined to 15 during week 100. Therefore, all males were terminated in weeks 100 - 102.

Clinical Signs

Tapinarof cream related clinical signs were limited to an increased incidence and/or frequency in males and females of red skin, skin lesions, and skin scabs. The incidence and severity of

these clinical signs were similar across the three dose groups. No other tapinarof cream related clinical signs were observed.

Body Weights
No treatment related effects on body weight were noted in this study.

Feed Consumption
No treatment related effects on food consumption were noted in this study.

Ophthalmoscopy
No treatment related effects on ophthalmic findings were noted in this study

Gross Pathology
Tapinarof cream related macroscopic signs were limited to an increased incidence and/or frequency in males and females of skin scabs. The incidence of these skin scabs was similar across the three dose groups.

Histopathology
Peer Review Conducted: Yes
Historical Control Provided for Tumor Incidence: Yes

Histopathology was performed on a standard list of tissues from all treated animals killed at scheduled sacrifice, plus all main-study premature decedents from all groups. Histopathological examination was performed for all gross lesions sampled at necropsy from animals in all groups.

Neoplastic
No statistically significant differences in tapinarof cream related tumor incidence were observed in mice of either sex in this study, according to the statistical criteria used by the ECAC.

Dr. Zhou listed papilloma in treated skin of male and female mice as a tumor type that showed a dose response increase in incidence based on trend analysis. However, the pairwise comparison of the high dose group and vehicle control group was not statistically significant. Therefore, these tumors are not considered tapinarof cream related tumors.

Table 77. Possible Statistically Significant Tumor Types in Mice

Tumor Types with Statistically Significant (at 0.05 significant level) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Placebo in Mice

SEX	Organ name	Tumor name	0 mg/kg/day Placebo P - Trend	22.3 mg/kg/day Low (L) P - C vs. L	64.6 mg/kg/day Mid (M) P - C vs. M	133.5 mg/kg/day High (H) P - C vs. H	0 mg/kg/day Sham P - C vs. PC
Male	Skin/Skin treated	Papilloma	0/60 (43)	1/60 (36)	2/60 (36)	3/59 (37)	0/60 (43)
			0.0424	0.4557	0.2045	0.0946	NS
Female	Skin Treated	Papilloma	0/60 (35)	1/60 (36)	1/60 (35)	4/59 (36)	0/60 (38)
			0.0148 *	0.5070	0.5000	0.0606	NS

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NS = Not significant.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively.

Non Neoplastic

Tapinarof cream treatment related effects on non-neoplastic findings included increased incidence and/or severity of minimal to moderate epidermal hyperplasia, minimal to mild mixed cell inflammation, minimal to moderate erosion/ulcer, minimal to mild dermal fibrosis at the treatment site. There was a dose dependent increase in the incidence and severity of these treatment site non-neoplastic findings.

Additional tapinarof cream treatment related effects on non-neoplastic findings included increased hematopoiesis in the spleen, increased myeloid to erythroid ratio in bone marrow and increased plasmacytosis in the mandibular and mesenteric lymph nodes in low, mid and high dose animals. These additional non-neoplastic findings were probably secondary to the effects noted at the treatment site.

Toxicokinetics

Toxicokinetic data was obtained during the first 26 weeks of the study. Plasma samples were collected on Days 28 and 182 from all dose group toxicokinetic animals.

There was a great variability in the plasma levels of tapinarof in all dose groups which is not uncommon in dermal studies. The systemic exposure appeared to increase with increased dose but did not appear to be a dose dependent increase on days 28 and 182. There was no apparent difference in systemic exposure between male and female mice. The systemic exposure appeared to be similar on days 28 and 182.

The toxicokinetic parameters are summarized in the following table.

Table 78. Toxicokinetic Parameters for Tapinarof (GSK2894512) on Days 28 and 182 in Male and Female Mice

Period	Dose Group	Dose Concentration (%)	Sex	Dose (mg/kg/day)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)
Day 28	3	0.5	M	29	37.7	23.6	1.00
			F	34	33.8	19.1	1.00
	4	1.5	M	85	188	97.9	1.00
			F	104	146	57.8	2.00
	5	3.0	M	169	560	110	4.00
			F	198	715	281	1.00
Day 182	3	0.5	M	23	14.1	3.66	1.00
			F	27	117	31.9	2.00
	4	1.5	M	67	96.5	31.6	1.00
			F	86	255	46.2	2.00
	5	3.0	M	127	259	66.4	1.00
			F	148	444	95.7	4.00

18.4. OCP Appendices (Technical documents supporting OCP recommendations)

18.4.1. Summary of Bioanalytical Methods and Validation

A tabular display of the bioanalytical assays used in the clinical development of tapinarof is shown in Table 76.

Table 79. Bioanalytical Assays Utilized in Support of Clinical Studies

Bioanalytical Assay	Bioanalytical Facility	Clinical Studies Supported	Validation Report and Amendments
07-0049	(b) (4)	WBI-1001-101 WBI-1001-201	07-0049-VPRT-01 (includes amendment 07-0049-VPRT-AM-01)
GSK2894512HUPLVA		IPS117191	2013N183118 2013N184001
G28HPP		201851 200920 203120 203121	2015N242183 (includes addendums 2016N280109, and 2017N327380)
GSK2894512HUTHVALA	GlaxoSmithKline, Ware, UK	201661	2014N221060
521-1834	(b) (4)	DMVT-505-2002 DMVT-505-3001 DMVT-505-3002	521-1834 VAR AM3

All validated assays used in support of the clinical studies were shown sufficiently accurate and precise over the ranges tested within the validation studies. The characteristics and performance of each of the validated methods are described in Table 80-Table 84.

Table 80. Summary Method Performance - 07-0049

Bioanalytical method validation report name, amendments, and hyperlinks	**Validation of a Liquid Chromatography Tandem Mass Spectrometry Assay Method for the Determination of WBI-1001 in Human Plasma (07-0049-VRPT-01, Includes amendment 07-0049-VRPT-01-AM-01)**		
Method description	Tapinarof (WBI-1001) and internal standard (IS), WBI-1062, were extracted from human plasma using a liquid-liquid extraction. The extracts were analyzed by HPLC-MS/MS using an atmospheric pressure electrospray interface in negative ion mode with multiple reaction monitoring.		
Materials used for standard calibration curve and concentration	Calibration standards were prepared in human plasma and analyzed in duplicate in each analytical batch. **Standard concentration levels:** 0.1, 0.2, 1, 2, 5, 10, 20, 35 and 50 ng/mL		
Validated assay range	0.1 to 50 ng/mL		
Material used for QCs and concentration	QC samples were prepared in human plasma and analyzed in replicates of five in each analytical batch. **QC concentration levels:** 0.1, 0.3, 8, 25, and 40 ng/mL		
Source and lots of reagents	Tapinarof, Lot AF04061, (b) (4)		
Regression model and weighting	Linear, 1/x2		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Table 3 of 07-0049-VRPT-01
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-3.0 to 2.2%	Table 3 of 07-0049-VRPT-01
	Cumulative precision (% CV) from LLOQ to ULOQ	≤ 9.3%	Table 3 of 07-0049-VRPT-01
Performance of QCs during accuracy and precision runs	**Accuracy (% bias) in QCs** Within run: Between run:	 -13.3 to 9.4% -2.5 to 1.0%	Tables 4, and 5 of 07-0049-VRPT-01
	Precision (%CV) in QCs Within run: Between run:	 ≤ 13.3% ≤ 8.8%	Tables 4, and 5 of 07-0049-VRPT-01

Selectivity	6 lots of blank human plasma were evaluated, and no significant interference was observed for tapinarof or the internal standard.	Table 25 of 07-0049-VRPT-01
Matrix effect	The effect of matrix on the ionization of tapinarof and internal standard was evaluated in 5 lots of plasma. No issues were noted. **Range of matrix enhancement for tapinarof:** 1.1 to 3.5% **Range of matrix enhancement for IS:** 3.2 to 3.4%	Tables 10, and 11 of 07-0049-VRPT-01
Specificity	6 lots of blank human plasma were evaluated by spiking tapinarof in at 0.1 ng/mL. Five of six lots met the acceptance criteria of % bias ≤ 20%. **Range for % bias:** -22.6 to 5.8%	Table 25 of 07-0049-VRPT-01
Interference	No concomitant medication interference testing was conducted.	Not Applicable
Hemolysis effect	Not evaluated in this validation	Not Applicable
Lipemic effect	Not evaluated in this validation	Not Applicable
Dilution linearity	QCs were prepared at 100 ng/mL and diluted with a factor of 2.5. **Range for % bias:** -3.8 to 0.6 %	Table 7 of 07-0049-VRPT-01
Bench-top stability	22 hours at room temperature	Table 15 of 07-0049-VRPT-01
Process stability	Reinjection reproducibility established for 174.87 hours at ambient temperature	Figures 18, and 19 of 07-0049-VRPT-01
Freeze-Thaw stability	3 cycles from -40°C and -70°C	Tables 13, and 14 of 07-0049-VRPT-01
Long-term storage	199 days at -40°C and -70°C	Tables 5, and 6 of Amendment 1 (07-0049-VRPT-01-AM-01)
Carry over	No specific carryover evaluation is referenced in the validation report.	Not Applicable
Recovery	Mean recovery range for tapinarof: 90.1 to 91.3% Mean recovery range for IS: 87.8 to 90.8%	Tables 8, and 9 of 07-0049-VRPT-01

CV = coefficient of variation; IS = internal standard; HPLC-MS/MS = high-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; QC = quality control

Table 81. Summary Method Performance - GSK2894512HUPLVA

Bioanalytical method validation report name, amendments, and hyperlinks	**GSK2894512: The Validation of a Method for the Determination of GSK2894512 in 50/50 Human Plasma/20nM Ascorbic Acid Aqueous Solution (v/v) (range 0.1 to 100 ng/mL, corresponding to 0.2 to 200 ng/mL in untreated plasma) using UHPLC-MS/MS (2013N183118, 2013N184001)**		
Method description	Tapinarof (GSK2894512) was extracted from 50/50 human plasma/20mM ascorbic acid by protein precipitation using acetonitrile containing isotopically labelled tapinarof ([$2H_7$]-GSK2894512) as an internal standard (IS). The extracts were analyzed by UHPLC-MS/MS using a TurboIonSpray® interface in negative ion mode with multiple reaction monitoring.		
Materials used for standard calibration curve and concentration	Calibration standards were prepared in 50/50 human plasma/20mM ascorbic acid and analyzed in duplicate in each analytical batch. **Standard concentration levels:** 0.2, 0.6, 2, 6, 20, 60, 160, and 200 ng/mL		
Validated assay range	0.2 to 200 ng/mL		
Material used for QCs and concentration	QC samples were prepared in 50/50 human plasma/20mM ascorbic acid and analyzed in replicates of six in each analytical batch. **QC concentration levels:** 0.2, 0.6, 6, 150, and 200 ng/mL		
Source and lots of reagents	Tapinarof, Lot U26136-95-1, USA		
Regression model and weighting	Linear, 1/x2		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 2 of 2013N183118
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-3.5 to 3.4%	Table 2 of 2013N183118
	Cumulative precision (% CV) from LLOQ to ULOQ	≤ 12.2%	Table 2 of 2013N183118
Performance of QCs during accuracy and precision runs	**Accuracy (% bias) in QCs** Within run: Between run:	 -3.7 to 14.7% 0.3 to 6.8%	Table 5 of 2013N183118
	Precision (%CV) in QCs Within run: Between run:	 ≤ 12.0% ≤ 5.1%	Table 5 of 2013N183118

Selectivity	6 lots of blank human plasma were evaluated, and no significant interference was observed for tapinarof or the internal standard.	Section 12.1 of 2013N183118
Matrix effect	The effect of matrix on the ionization of tapinarof and internal standard was evaluated in 8 lots of plasma. No issues were noted. **Range for IS normalization matrix factor:** 0.94 to 0.98	Table 4 of 2013N183118
Specificity	No quantitative specificity experiment was performed.	Not Applicable
Interference	No concomitant medication interference testing was conducted.	Not Applicable
Hemolysis effect	1 lot of hemolyzed plasma was evaluated to assess the matrix effect. No issues noted.	Table 4 of 2013N183118
Lipemic effect	1 lot of hyperlipemic plasma was evaluated to assess the matrix effect. No issues noted.	Table 4 of 2013N183118
Dilution linearity	QCs were prepared at 750 ng/mL and diluted with a factor of 10. **Range for % bias:** -5.8 to 1.7 %	Table 17 of 2013N183118
Bench-top stability	25 hours at room temperature	Table 10 of 2013N183118
Process stability	27 hours at room temperature	Table 16 of 2013N183118
Freeze-Thaw stability	3 cycles from -20°C and -80°C	Tables 14 and 15 of 2013N183118
Long-term storage	112 days at -20°C and 376 days at -80°C	Tables 4, and 5 of 2013N184001
Carry over	Carry over was less than 5% of the response at the LLOQ for the internal standard. On one occasion, carryover was more than 20% of the response at the LLOQ.	Section 12.2 of 2013N183118
Recovery	Mean recovery range for tapinarof: 92.5 to 95.9%	Table 3 of 2013N183118

CV = coefficient of variation; IS = internal standard; UHPLC-MS/MS = ultra-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; QC = quality control

Table 82. Summary Method Performance - G28HPP

Bioanalytical method validation report name, amendments, and hyperlinks	**Validation of a Method for the Determination of GSK2894512 in Ascorbic Acid Treated Human Plasma by HPLC with MS/MS Detection (2015N242183, Includes addendums 2016N280109, and 2017N327380)**		
Method description	Tapinarof (GSK2894512) and its internal standard ([$^2H_7$]- GSK2894512) were extracted from ascorbic acid treated human plasma using a liquid-liquid extraction. The extracts were analyzed by HPLC-MS/MS using a TurboIonSpray® interface in negative ion mode with multiple reaction monitoring.		
Materials used for standard calibration curve and concentration	Calibration standards were prepared in human plasma, then an equal volume of 20mM ascorbic acid was added to each standard. Standards were analyzed in singlet in each analytical batch. **Standard concentration levels:** 0.04, 0.08, 0.25, 0.8, 3, 10, 16 and 20 ng/mL		
Validated assay range	0.04 to 20 ng/mL		
Material used for QCs and concentration	QC samples were prepared in human plasma, then an equal volume of 20mM ascorbic acid was added to each QC. QCs were analyzed in replicates of six in each analytical batch. **QC concentration levels:** 0.04, 0.12, 1, and 15 ng/mL		
Source and lots of reagents	Tapinarof, Lot U25900-12-1, USA		
Regression model and weighting	Linear, $1/x^2$		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 6.6 of 2015N242183
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-2.8 to 3.5%	Table 6.6 of 2015N242183
	Cumulative precision (% CV) from LLOQ to ULOQ	≤ 3.2%	Table 6.6 of 2015N242183
Performance of QCs during accuracy and precision runs	**Accuracy (% bias) in QCs** Within run: Between run:	 -6.3 to 4.5% -2.5 to 1.3%	Table 6.8 of 2015N242183
	Precision (%CV) in QCs Within run: Between run:	 ≤ 11.2% ≤ 9.1%	Table 6.8 of 2015N242183

Selectivity	6 lots of blank human plasma were evaluated and no interference peaks were detected for tapinarof or its internal standard.	Section 4.3 of 2015N242183
Matrix effect	The effect of matrix on the ionization of tapinarof and internal standard was evaluated in 6 lots of plasma. No issues were noted. **Range for IS normalization matrix factor:** 0.940 to 0.961	Table 6.4 of 2015N242183
Specificity	6 lots of blank human plasma were evaluated by spiking tapinarof in at 0.12 ng/mL. All lots met the acceptance criteria of % bias ≤ 15%. **Range for % bias:** -6.7 to 2.5%	Table 6.2 of 2015N242183
Interference	QCs prepared at 0.12 ng/mL of tapinarof were spiked with a cocktail containing ibuprofen, aspirin, diclofenac, and naproxen and analyzed in replicates of three. The presence of ibuprofen, aspirin, diclofenac, and naproxen did not impact the ability to measure tapinarof. **Range for % bias:** -8.3 to 3.3 %	Table 6.3 of 2015N242183
Hemolysis effect	QCs were prepared in hemolyzed plasma at 0.12 and 15 ng/mL and analyzed in replicates of six. No issues were noted. **Range for % bias at 0.12 ng/mL:** 1.7 to 5.8% **Range for % bias at 15 ng/mL:** -0.7 to 3.3%	Table 6.23 of 2015N242183
Lipemic effect	QCs were prepared in hyperlipidemic plasma at 0.12 and 15 ng/mL and analyzed in replicates of six. The original experiment did not meet acceptance criteria at 15 ng/mL with a mean % bias of -15.3 with suppression of analyte and IS signal noted. The experiment was repeated successfully twice at 0.12 and 15 ng/mL in replicates of six. **Range for % bias at 0.12 ng/mL:** -15.0 to 8.3% **Range for % bias at 15 ng/mL:** -14.7 to 0.0%	Table 6.24 of 2015N242183
Dilution linearity	QCs were prepared at 100 ng/mL and diluted with a factor of 10. **Range for % bias:** -2.5 to 1.3 %	Table 6.8 of 2015N242183
Bench-top stability	25 hours at room temperature	Table 6.19 of 2015N242183
Process stability	50 hours at 2 to 8°C	Table 6.16 of 2015N242183
Freeze-Thaw stability	4 cycles from -10 to -30°C 4 cycles from -60 to -80°C	Table 6.18 of 2015N242183
Long-term storage	85 days at -10 to -30°C 310 days at -60 to -80°C	Table 6.22 of 2015N242183 Table 6.5 of Addendum 2 (2017N327380)
Carry over	Carryover was assessed in each analytical batch as per the validation plan. Carryover of >20% that did not impact the tests conducted within was noted in one batch.	Section 4.6 of 2015N242183
Recovery	Mean recovery range for tapinarof: 52.2 to 60.5% Mean recovery range for IS: 52.9 to 62.4%	Table 6.10 of 2015N242183

CV = coefficient of variation; IS = internal standard; HPLC-MS/MS = high-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; QC = quality control

Table 83. Summary Method Performance - GSK2894512HUTHVALA

Bioanalytical method validation report name, amendments, and hyperlinks	**The Abbreviated Validation of a Method for the Determination of GSK2894512 (range 0.5 to 1000 ng/mL) in Human Skin Homogenate using UHPLC-MS/MS (2014N221060)**		
Method description	Tapinarof (GSK2894512) was extracted from human skin homogenate by protein precipitation using acetonitrile with 0.1% ammonia solutions containing isotopically labelled tapinarof ([$2H_2 13C_6$]- GSK2894512) as an internal standard (IS). The extracts were analyzed by UHPLC-MS/MS using a TurboIonSpray® interface in negative ion mode with multiple reaction monitoring.		
Materials used for standard calibration curve and concentration	Calibration standards were prepared in human skin homogenate and analyzed in duplicate in each analytical batch. **Standard concentration levels:** 0.5, 1, 5, 10, 100, 400, 800, and 1000 ng/mL		
Validated assay range	0.5 to 1000 ng/mL		
Material used for QCs and concentration	QC samples were prepared in human skin homogenate and analyzed in replicates of six in each analytical batch. **QC concentration levels:** 0.5, 1.5, 10, 800, and 1000 ng/mL		
Source and lots of reagents	Tapinarof, Lot U25900-12-1, USA		
Regression model and weighting	Linear, 1/x2		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Table 1 of 2014N221060
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-6.3 to 5.9%	Table 1 of 2014N221060
	Cumulative precision (% CV) from LLOQ to ULOQ	Not applicable	Not Applicable
Performance of QCs during accuracy and precision runs	**Accuracy (% bias) in QCs** Within run: Between run:	 -5.7 to 9.5% Not applicable	Table 2 of 2014N221060
	Precision (%CV) in QCs Within run: Between run:	 ≤ 6.4% Not applicable	Table 2 of 2014N221060

Selectivity	A double blank sample was included in the validation run and no unacceptable interferences were observed.	Section 4.1 of 2014N221060
Matrix effect	No evaluation of matrix effect was conducted in this study	Not Applicable
Specificity	No quantitative specificity experiment was conducted.	Not Applicable
Interference	Lidocaine and epinephrine at 1 mg/mL were added to QCs containing 0.5 ng/mL of tapinarof. The presence of lidocaine and epinephrine did not impact the ability to measure tapinarof. **Range for % bias:** 4.8 to 39.0 %	Table 9 of 2014N221060
Hemolysis effect	Not Applicable	Not Applicable
Lipemic effect	Not Applicable	Not Applicable
Dilution linearity	QCs were prepared at 2000 ng/mL and diluted with a factor of 10. **Range for % bias:** 1.1 to 5.4 %	Table 8 of 2014N221060
Bench-top stability	24 hours at ambient temperature	Table 5 of 2014N221060
Process stability	Reinjection reproducibility established for 96 hours at ambient temperature	Table 7 of 2014N221060
Freeze-Thaw stability	1 cycle from -80°C	Table 6 of 2014N221060
Long-term storage	**211 days at -80°C in human skin homogenate** QCs used in sample analysis were prepared on 25Mar15 and analyzed on 22Oct15.	Sections 1 and 5.1 of 2016N284109
Carry over	No specific carryover evaluation is referenced in the validation report.	Not Applicable
Recovery	No evaluation of recovery was conducted in this study	Not Applicable

CV = coefficient of variation; IS = internal standard; UHPLC-MS/MS = ultra-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; QC = quality control

Table 84. Summary Method Performance - 521-1834

Bioanalytical method validation report name, amendments, and hyperlinks	**Validation of a Method for the Determination of Tapinarof and Tapinarof Sulfate in Human Plasma by LC-MS/MS (521-1834 VAR AM3)**		
Method description	Tapinarof and tapinarof sulfate were extracted from human plasma using a solid phase extraction. The extracts were analyzed by HPLC-MS/MS using a TurboIonSpray® interface in negative ion mode with multiple reaction monitoring.		
Materials used for standard calibration curve and concentration	Calibration standards were prepared in human plasma and analyzed in duplicate in each analytical batch. **Standard concentration levels (tapinarof):** 50, 100, 250, 750, 2500, 7500, 22500, and 25000 pg/mL **Standard concentration levels (tapinarof sulfate):** 10, 20, 50, 150, 500, 1500, 4500, and 5000 pg/mL		
Validated assay range	50 to 25000 pg/mL for tapinarof, 10 to 5000 pg/mL for tapinarof sulfate		
Material used for QCs and concentration	QC samples were prepared in human plasma and analyzed in replicates of six in each analytical batch. **QC concentration levels (tapinarof):** 50, 150, 1250, 10000, and 20000 pg/mL **QC concentration levels (tapinarof sulfate):** 10, 30, 250, 2000, and 4000 pg/mL		
Source and lots of reagents	Tapinarof, Lot 2894C502, USA		
Regression model and weighting	Linear, 1/x2		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ (tapinarof)	8	Table 5 of 521-1834 VAR AM3
	Number of standard calibrators from LLOQ to ULOQ (tapinarof sulfate)	8	Table 6 of 521-1834 VAR AM3
	Cumulative accuracy (% bias) from LLOQ to ULOQ (tapinarof)	-1.6 to 1.6%	Table 5 of 521-1834 VAR AM3
	Cumulative accuracy (% bias) from LLOQ to ULOQ (tapinarof sulfate)	-0.4 to 0.7%	Table 6 of 521-1834 VAR AM3
	Cumulative precision (% CV) from LLOQ to ULOQ (tapinarof)	≤ 8.5%	Table 5 of 521-1834 VAR AM3
	Cumulative precision (% CV) from LLOQ to ULOQ (tapinarof sulfate)	≤ 4.1%	Table 6 of 521-1834 VAR AM3
Performance of QCs during accuracy and precision runs	**Accuracy (% bias) in QCs (tapinarof)** Within run: Between run:	 -0.7 to 4.5% 0.0 to 3.5%	Table 9 of 521-1834 VAR AM3
	Precision (%CV) in QCs (tapinarof) Within run: Between run:	 ≤ 10.4% ≤ 7.0%	Table 9 of 521-1834 VAR AM3
	Accuracy (% bias) in QCs (tapinarof sulfate) Within run: Between run:	 -0.3 to 9.0% 0.8 to 6.0%	Table 10 of 521-1834 VAR AM3
	Precision (%CV) in QCs (tapinarof sulfate) Within run: Between run:	 ≤ 3.8% ≤ 3.5%	Table 10 of 521-1834 VAR AM3

Selectivity (tapinarof)	Six lots of blank human plasma were tested and no unacceptable interference peaks were present for tapinarof or its internal standard.	Table 11 of 521-1834 VAR AM3
Selectivity (tapinarof sulfate)	Six lots of blank human plasma were tested and no unacceptable interference peaks were present for tapinarof sulfate or its internal standard.	Tables 12 of 521-1834 VAR AM3
Matrix effect (tapinarof)	The effect of matrix on the ionization of tapinarof was evaluated in 6 lots of plasma. No issues were noted. **Range for IS normalization matrix factor:** 0.953 to 1.084	Table 25 of 521-1834 VAR AM3
Matrix effect (tapinarof sulfate)	The effect of matrix on the ionization of tapinarof sulfate was evaluated in 6 lots of plasma. No issues were noted. **Range for IS normalization matrix factor:** 1.004 to 1.100	Table 26 of 521-1834 VAR AM3
Specificity (tapinarof)	Six lots of blank human plasma were tested by spiking six lots with tapinarof at 50 pg/mL. Five out of six lots met the acceptance criteria of % bias ≤ 20%. **Range for % bias:** -4.6 to 33.4%	Table 13 of 521-1834 VAR AM3
Specificity (tapinarof sulfate)	Six lots of blank human plasma were tested by spiking six lots with tapinarof sulfate at 10 pg/mL. Four out of six lots met the acceptance criteria of % bias ≤ 20%. **Range for % bias:** 9.0 to 22.0%	Table 14 of 521-1834 VAR AM3
Interference	No concomitant medication interference testing was conducted.	Not Applicable
Hemolysis effect (tapinarof)	Two concentrations of tapinarof, 150 and 20000 pg/mL, were prepared in 2% hemolyzed plasma and analyzed in replicates of five. Hemolyzed matrix was shown to not have an impact on assay performance. **Range for % bias at 150 pg/mL:** -16.0 to -0.7% **Range for % bias at 20000 pg/mL:** -2.5 to -1.5%	Table 15 of 521-1834 VAR AM3
Hemolysis effect (tapinarof sulfate)	Two concentrations of tapinarof sulfate, 30 and 4000 pg/mL, were prepared in 2% hemolyzed plasma and analyzed in replicates of five. Hemolyzed matrix was shown to not have an impact on assay performance. **Range for % bias at 30 pg/mL:** -3.7 to 3.7% **Range for % bias at 4000 pg/mL:** -3.8 to -1.0%	Table 16 of 521-1834 VAR AM3
Lipemic effect (tapinarof)	Two concentrations of tapinarof, 150 and 20000 pg/mL, were prepared in lipemic plasma and analyzed in replicates of five. Lipemic matrix was shown to not have an impact on assay performance. **Range for % bias at 150 pg/mL: -**6.0 to 0.7% **Range for % bias at 20000 pg/mL:** -2.0 to -0.5%	Table 17 of 521-1834 VAR AM3
Lipemic effect (tapinarof sulfate)	Two concentrations of tapinarof sulfate, 30 and 4000 pg/mL, were prepared in lipemic plasma and analyzed in replicates of five. Lipemic matrix was shown to not have an impact on assay performance. **Range for % bias at 30 pg/mL:** -3.7 to 5.3% **Range for % bias at 4000 pg/mL:** -2.5 to 0.3%	Table 18 of 521-1834 VAR AM3
Dilution linearity (tapinarof)	QCs were prepared at 100000 pg/mL and diluted with a factor of 50. **Range for % bias:** -4.7 to -0.9 %	Table 19 of 521-1834 VAR AM3
Dilution linearity (tapinarof sulfate)	QCs were prepared at 20000 pg/mL and diluted with a factor of 50. **Range for % bias:** -3.5 to -0.5 %	Table 20 of 521-1834 VAR AM3

Bench-top stability	24 hours in an ice bath	Tables 31, and 32 of 521-1834 VAR AM3
Process stability	153 hours at 4°C	Tables 37, and 38 of 521-1834 VAR AM3
Freeze-Thaw stability	5 cycles from -20 and -70°C	Tables 33, 34, 35 and 36 of 521-1834 VAR AM3
Long-term storage	368 days at -20 and -70°C	Tables 43, 44, 45, and 46 of 521-1834 VAR AM3
Carry over	Carry over was within acceptable limits for all validation runs.	Tables 21, and 22 of 521-1834 VAR AM3
Recovery	Mean recovery range for tapinarof: 70.4 to 74.6% Mean recovery range for tapinarof IS: 71.0 to 73.2% Mean recovery range for tapinarof sulfate: 63.9 to 67.6% Mean recovery range for tapinarof sulfate IS: 63.9 to 68.4%	Tables 27, 28, 29, and 30 of 521-1834 VAR AM3

CV = coefficient of variation; IS = internal standard; HPLC-MS/MS = high-performance liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; ULOQ = upper limit of quantitation; QC = quality control

18.5. Additional Clinical Outcome Assessment Analyses

Not applicable.

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/s/

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05/16/2022 11:40:13 AM

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on behalf of Barbara Hill

ANDREW C GOODWIN
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Signing on behalf of Nisha Kwatra.

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