CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215272Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	3/31/2022
From	Phil Phuc Nguyen, M.D., Medical Officer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Acting Branch Chief/ Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Sally Lewis M.D., Medical Officer Snezana Trajkovic M.D., Team Lead Kendall Marcus, M.D., Division Director Division of Dermatology and Dentistry
NDA	215272
Applicant	Dermavant
Drug	VTAMA (tapinarof) cream 1%
NME	Yes
Therapeutic Classification	Aryl hydrocarbon receptor (AhR) modulating agonist
Proposed Indication	Treatment of plaque psoriasis
Consultation Request Date	5/27/2021
Summary Goal Date	2/28/2022
Action Goal Date	2/28/2022
PDUFA Date	3/31/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dermavant Sciences, Inc. has submitted data from two phase-3 studies, DMVT-505-3001 and DMVT-505-3002, to the Agency in support of a new drug application for VTAMA (tapinarof) Cream, 1%, indicated for the treatment of plaque psoriasis in adults. Four clinical investigators (Drs. Hong, Thorla, Bissonnette, and Ehst) were selected for surveillance clinical inspections.

Based on these inspections, the submitted phase 3 studies appear to have been adequately conducted and the study data generated by the inspected entities appear acceptable in support of the proposed indication in the NDA. The inspections identified observations that are discussed under the "Results" section of this document are unlikely to impact the overall efficacy or safety analysis.

II. BACKGROUND

Tapinarof is a nonsteroidal, small molecule aryl hydrocarbon receptor (AhR) modulating agent being developed as a novel anti-inflammatory agent. It has not been previously approved or marketed in the United States and therefore, it is classified as a new molecular entity (NME).

The reported mechanism of action is related to the inhibition of secretion of pro-inflammatory cytokines from activated T-cells, keratinocytes, and endothelial cells.

The sponsor conducted two identical double-blind, randomized, vehicle-controlled, phase 3, multicenter studies in adult patients with plaque psoriasis. Clinical investigators for studies DMVT-505-3001 (Study 3001) and DMVT-505-3002 (Study 3002) were selected for surveillance investigations. Both studies were conducted in the US and Canada.

Per the protocol, the primary endpoint for both studies is the portion of subjects who achieved a Physician's Global Assessment (PGA) score of clear (0) or almost clear (1) with a minimum 2-grade improvement from baseline (PGA Treatment Success) at Week 12. Secondary endpoints of note include the proportion of subjects with equal or greater than 75% improvement in Psoriasis Area and Severity Index (PASI) from baseline to Week 12.

Eligible subjects were to be adults 18 to 75 years of age with a clinical diagnosis of chronic plaque psoriasis and stable disease for at least 6 months prior to the study. Subjects also were to have a Body Surface Area (BSA) involvement ≥ 3% and ≤ 20%, with the subject's scalp, palms, fingernails, toenails, and soles excluded from the percent of total BSA estimates. Subjects were also to have a PGA score of 2 (mild), 3 (moderate), or 4 (severe) at Screening and Baseline. Subjects with mild and severe psoriasis were to be limited to approximately 10% each of the total randomized population. Subjects were to be excluded if they were pregnant; had psoriasis other than the plaque variant; and any sign of infection of any of the psoriatic lesions.

Following a 34-day screening period, eligible subjects were to be randomized at a 2:1 ratio to receive once-daily treatment with tapinarof cream 1%, or vehicle cream. Subjects were to return to the clinic at Weeks 2, 4, 8, and 12 for efficacy and safety assessments. Additionally, subjects were to be contacted by phone at Weeks 6 and 10 to assess adverse events (AEs) and concomitant medications, to review study drug administration instructions, and to confirm the subject's continued participation in this study.

The PGA score was to be used to assess the primary endpoint in this study. The PGA is a clinical tool for assessing the current state/severity of a subject's psoriasis at a given timepoint. It is a static, 5-point morphological assessment of overall disease severity, as determined by the Investigator, using the clinical characteristics of erythema, scaling, and plaque thickness/elevation as guidelines; higher PGA scores represent more severe disease. The % BSA affected is not considered in the scoring of the PGA.

The % BSA value is an estimate of involved BSA and contributes to the PASI score, a secondary endpoint. As determined by the Investigator, the total palmar surface of the subject's palm and digits may be assumed to be approximately equivalent to 1% BSA. Investigators are to estimate the involved area by determining the number of full handprints, plus the number of handprints covered if several smaller lesions are per the sponsor, 'pushed together'. Each region can have up to 100% involvement, with the head and neck region being 10% of overall BSA, and 1 hand-sized plaque being approximately 10% of head and neck area. Estimates of

the % involvement in each body region were to be multiplied by the fraction of the total body area to obtain the total % BSA involved by region and overall.

The Psoriasis Area and Severity Index (PASI) scoring system, a secondary endpoint, takes into account the overall severity of erythema (redness), induration (plaque thickness), and scale, and the extent of %BSA estimated to be affected with psoriasis. %BSA affected is grouped into a 7-point scale (0 to 6) based on combining BSA of different body regions, and assigned points based on %BSA ranges: 0%; <10%; 10 to <30 %; 30 to <50%; 50 to <70%; 70 to < 90%; and greater or equal to 90%. Higher PASI scores indicate more severe disease. PASI is a static assessment made without reference to previous scores.

At the end of the 12 weeks of treatment in this study, subjects had the option to enroll in a separate open-label long-term safety and efficacy study for up to an additional 40 weeks of treatment. Subjects who chose not to participate in the open-label long-term study or failed inclusion in the open label study completed a Follow-up Visit approximately 4 weeks (Week 16 visit) after the end of treatment in this study. Subjects who withdrew from the study before Week 12 completed an Early Termination Visit.

Study DMVT-505-3001 (Study 3001)
Title: *A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults*

Per the clinical summary report, this study was conducted at 48 study centers in the United States and Canada. The First Subject-First Visit occurred April 25th, 2019 and the Last Subject-Last Visit happened May 26th, 2020. 510 subjects were enrolled, and a total of 269 (79.1%) tapinarof 1% and 130 (76.5%) vehicle-cream subjects completed the study.

Study DMVT-505-3002 (Study 3002)
Title: *A Phase 3 Efficacy and Safety Study of Tapinarof for the treatment of Plaque Psoriasis in Adults*

Per the clinical summary report, this study was conducted across 51 study centers in the United States and Canada. The first subject-first visit was May 30th, 2019 and the last subject-last visit was May 13th, 2020. 515 subjects were enrolled, and a total of 282 (82.2%) tapinarof 1% and 142 (82.6%) vehicle-cream subjects completed the study.

III. RESULTS (by Site)

1. Chih-Ho Hong M.D.
   15300 105th Ave, Suite 20, Surrey, BC V3R 6A7, Canada
   Study: DMVT-505-3002
   Site Number: 2901
   Dates of Inspection: 11/29/2021-12/03/2021

This inspection was conducted on-site. At the time of the inspection, 31 subjects were screened and 30 enrolled into the study. There were no issues with the informed consent process. The inspection revealed no deficiencies with maintenance of the blind. Data listings for 17 subjects were compared against source data. Primary efficacy endpoint data (PGA scores at week 12) were verified for the 17 subjects reviewed, and there were no unreported adverse events. This determination is made based on comparing the data listings to the source data.

Difference in % BSA involvement from data listing as compared to source records were identified. It was noted that data was at times rounded when being entered into EDC. The protocol did not require rounding, and the protocol uses examples of integers that are not rounded: for example, the protocol states that "1 hand-sized plaque is 2.5% BSA" for lower extremities. It was noted that per the CI, study monitors reportedly instructed the CI to record in the EDC whole number values. Rounding of %BSA regional involvement and resultant changes to total % BSA involvement was noted for the following subjects:

Table 1: Subjects with Body Surface Area (%BSA) rounding observed

Subject ID#/(Arm)	BSA Data time point	Source Records, total % BSA	Data listing, total %BSA
(b) (6) (treatment)	Week8	2.5%	2.6%
(vehicle)	Baseline, week2, week4, week12	14%, 14, 14, 14	14.1%, 14.1, 14.1, 14.1
(vehicle)	Baseline	4%	4.4%
(treatment)	Screening, baseline, week2, week4,	5%,5,5,1	5.2%, 5.2, 5.2, 1.2
(treatment)	Baseline	6.35%	6.8%
(treatment)	Screening, week12	19%	18.99%
(vehicle)	Week2	9%	9.01%

Table 2: Example of regional %BSA rounding on total %BSA; Subject (b) (6) /(treatment), Baseline

Body Region	*Estimates of % involvement for each region (0-100%)*			*%BSA calculated*	
	Source records before rounding	*EDC data after rounding to whole numbers*	*multiplier*	*Source record*	*Data listing (with rounding)*
head and neck	*2.5%*	*3%*	*x 0.1*	0.25%	0.3%
arm/upper extremities	*15%*	*15%*	*x 0.2*	3%	3%
trunk (including axillae and genitals)	*0.33%*	*1%*	*x 0.3*	0.1%	0.3%
legs/lower extremities (include buttocks)	*7.5%*	*8%*	*x 0.4*	3%	3.2%
Total involved %BSA; sum of the 4 regional values (0-100%)				6.35%	6.8%

Reviewer comments: The %BSA differences do not affect the overall conclusions of the study since these differences are small (in the 0.1% to 0.5% range) and none of the cases of %BSA discrepancy between source records and data listings would have resulted in a change in the PASI calculations

Except for the observations above, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

2. Ira Thorla M.D.
   10154 Jefferson Hwy., Baton Rouge, LA 70809, United States
   Study: DMVT-505-3001
   Site Number: 1006
   Dates of Inspection: 11/15/2021-11/18/2021

This inspection was conducted on-site. At the time of the inspection, 25 subjects were screened and 18 enrolled into the study. Data listings for 100% of subjects were compared against source data. The primary endpoint, PGA scores at week 12 was confirmed for all subjects. There were no issues with the informed consent process. The inspection revealed no deficiencies with maintenance of the blind.

For Subject (b) (6) (treatment arm), there was one unreported AE: staphylococcus infection, on (b) (6), and deemed as moderate, resolving, and not related to the study drug by the CI. The infection was treated with the two medications listed in Table 3, both of which are unreported in the data listings.

Table 3: Unreported medication

Subject ID/Arm	Unreported Medication	Dates
(b) (6) /(treatment)	clindamycin 300 mg TID	(b) (6) to (b) (6)
	mupirocin ointment 2% BID	(b) (6) to (b) (6)

The second observation involves instances of misreporting of % BSA involvement in EDC. The corrected PASI scores for these instances, calculated from source records, is shown below.

Table 4: %BSA data discrepancies and corrected PASI scores

Subject/arm	*Time Point*	*Data listing total % BSA*	*Source record total % BSA*	*Data listing PASI score*	*Corrected PASI score using source records*
(b) (6) / treatment	Week 4 (visit 4)	10.2%	12.5%	5.2	5.2
(b) (6) / treatment	Week 2 (visit 3)	3.3%	11.1%	5.3	5.3
(b) (6) / placebo	Week 2 (visit 3)	6.1%	21.7%	3.8	3.8

Reviewer comments: This misreporting of %BSA values did not change PASI scores.

Except for the observations above, overall, the inspection revealed adequate adherence to the regulations and the investigational plan. With the corrections above for the unreported AE and for the incorrect %BSA values, data from this site appear acceptable in support of this NDA.

3. Robert Bissonnette M.D.
   3530 Boulevard Saint-Laurent, Suite 400, Montreal, QC H2X 2V1, Canada
   Study: DMVT-505-3001
   Site Number: 1904
   Dates of Inspection: 12/10/2021-12/16/2021

This inspection was conducted on-site. At the time of the inspection, 41 subjects were screened and 33 enrolled into the study. Data listings for 14 subjects were compared against source data, with no discrepancies. There were no issues with the informed consent process. The inspection revealed no deficiencies with maintenance of the blind. There was no evidence of under-reporting of adverse events or under-reported protocol deviations.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

4. Benjamin Ehst M.D.
   9495 SW Locust Street, Suite G, Portland, OR 97223, United States
   Study: DMVT-505-3002
   Site Number: 2024
   Dates of Inspection: 09/28/2021 – 09/30/2021

This inspection was conducted on-site. At the time of the inspection, 21 subjects were screened, and 18 were enrolled. The primary endpoint: PGA scores at week 12, for all enrolled subjects were reviewed against source data, with no discrepancies. There was no evidence of under-reporting of protocol deviations. The inspection revealed no deficiencies with maintenance of the blind.

One adverse event was identified by the CI in source records but not reported to the Agency, and one adverse event was identified by the CI in source records but incorrectly reported to the Agency as not related to the study drug. They are summarized below.

Table 5: Adverse Events not Reported or Otherwise Mis-Reported

Subject/Arm	Adverse Event/ Severity	Dates	Notes
(b) (6) / treatment	Gastroenteritis/mild	(b) (6)	Not reported to agency; CI note not related to study drug
(b) (6) / treatment	Chest skin pain/mild	(b) (6)	Deemed to be related to study drug, but misreported as not related in eCRF

Reviewer comments: The events were mild in severity and did not result in significant harm to subjects. We note that dermatitis/contact dermatitis is already mentioned in the proposed package insert.

Except the findings described above, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

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/s/

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Division of Pediatric and Maternal Health Review

Date: March 2, 2022 **Date consulted:** December 14, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: VTAMA (tapinarof) cream, 1%

Drug Class aryl hydrocarbon receptor (AhR) agonist

NDA: 215272

Applicant: Dermavant Sciences, Inc.

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Proposed Indications:

- Topical treatment of plaque psoriasis in adults

Materials Reviewed:

- DPMH consult request, dated December 14, 2021, DARRTS

Reference ID: ID: 4904258

- Applicant's submission for NDA 215272 of May 26, 2021

Consult Question: DDD requests DPMH-MHT assistance in the Pregnancy and Lactation subsections of the labeling as per PLLR.

INTRODUCTION AND BACKGROUND

On May 26, 2021, Dermavant Sciences, Inc., submitted an original application, first-in-class, new molecular entity (NME), NDA 215272, VTAMA (tapinarof) cream, 1% for topical treatment of plaque psoriasis in adults.
On December 14, 2021, DDD consulted DPMH to provide input to the Pregnancy and Lactation subsections of the labeling as per PLLR.

Psoriasis and Pregnancy

Psoriasis is a chronic skin disorder characterized by well-demarcated erythematous papules and plaques with a silver scale. It commonly occurs on the extensor surface of the elbows or knees, or the scalp. Psoriasis affects 2% to 3% of the population, men and women equally.[1] Psoriasis commonly occurs in females of reproductive age because three-quarters of patients develop the disease before reaching age 40 years.[2] The disease activity during pregnancy is unpredictable and, therefore, it is possible that treatment may be needed.[3] Psoriasis improves during pregnancy in 40 to 60 percent of females, worsens in 10 to 20 percent, and remains stable in the remainder.[4] In the postpartum period, psoriasis severity remains the same or worsens in most females.[5] Few studies have investigated the impact of psoriasis on pregnancy outcomes, leaving the relationship between psoriasis and pregnancy outcomes unclear.[5,6] A 2016 systematic review of observational studies that evaluated the relationship between psoriasis and pregnancy outcomes found that four of the nine included studies reported increased risk for at least one adverse fetal outcome (spontaneous abortion, caesarean delivery, low birth weight, macrosomia, large-for gestational age, or a composite outcome that included prematurity and low birth weight).[7] A recent observational cohort study of 220 females and 298 pregnancies, with 252 exposed to biologics, did not show significant difference in the rates of spontaneous abortion, neonatal problem, and congenital anomalies in females with moderate-to-severe psoriasis compared to the general US population.[8]
Psoriasis involving limited areas of skin (eg, less than 5 to 10 percent the body surface area)

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[1] Bae Y, Van Voorhees A, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol vol 67, Number 3:459-477. 2012.
[2] Barker JN. Genetic aspects of psoriasis. Clin Exp Dermatol 2001; 26:321.
[3] Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. Am J Clin Dermatol. 2015 Oct; 16(5):389-98.
[4] Pomeranz MK, Strober BE. Management of psoriasis in pregnancy. UpToDate. https://www.uptodate.com/contents/management-of-psoriasis-in pregnancy? 1
[5] Bobotsis R, Gulliver WP, Monaghan K, et al. Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies. Br J Dermatol 2016; 175:464.
[6] Bröms G, Haerskjold A, Granath F, et al. Effect of Maternal Psoriasis on Pregnancy and Birth Outcomes: A Population-based Cohort Study from Denmark and Sweden. Acta Derm Venereol 2018; 98:728
[7] Bobotsis R, Gulliver WP, Monaghan K, Lynde C, Fleming P.Psoriasis and adverse pregnancy outcomes: A systematic review of observational studies.Br J Dermatol. 2016 Sep;175(3):464-72.
[8] Kimball AB, Guenther L, Kalia S, et al. Pregnancy Outcomes in Women with Moderate-to-Severe Psoriasis. From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2021;157(3):301–306

can often be managed topically. Topical therapy and phototherapy are generally preferred over systemic therapy for the treatment of pregnant individuals because of concern for safety.[9,10] Based on limited safety data, clinical guidelines for management of psoriasis during pregnancy and lactation recommend the following:

- First line: moisturizers and topical steroids (preferably low-medium potency)
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors and cyclosporine.

Drug Characteristics[11]

Drug Class	aryl hydrocarbon receptor (AhR) agonist
Mechanism of Action	The specific mechanisms by which VTAMA (tapinarof) exerts its therapeutic action in psoriasis patients are unknown
Molecular Weight	254.32 Daltons
Protein Binding	99.3%
Terminal Half-Life	(b) (4)
Bioavailability	Low systemic absorption (plasma concentrations were below quantifiable limits (BQL) of the assay (< 50 pg/mL) in 68% of PK samples.

REVIEW

PREGNANCY

Review of Nonclinical Data

As per the applicant, in an embryofetal development study in rats, tapinarof at subcutaneous doses up to 34 mg/kg/day (268 times the maximum recommended human dose (MRHD) based on AUC comparisons) had no effect on pregnant rat maternal body weight gain or food consumption, but incomplete ossification of nasal bones was observed at the highest dose of 34 mg/kg/day. In an embryofetal development study in pregnant rabbits administered tapinarof via subcutaneous injection twice daily at doses up to 3 mg/kg/day (16 times the MRHD based on AUC comparison), maternal toxicity, increased post-implantation loss and fetal skeletal variations were observed at the highest dose. No tapinarof-related findings were noted in a continuous subcutaneous infusion embryo-fetal development study in rabbits administered doses up to 3 mg/kg/day (20 times the MRHD based on AUC comparison). In a prenatal and postnatal development study in rats, tapinarof was administered by subcutaneous injection at doses up to 30 mg/kg/day (268 times the MRHD based on AUC comparisons). Tapinarof-related effects on fetal survival and viability (reduced litter sizes and deceased fetal weights) were noted at a dose exposure 45 times the exposure at the MHRD.

[9] Sun W, Dinatale M. Review of psoriasis in pregnancy, DARRTS, July 20, 2021, Reference ID: 4826813
[10] Baisden K, Johnson T. Review of psoriasis in pregnancy, DARRTS, February 5, 2021, Reference ID: 4741087
[11] Edits to the proposed labeling by Clinical Pharmacology

Systemic exposure to tapinarof after oral dosing in nonclinical studies was low and absolute bioavailability was estimated to be < 5%.

Review of Clinical Data

Review of Literature

No literature is available on tapinarof use in pregnant women to evaluate drug-associated risks, including major birth defects, miscarriage, or adverse maternal or fetal outcomes. No further information is provided.

DPMH Review

DPMH conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases for tapinarof and use in pregnancy. No publications were identified. Micromedex/TERIS databases did not reveal any information. Briggs GG and Freeman RK in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, does not have any reference to the drug.

Review of Pharmacovigilance Database (PV)

The applicant performed 18 clinical trials during the product development. Pregnant women were excluded from the trials. Patients who became pregnant during the trials were discontinued from the trial.

Five subjects (< 1%) and 1 subject partner became pregnant during the clinical trials. Of these, 5 had received tapinarof and 1 had received vehicle. 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.

Reviewer Comment

No literature is available on tapinarof use in pregnant women. Five reported pregnancies with 4 normal babies delivered and one elective termination, not related to the drug, are insufficient to evaluate drug-associated risks, including major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Summary

Review of the literature and applicant's pharmacovigilance are insufficient to demonstrate an association of adverse developmental outcomes with maternal use of tapinarof during pregnancy. As per clinical pharmacology,

> in the maximal use PK study, a majority of the PK samples (68% of the total PK samples) were below quantifiable limits (lower limit of quantification was 50 pg/mL). The levels in plasma in the samples with measurable concentrations were low on Day 1, mean ± SD values of Cmax and $AUC_{0\text{-last}}$ were 0.90 ± 1.4 ng/mL and 4.1 ± 6.3 ng.h/mL, respectively.

Due to the low systemic absorption for this topical product (together with the majority of PK samples being below quantifiable limits) and the lack of adverse developmental effects observed in animal reproduction studies at clinically equivalent dose exposures, DPMH had concluded that a postmarketing requirement (PMR) for a pregnancy exposure registry is not

recommended for tapinarof. However, through email communication with DDD, the clinical team requested PMRs for pregnancy be considered because alternative treatments carry some potential risk to the developing fetus (e.g., topical steroids, retinoids) and another topical treatment option for psoriasis during pregnancy would further address patient reluctance to take an oral or subcutaneous medication. In addition, they consider PMR studies of tapinarof use during both pregnancy and lactation will help to characterize the safe use of tapinarof in these patient subpopulations and inform labeling.

LACTATION

Review of Nonclinical Data

From a prenatal and postnatal development study in pregnant/lactating female rats after subcutaneous administration, tapinarof was quantifiable in offspring plasma samples on postnatal day 10 at doses of 6 and 30 mg/kg/day, suggesting that tapinarof is present in animal milk. Tapinarof is highly protein bound, i.e. 99%. Both protein bound and unbound drug is excreted through the breast milk. As per nonclinical reviewer Dr. Cindy Li,

> Tapinarof at 0 (30% Captisol), 1, 6, or 30 mg/kg/day was administered subcutaneously once daily to pregnant F0 female rats (24-26/group) from GD 6 through Lactation Day 20. In the 6 and 30 mg/kg/day dose groups, tapinarof was quantifiable in 2 of 18 or 6 of 12 F1 plasma samples on PND 10 (range: 0.326 to 0.506 ng ng/mL at 6 mg/kg/day and 0.301 to 0.985 ng ng/mL at 30 mg/kg/day). The study did not have the direct measurement of tapinarof in animal milk.

Reviewer Comment

Uncertainty remains, as it is not known how the rat pup exposure to tapinarof from milk following maternal subcutaneous tapinarof administration compares to the potential human infant exposure to tapinarof from human milk following maternal topical tapinarof administration.

Review of Clinical Data

Review of Literature

Applicant Review

The applicant did not provide any publications on lactation and use of tapinarof.

DPMH Review

DPMH also conducted a literature search in PubMed, Embase and the TERIS and ReproTox databases, Briggs GG, and Freeman RK in Drugs in Pregnancy and Lactation and Thomas Hale in Medications and Mothers' Milk for tapinarof and use in lactation. No literature was identified.

Summary

The available data suggests that tapinarof is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. With its small molecular weight, it makes tapinarof also a candidate for being present in human milk. Nonetheless, with its high protein binding and low systemic absorption following topical administration, DPMH concluded that a PMR for a lactation study, milk only, is not warranted because the expectation that this drug will be present in human milk is low, and the effects on the breastfed child would

be minimal. However, through email communication with DDD, the clinical team requested a PMR for lactation be considered to help to characterize the safe use of tapinarof in the lactating patient and inform labeling.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Review of Nonclinical Data

As per applicant, tapinarof demonstrated no evidence of mutagenic or clastogenic potential based on the results of three in vitro tests (Ames assay, chromosomal aberration assay, mouse lymphoma assay) and two in vivo tests (mouse and rat micronucleus assays).
Tapinarof did not impair female fertility at subcutaneous doses up to 30 mg/kg/day (268 times the MRHD based on AUC comparisons) when administered to rats.

Review of Clinical Data

The applicant did not provide any information/publications on the effects of tapinarof on human fertility. No PV data has been reported.
DPMH did not identify any publications with adverse effects of tapinarof on human fertility.

Summary

Review of the literature and applicant's pharmacovigilance yielded no cases relevant to tapinarof effects on human fertility. Because the drug is neither genotoxic nor clastogenic, and no adverse developmental effects were observed in animal reproduction studies at clinically equivalent dose exposures, pregnancy testing, and contraception use is not recommended. Tapinarof did not impair female fertility in animal studies. Therefore, the subsection 8.3 Females and Males of Reproductive Potential will be omitted from the labeling.

CONCLUSIONS

As tapinarof is systemically absorbed and use is anticipated in females of reproductive potential, PMR studies of tapinarof use during both pregnancy and lactation are recommended to address the sparse clinical data for this new molecular entity and characterize the safe use of tapinarof in these patient subpopulations. DPMH recommends the following language for pregnancy and lactation PMR studies for tapinarof:

1.•Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to VTAMA (tapinarof) cream, 1%, during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

2.•Conduct an additional pregnancy study that uses a different design from the Pregnancy Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and

preterm birth in women exposed to VTAMA (tapinarof) cream, 1%, during pregnancy compared to an unexposed control population.

3.•Perform a lactation study (milk only) in lactating women who have received therapeutic doses of VTAMA (tapinarof) cream, 1%, to assess concentrations of tapinarof in breast milk using a validated assay and to assess the effects on the breastfed infant.

Any further discussion about the study designs and study population will be discussed after approval, at the time of the draft study protocol review.

Tapinarof labeling has been edited to comply with the current practices for PLLR. DPMH revised labeling subsections 8.1 and 8.2 (see below). DPMH refers to the final NDA action for final labeling.

RECOMMENDATIONS

DPMH has the following recommendations for tapinarof labeling.

(b) (4)

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/s/

CHRISTOS MASTROYANNIS
03/02/2022 01:44:54 PM

TAMARA N JOHNSON
03/02/2022 01:48:01 PM

LYNNE P YAO
03/02/2022 02:37:24 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 27, 2022

To: Felicia Lewis**,** MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Jennifer Harmon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for VTAMA™ (tapinarof) cream, for topical use

NDA: 215272

In response to DDD's consult request dated July 13, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for VTAMA™ (tapinarof) cream, for topical use.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on January 25, 2022.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Applicant to the electronic document room on May 26, 2021, and we have no comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
01/27/2022 02:36:58 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 27, 2022
To:	Jennifer Harmon, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name)/Dosage Form and Route:	VTAMA (tapinarof) cream, for topical use
Application Type/Number:	NDA 215272
Applicant:	Dermavant Sciences, Inc.

1 INTRODUCTION

On May 26, 2021, Dermavant Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 215272 for VTAMA (tapinarof) cream, for topical use. The proposed indication for VTAMA (tapinarof) cream is for the treatment of plaque psoriasis in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on July 13, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VTAMA (tapinarof) cream.

2 MATERIAL REVIEWED

- Draft VTAMA (tapinarof) cream PPI received on May 26 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 25, 2022.
- Draft VTAMA (tapinarof) cream Prescribing Information (PI) received on May 26, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 25, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

JESSICA M CHUNG
01/27/2022 03:55:02 PM

LAURIE J BUONACCORSI
01/27/2022 04:00:25 PM

SHAWNA L HUTCHINS
01/27/2022 04:02:03 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-215272
Submission Number	001 (New NDA)
Submission Date	5/26/2021
Date Consult Received	7/16/2021
Drug Name	VTAMA (tapinarof) cream, 1%
Indication	Plaque Psoriasis
Therapeutic Dose	1% cream, once daily (as a thin layer of cream to affected areas)
Clinical Division	DDD
Protocol Review	NA

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 7/16/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 02/13/2020 in DARRTS (link);
- Previous IRT review dated 07/15/2019 in DARRTS (link);
- Sponsor's clinical study protocol # DMVT-505-2002 (SN0001; link);
- Sponsor's cardiac safety report for study # DMVT-505-2002 (SN001; link);
- Sponsor's statistical analysis plan for study # DMVT-505-2002 (SN001; link);
- Sponsor's clinical study report # DMVT-505-2002 (SN0001; link);
- Investigator's brochure (SN0006; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0006; link).

1 SUMMARY

No significant QTcF prolongation effect of tapinarof cream 1%, *w/w* was detected in this QT assessment.

The effect of tapinarof cream 1%, *w/w* was evaluated in Study # DMVT-505-2002. This was a Phase 2a, multicenter, open-label study evaluating the safety and pharmacokinetics of topical tapinarof cream in adult patients with extensive plaque psoriasis. This was a maximal use pharmacokinetics study with highest exposures (BSA 21 to 46%) using 1% once daily application, which is higher than therapeutic exposures at proposed recommended doses (Section 3.1). In addition, there are no clinical scenarios (e.g., drug interaction or organ impairment) with increased exposures. Considering the that lower exposures are achieved in healthy subjects due to limited absorption from intact skin, the QT assessment included integrated non-clinical and clinical risk assessment approach. Clinical data from Study # DMVT-505-2002 were analyzed using by-time analysis as the

primary analysis, which did not suggest that tapinarof cream 1% is associated with significant QTc prolonging effect (refer to Section 4.3) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results.

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	**Treatment**	**Time** (h)	**ΔΔQTcF** (msec)	**90% CI** (msec)
QTc	Tapinarof Cream 1%	Day 1 Hour 2	-1.0	(-6.8, 4.9)
QTc	Tapinarof Cream 1%	Day 29 Hour 1	-1.3	(-8.4, 5.9)

For further details of the FDA analysis, please Section 4.

Although the hERG assay showed some deviations from best practices (Section 3.1.2), these limitations are not expected to impact the substantially large hERG safety margin (Appendix). Findings of this analysis are further supported by the exposure-response analysis (Section 4.5) and categorical analysis (Section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the CSS-IRT. Our changes are highlighted (*addition*, ~~*deletion*~~). Each Section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

(b) (4)

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Dermavant Sciences GmbH is developing tapinarof for the topical treatment of plaque psoriasis. Tapinarof (DMVT-505; MW: 254.32 g/mol) is an aryl hydrocarbon receptor modulating agent.

The product is formulated as a cream (containing 1% w/w tapinarof, 10 mg/gram) for topical application. The proposed dosing of 1% cream is once daily application as a thin layer of cream to affected areas (BSA ~8%). At the proposed dosing, the peak concentrations of 0.898 ng/mL (~3.5 nM) and 1.23 ng/mL (~5 nM) are expected in psoriasis (Day 1, Study # DMVT-505-2002) and atopic dermatitis (Study # 201851), respectively. Thus, the peak concentrations in subjects with atopic dermatitis are higher compared to those with plaque psoriasis. There is no accumulation with multiple dosing instead the peak concentrations are deceased with repeat dosing as the skin normalizes with treatment (Study # DMVT-505-2002 & Study # 201851).

(b) (4)

there is a limited utility of conducting a thorough QT study in healthy subjects if the exposures of tapinarof achieved are not reflective of the clinical scenarios. Previous clinical studies indicated considerably lower exposures achieved in healthy subjects due to limited absorption of tapinarof form intact skin. The IRT review indicated that the combination of non-clinical safety pharmacology studies (with hERG safety margin >30,000) with the clinical QTc assessment from the maximal use study (Study # DMVT-505-2002) may potentially be adequate to assess the risk of QTc prolongation of tapinarof. Refer to previous IRT review dated 07/15/2019 and 02/13/2020 in DARRTS.

The sponsor utilized a nonclinical-clinical integrated risk assessment approach with clinical data from maximal use PK study (DMVT-505-2002). This was a Phase 2a, multicenter, open-label study evaluating the safety and pharmacokinetics of topical tapinarof cream in patients with extensive plaque psoriasis (moderate to severe disease; n=21). This was a maximal use pharmacokinetics study with highest exposures achieved using 1% once daily application (for 29 days; BSA at baseline: 21 to 46%), which is higher than therapeutic exposures at proposed recommended doses. The study consisted of three phases - screening (up to 34 days), treatment (29 days), and follow-up (7-10 days). Continuous Holter recordings were planned on Days −1, 1, 2, 29, and 30. ECGs were extracted (on Day 1 and Day 29) at the same time points as PK samples, i.e., pre-dose, and at 1, 2, 3, 4, 5, 8, 12, and 24 h post-dose. Based on the maximal use conditions, the peak concentration (Cmax: 0.898 ng/mL) observed with studied dose (i.e., 1% w/w once daily application) is expected to cover the therapeutic exposures associated with the maximum proposed dose.

3.1.2 Nonclinical Safety Pharmacology Assessments

Original electrophysiology records for the hERG study were provided by the sponsor. We reanalyzed these records to assess data quality and verify study report conclusions (Appendix).

In summary, the hERG assay showed deviations (e.g., room temperature, a slow stimulating intervals, and samples were collected from stock solutions for drug concentration verification) from best practice recommendations for an in vitro assay according to the new draft ICH S7B Q&A 2.1 (link). Although this hERG assay did not meet best practices for an in vitro assay, the assay results show that tapinarof has a low risk for QTc prolongation by direct inhibition of hERG current at therapeutic exposure (hERG margin: > 105449x). These limitations of the hERG assay are not expected to impact this substantially large hERG safety margin.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, the largest upper bound of 90% confidence interval of ΔQTcF for tapinarof cream treatment was below 10 msec.

Reviewer's comment: *The sponsor's QTcF and HR profiles are similar to reviewers' assessment. Please Section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

The sponsor's bias assessment indicated that BA slope was 0.00 (95%CI: -0.010 to 0.006). These sponsor's results suggest that the observed bias is less likely to impact the result of the analysis.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (<45 or >100 beats/min with 25% over baseline), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *The sponsor's results are consistent with reviewers' assessment. Three subjects having HR above 100 bpm with corresponding change from baseline below 25% were further noted in reviewer's outlier counts. Please Section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

In addition to by-time analysis, the sponsor also performed PK/PD analysis exploring the relationship between concentration of tapinarof and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach (using conc above BLQ). The sponsor analysis did not suggest a concentration dependent increase in QTcF with a numerically negative slope of -0.00016 msec/pg/mL (90% CI -0.002172 to 0.001844 msec/ng/mL). The model predicted ΔQTcF (upper confidence interval) values of -3.35 (-0.67) msec at the mean peak concentrations (geomean Cmax ~137.9 ng/mL) following once daily topical

application of 1% cream. The results of the sponsor's analysis suggest an absence of significant QTc prolongation at the proposed therapeutic dose (i.e., 1% w/w, once daily daily).

Reviewer's comment*: Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.*

3.2.4 Safety Analysis

Twenty-one subjects received study drug and were included in the Safety Analysis Set. All TEAEs were Grade 3 or less, with the majority of TEAEs being Grade 1 (7 subjects [33.3%]). Two subjects reported Grade 3 TEAEs of pancreatitis (1 subject [4.8%]) and furuncle (1 subject [4.8%]). The Grade 3 pancreatitis was also considered as an SAE.

There were no deaths, and no subject had a TEAE leading to discontinuation of study drug. There were no cardiac TEAEs.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes a compound symmetric covariance matrix to explain the associations among repeated measures within the treatment.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

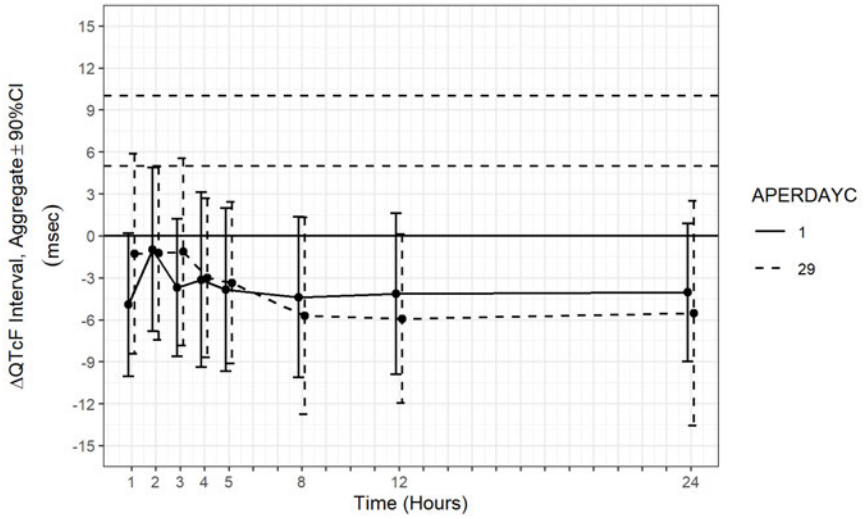


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	Analysis Nominal Period Day (C)	N	Time (Hour)	ΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
Tapinarof Cream 1%	1	21	2.0	-1.0	(-6.8 to 4.9)
Tapinarof Cream 1%	29	17	1.0	-1.3	(-8.4 to 5.9)

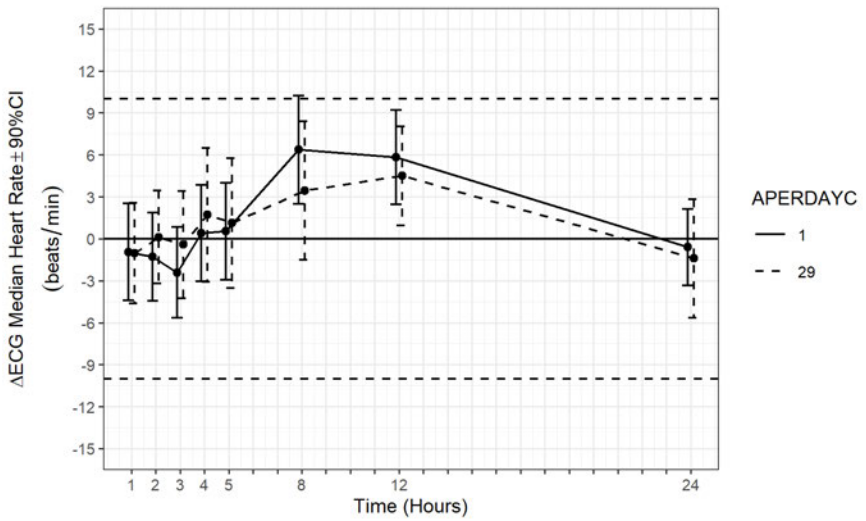
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

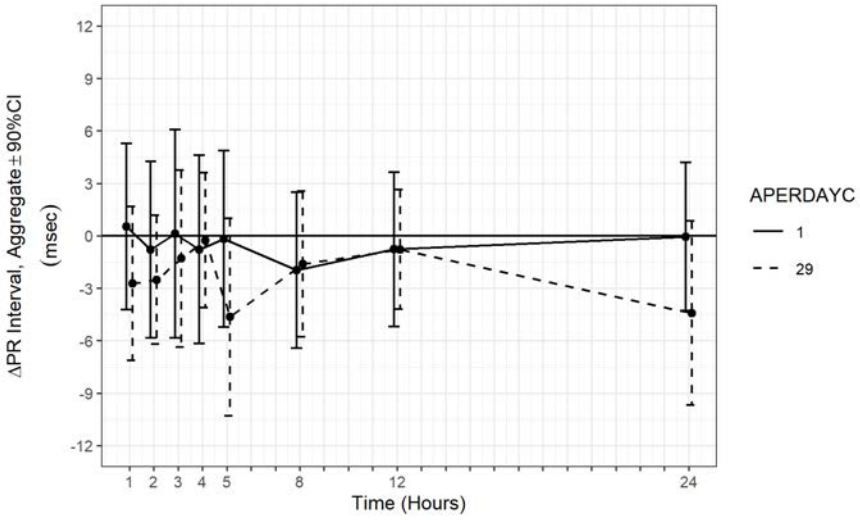
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

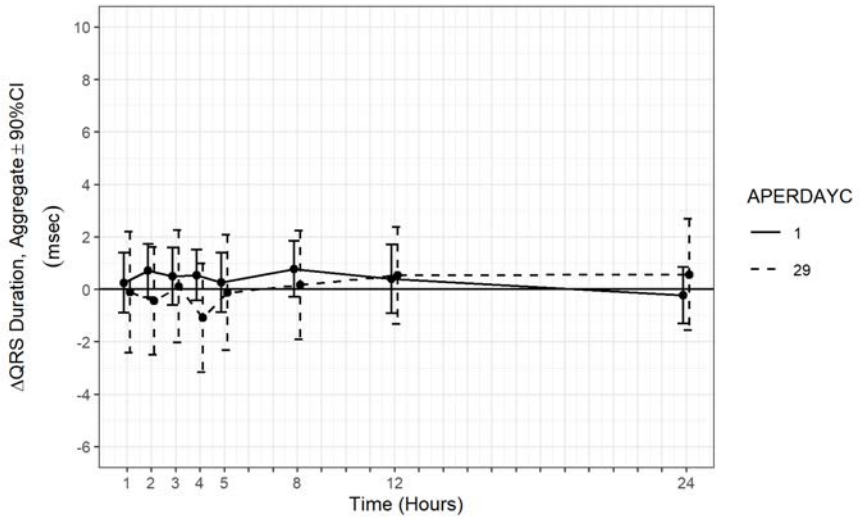
Figure 3: Mean and 90% CI of ΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects had observed QTcF above 500 msec or ΔQTcF above 60 msec after receiving Tapinarof.

4.4.2 HR

Table 3 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were three subjects who had observed HR between 100 to 110 bpm with corresponding change from baseline below 25% after receiving Tapinarof cream 1%.

Table 3: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tapinarof Cream 1%	21	337	18 (85.7%)	333 (98.8%)	3 (14.3%)	4 (1.2%)

4.4.3 PR

None of the subjects had observed PR above 220 msec.

4.4.4 QRS

None of the subjects had observed QRS above 120 msec.

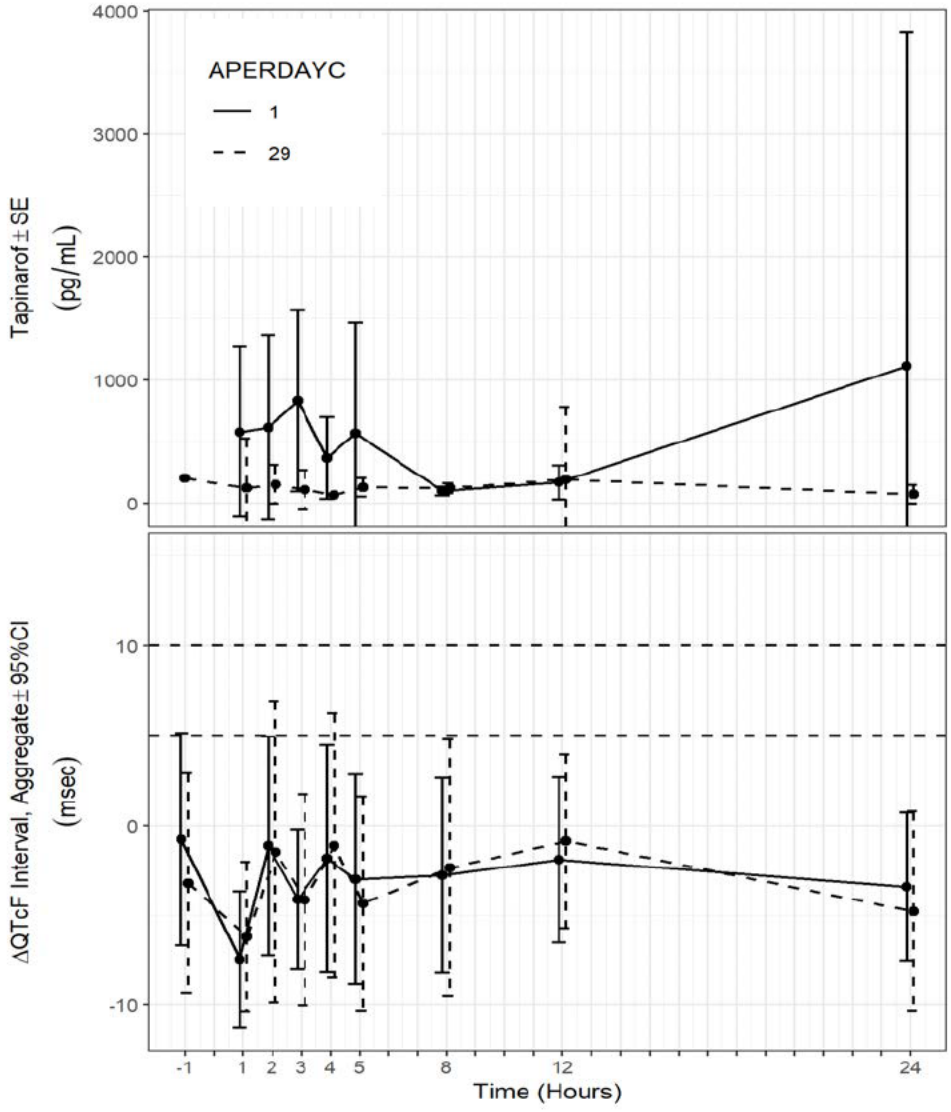
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of tapinarof and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (Day 1 and Day 29; Subject # (b) (6) was excluded form analysis due to time difference in PK/ECG collection).

Prior to evaluating the relationship between tapinarof concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between tapinarof concentration and ΔQTcF and 3) a non-linear relationship.

An evaluation of the time-course of tapinarof concentration and changes in ΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of tapinarof indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10-bpm (Sections 4.3.2 and 4.4.2).

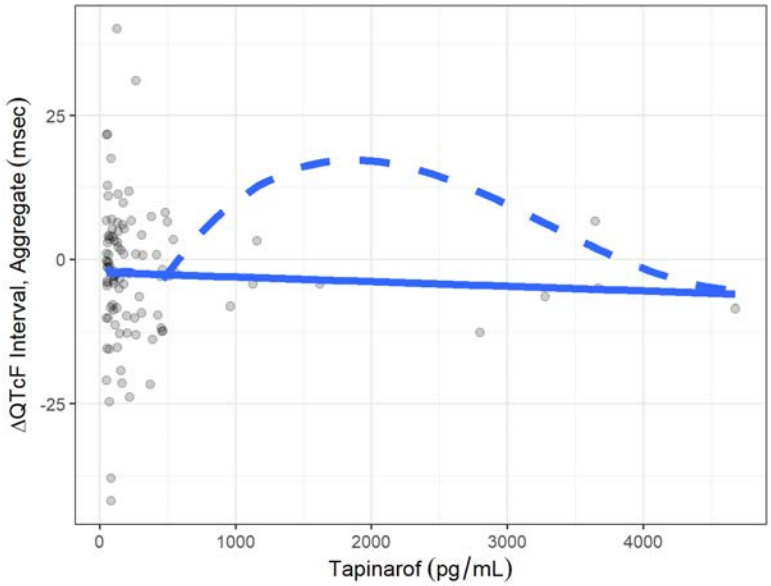
Figure 5: Time-course of Tapinarof Concentration (top) and QTcF (bottom)[1]



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between tapinarof concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between tapinarof concentration and ΔQTcF and supports the use of a linear model.

[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 4.

Figure 7: Goodness-of-fit Plot for QTcF

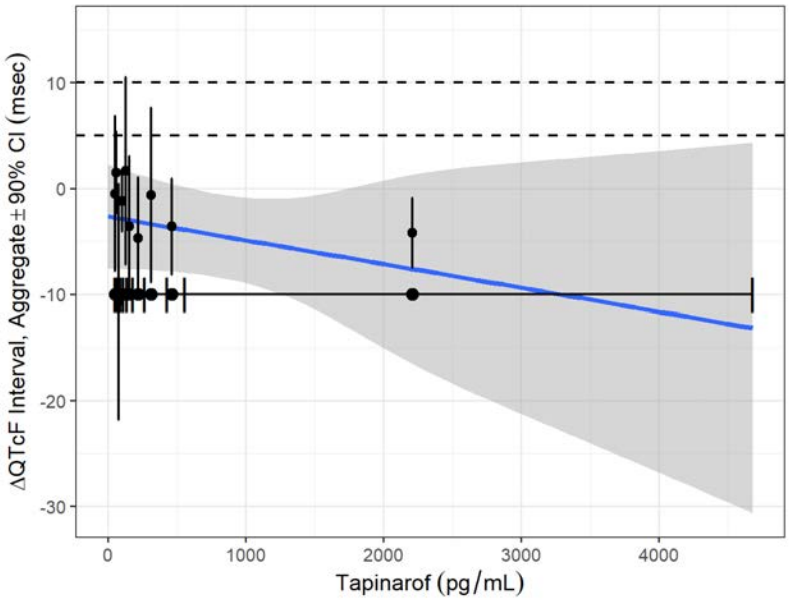


Table 4: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Tapinarof (pg/mL)	ΔQTcF Interval, Aggregate (msec)	90.0% CI (msec)
Tapinarof Cream 1%	29	156.9	-3.0	(-7.6 to 1.6)
Tapinarof Cream 1%	1	439.7	-3.7	(-7.8 to 0.5)

5 APPENDIX I: REVIEW OF SUPPORTING NONCLINICAL DATA

Tapinarof (DMVT-505, GSK2894512. MW: 254.32 g/mol) is being developed for the topical treatment of atopic dermatitis and plaque psoriasis. Considering that the exposures of tapinarof in atopic dermatitis patients are relatively low (peak concentration of 1.23 ng/mL), we would consider that the combination of non-clinical safety pharmacology studies and the clinical QTc assessment in the maximal use study would be adequate to assess the risk of QTc prolongation with this product. The Review Division agreed with our suggestion and we request the sponsor to submit the hERG raw data for review.

5.1 SPONSOR'S SUBMISSION

The nonclinical study report 2013N170846 (link) describes the potential effects of tapinarof on the hERG current, a surrogate for IKr that mediate membrane potential repolarization in cardiac myocytes. The hERG current was assessed at room temperature using a step-step voltage protocol (from a holding potential of -80 mv to a depolarizing pulse of 20 mV for 5 second, followed by a repolarizing pulse to -50 mV for 5 second). The voltage protocol was repeated every 15 seconds. Data was digitized at a sampling rate of 2500 Hz. The positive control (100 nM E-4031) inhibited hERG potassium current by 87.7%. Solution samples were collected from the test solutions prior to perfusion. The actual concentrations of tapinarof in all test article stock solution samples taken during the study was within ± 10% of nominal. Therefore, the nominal concentrations were used to describe the drug effects.

Tapinarof inhibited hERG currents by 17.1%, 42.3%, 82.6% and 95.7% at the concentrations of 1.16, 3.47, 11.56 and 34.7 µM, respectively. The calculated IC50 value for inhibition of hERG tail current was 4.02 µM.

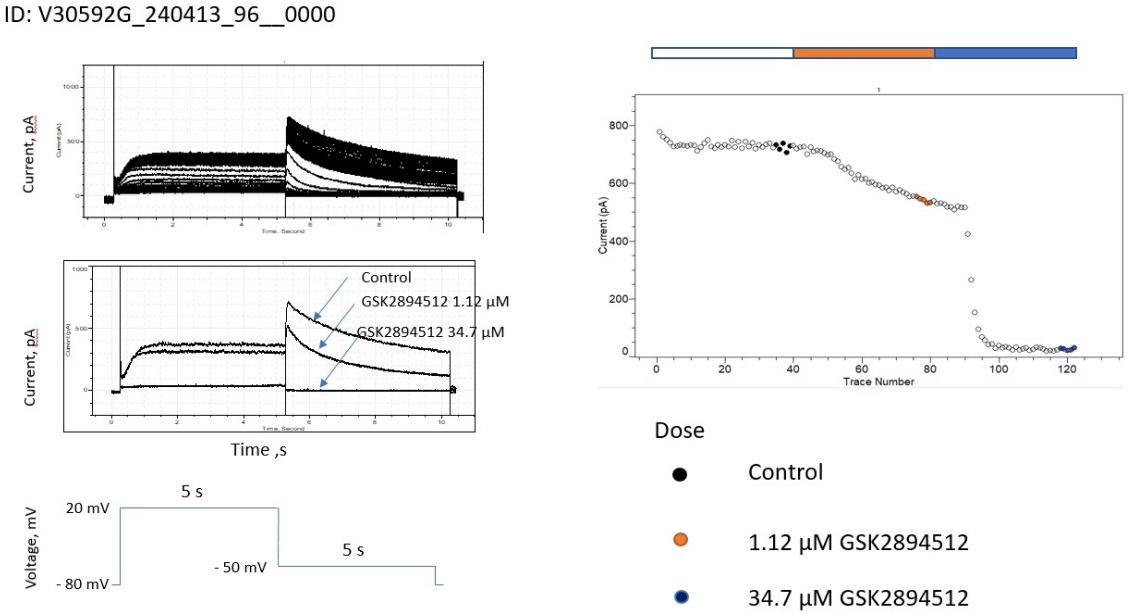
5.2 REVIEWER'S ASSESSMENT AND DATA REANALYSIS

Original electrophysiology records for the hERG assay (study 2013N170846) were provided by the sponsor. An IRT reviewer reanalyzed these records to assess data quality and verify study report conclusions. For data quality assessment, current from all traces were examined to verify stability, and time course plots were constructed to verify that current amplitude in control solution were stable prior to drug application, and that drug effects reached steady state.

The step-step voltage protocol used by the sponsor is different from that recommended by the FDA (link). The reviewer does not anticipate protocol difference to impact hERG current pharmacology. The experiments were conducted at room temperature, which is different from that recommended physiological temperature (35-37 ^{o}C) by the FDA (link). The potential impact of temperature in IC50s is drug-dependent and can result in 2-fold or larger shifts in the IC50 value when conducting experiments at room temperature instead of 35-37°C. The stimulating frequency was 15 s, which is significantly slower than that recommended by the FDA (5 s). The reviewer expects the limitation (slow stimulating rate) may impact hERG current pharmacology if the drug blockade is frequency dependent. In addition, solutions samples for drug concentration verification were collected from the stock solutions, not from the recording chamber. The reviewer concerned that the measured drug concentrations may be underestimated due to possible drug loss in perfusion system.

Representative analysis from one cell of hERG study (V30592G_240413_96__0000) is shown in Figure 8. The top left panel shows all recorded traces from this cell; the middle left panel shows the last traces in control and in drug application; the bottom left panel, the voltage waveform used to evoke hERG current. The time course plot (peak tail current at -50 mV) of hERG current is shown on the right panel. Non-hERG currents (background currents) were not assessed at the end of each recording in this assay. Therefore, non-hERG current subtraction couldn't be performed by the reviewer. The reviewer anticipates that the limitation (no background current subtraction) may impact hERG current pharmacology (i.e., IC50 calculation).

Figure 8 Representative hERG assay from cell V30592G_240413_96_0000



The hERG current amplitudes from the last 5 traces acquired in control (black solid circles) and in drug solution (orange and blue solid circles) were then averaged to calculate % inhibition by that concentration. Results of tapinarof and positive control on hERG current are summarized in Table 5.

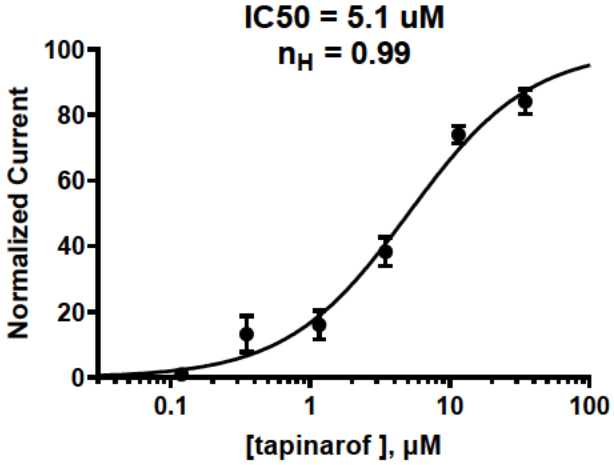
Table 5. Effects of tapinarof on hERG current

Test article	N	Mean (%)	SD (%)	SEM(%)
Vehicle Control	4	10.7	3.8	1.9
TAPINAROF 0.12 µM	3	12.7	2.2	1.2
TAPINAROF 0.35 µM	4	23.9	5.5	2.8
TAPINAROF 1.16 µM	5	26.8	4.3	1.9
TAPINAROF 3.47 µM	5	49.1	4.4	2.0
TAPINAROF 11.56 µM	4	84.7	2.6	1.3
TAPINAROF 34.7 µM	5	94.8	3.8	1.7

E-4031 100 nM	3	73.5	26.5	15.3

While there are numerical differences in the results from FDA's independent analysis compared to the sponsor's, these do not change overall conclusions. That is, FDA's independent analysis of the submitted electrophysiology data shows that tapinarof acutely inhibited hERG current by 12.7%, 23.9%, 26.8%,49.1%, 84.7 and 94.8% at 0.12 µM, 0.35 µM, 1.16 µM, 3.47 µM, 11.56µM and 34.7 µM, respectively. The calculated IC50 (after corrected with vehicle control and run-down) is 2.3 µM (Figure 9)

Figure 9. Dose-response curve of the effects of tapinarof on hERG current



The safety margins of tapinarof against hERG currents is provided in the following table:

Table 6 Safety margins of tapinarof on hERG current

	Cmax (ng/mL)	Protein Binding	Free Cmax (ng/mL)	hERG IC50 (µM)	Mol Weight (g/mol)	Safety Margin (Ratio)
Tapinarof	1.23	99%	0.0123	5.1	254.32	105,449x

5.3 SUMMARY

The comparisons of sponsor's hERG assay and the best practice recommendations by the new draft ICH S7B Q&A 2.1 are summarized in Table 7.

Table 7 Comparison of sponsor's hERG assay with the new draft ICH S7B Q&As best practice recommendations

Elements	Sponsor's hERG assay	Best Practice recommendations	Present ?
Temperature	room temperature	physiological (35 – 37°C)	No

Voltage protocol	step-step protocol	The voltage protocols used to evoke ionic currents should approximate the appropriate elements of a ventricular action potential and be repeated at physiologic intervals to ensure examination and capture of frequency-dependent effects of the test drug. The voltage protocol should include steps that enable monitoring of cell health and consistent electrophysiological recordings throughout the experiment.	No
Stimulating interval	15 seconds	5 seconds	No
Recording Quality	Sufficient number of traces have been recorded in both control solution and after drug application.	A sufficient number of traces should be recorded in control solution to illustrate that steady state level is achieved prior to drug application, and that drug effect reached steady state.	Yes
Background current subtraction	No	a full blocker (E-4031 at 0.5 ~1 μM) should be added at the end of the experiment	No
Concentration verification	Solution samples collected from the stocks recording solutions for drug concentration analysis	The concentrations of drug to which the cells were exposed should be verified by a validated analytical method.	No
Positive Control	E-4031 (100 nM) inhibited current by 80%	two or more concentrations spanning 20–80% block.	No
Negative control	DMSO (0.3%) included	Vehicle (negative) controls should be included in the study to provide an assessment of recording stability and level of background current.	Yes

In summary, the hERG assay showed deviations (e.g., room temperature, a slow stimulating intervals, and samples were collected from the stock solutions for drug concentration verification) from best practice recommendations for an in vitro assay according to the new draft ICH S7B Q&A 2.1 (link). Although this hERG assay did not meet best practices for an in vitro assay, the assay results show that tapinarof has a low risk for QTc prolongation by direct inhibition of hERG current at therapeutic exposure (hERG

margin: > 105449x). The limitations of the hERG assay will not substantially impact this large hERG safety margin.

6 APPENDIX II: OBSERVED CONCENTRATION VALUES

Figure 10 shows QTcF change from baseline versus concentration at Day 1 and Day 29. Figure 11 shows concentration (TAPI) versus time at Day 1 and Day 29. Each color represents one subject. There were a limited number of observations at higher concentration, and therefore the confidence region at Figure 7 is wider at the right-hand side. The observed concentration at Day 1 Hour 24 has a large value and that causes wide confidence interval for Hour 24 at the top panel of Figure 5.

Figure 10 QTcF_CFB vs. Concentration (TAPI, pg/mL)

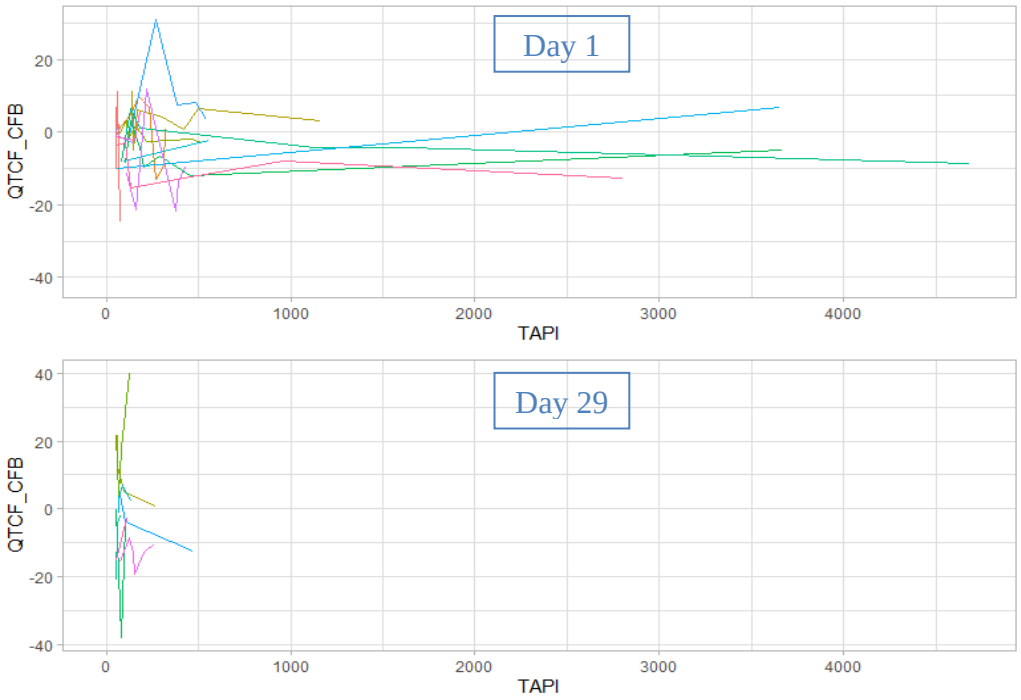
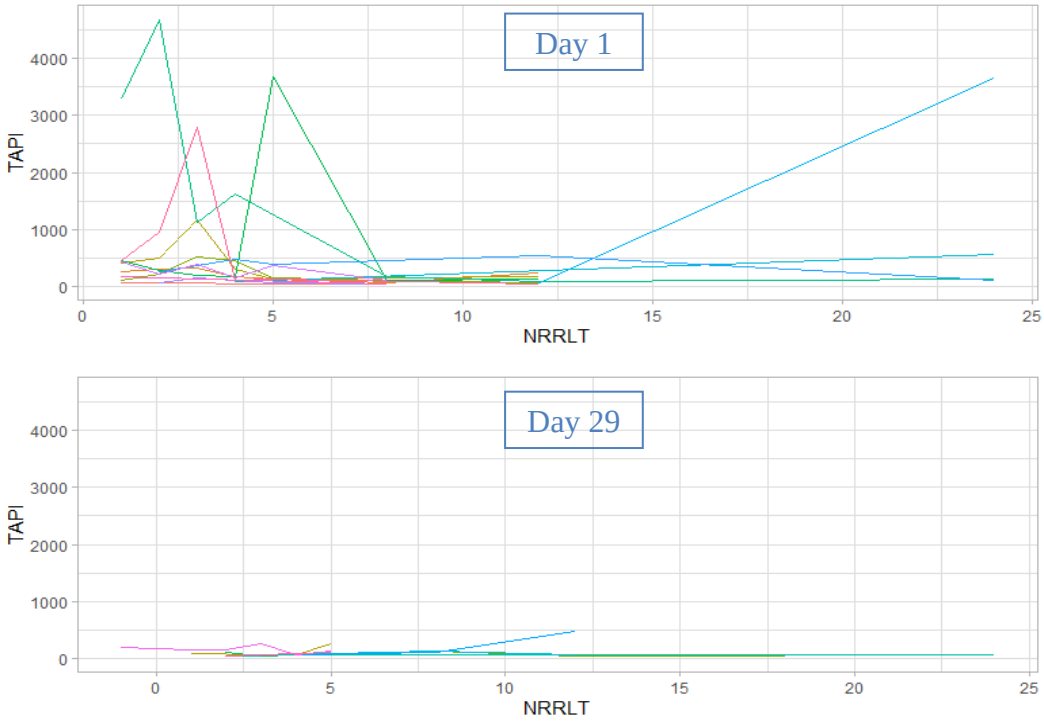


Figure 11 Concentration (TAPI, pg/mL) vs. Time at Day 1



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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 27, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 215272
Product Name, Dosage Form, and Strength:	Vtama (tapinarof) cream, 1%
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Dermavant Sciences, Inc.
FDA Received Date:	May 26, 2021 and August 23, 2021
OSE RCM #:	2021-1180
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Vtama (tapinarof) cream, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Vtama prescribing information (PI), patient package insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), Patient Package Insert (PPI), interim container labels, container labels, and carton labeling. The labels and labeling can be improved to prevent wrong strength errors and deteriorated drug errors and to facilitate product identification. The carton labeling can also be improved to align formatting of product identifiers with the FDA released draft guidance on product identifiers[a]

4 CONCLUSION & RECOMMENDATIONS

[a] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

We conclude that the proposed Prescribing Information (PI) and Patient Package Insert (PPI) are acceptable from a medication error perspective. However, the proposed container labels and carton labeling can be improved. We recommend the following be implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DERMAVANT SCIENCES, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The established name and strength lacks prominence commensurate with the net quantity statement. Decrease the prominence of the net quantity statement and relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

B. Container Labels

1. Commercial size

a. Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to tube curvature.[b]

b. To ensure consistency with the Prescribing Information, revise the statement, "(b) (4) " to read "Recommended Dosage: See prescribing information."

c. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to

[b] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. Physician sample size
    a. To ensure consistency with the Prescribing Information, revise the statement, "[redacted (b) (4)]" to read "Recommended Dosage: See prescribing information."
    b. We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

C. Carton Labeling
1. To ensure consistency with the Prescribing Information, revise the statement, "[redacted (b) (4)] to read "Recommended Dosage: See prescribing information."
2. We did not identify a placeholder ("LOT" or "EXP") for the lot number and expiration date on the proposed carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

3. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. The human-readable product identifier contains the NDC, serial number, lot, and expiration date. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.

   NDC: [insert product' s NDC]
   SERIAL: [insert product' s serial number]
   LOT: [insert product' s lot number]
   EXP: [insert product' s expiration date]

[1] The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vtama received on August 23, 2021 from Dermavant Sciences, Inc..

Table 2. Relevant Product Information for Vtama	
Initial Approval Date	N/A
Active Ingredient	tapinarof
Indication	topical treatment of plaque psoriasis in adults
Route of Administration	topical
Dosage Form	cream
Strength	1%
Dose and Frequency	apply a thin layer of VTAMA Cream to affected areas once daily
How Supplied	60 g NDC 81672-5051-01
Storage	- 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. - Keep out of reach of children.
Container Closure	laminated tubes

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Vtama labels and labeling submitted by Dermavant Sciences, Inc..

- Container Label received on May 26, 2021
- Carton Labeling received on May 26, 2021
- Professional Sample Container Label received on May 26, 2021
- Professional Sample Carton Labeling received on May 26, 2021
- Prescribing Information (Image not shown) received on August 23, 2021, available from \\CDSESUB1\evsprod\nda215272\0008\m1\us\m1-14-1-3-draft-labeling-text_uspi.pdf
- Patient Package Insert (Image not shown) received on May 26, 2021, available from \\CDSESUB1\evsprod\nda215272\0001\m1\us\m1-14-1-3-draft-labeling-text_patien_label.pdf

G.2 Label and Labeling Images

Container Label

(b) (4)

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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