Office of Clinical Pharmacology Review

NDA Number	207154 S-004
Link to EDR	Application 207154 - Sequence 0054 - 0054 (234) 03/15/2019 Multiple Submissions /Multiple Categories/Subcategories
Submission Date	03/15/2019 (SDN 234)
Submission Type	Efficacy Supplement (PMR 3017-1)
Brand Name	ACZONE® gel, 7.5%
Generic Name	Dapsone gel, 7.5%
Dosage Form and Strength	Gel, 7.5 %
Route of Administration	Topical
Proposed Indication	Acne Vulgaris in patients 9 years of age and older
Applicant	Almirall, LLC
Related IND	054440
OCP Primary Reviewer	Luke Oh, Ph.D.
OCP Secondary Reviewer	Chinmay Shukla, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Aczone® (dapsone) gel, 7.5% was approved in 2016 for a treatment of acne vulgaris in patients 12 years of age and older. The original approval had a postmarketing requirement (PMR 3017-1) to assess the pharmacokinetics (PK), safety and treatment effect of dapsone gel in subjects 9 to 11 years of age. The purpose of this efficacy supplement is to fulfil the PMR and to extend the indication in patients down to 9 years of age. The Applicant submitted Phase 4 pediatric study report (Study #1679-401-006).

Reference ID: 4474773

1.1 Recommendations:

NDA 207154/S-004 is acceptable from a Clinical Pharmacology perspective pending agreement on recommended labeling changes. PMR 3017-1 is considered as fulfilled from a Clinical Pharmacology perspective.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

The Applicant assessed PK of dapsone and its metabolites [dapsone hydroxylamine (DHA) and N-acetyl dapsone (NAD)] in 16 subjects 9 to 11 years old with acne vulgaris under maximal use conditions. Subjects in a PK-cohort received topical application of the drug on the entire face, neck, upper chest, upper back and shoulders once daily for 8 days. Plasma concentrations were assessed at pre-dose and at 10-hour post-dose on Day 8 (Week 1 visit).

The Mean ± SD of plasma dapsone concentration at the 10-hour post dose-time point at Week 1 visit was 20.0 ± 12.5 ng/mL and for DHA and NAD metabolites the mean ± SD plasma concentrations the Week 1 visit were 1.40 ± 1.10 ng/mL and 9.01 ± 7.37 ng/mL, respectively.

2. QUESTIONS BASED REVIEW

Not Applicable

3. DETAILED LABELING RECOMMENDATION

Clinical pharmacology provided following addition to labeling recommendations:

8.4 Pediatric Use

Plasma concentrations of dapsone and its metabolites was assessed in a subset of 16 subjects 9 to 11 years of age with acne vulgaris following once daily topical application for 8 days *[see Clinical Pharmacology (12.3)]*

12.3 Pharmacokinetics

In an open label safety and pharmacokinetic study in pediatric subjects 9 to 11 years of age with acne vulgaris, a subset of subjects (N = 16) received once daily topical application of approximately 2 grams of ACZONE Gel, 7.5%, to the entire face, shoulders, upper chest and upper back for 8 days. On Day 8, the systemic concentrations were at or near steady state and the mean ± SD systemic concentration of dapsone at 10 hours post dose was 20 ± 12.5 ng/mL.

Reference ID: 4474773

4. INDIVIDUAL STUDY REVIEW

Study 1679-401-006

Title: An open-label Phase 4 safety and efficacy trial of ACZONE® (Dapsone) Gel, 7.5% in 9 to 11 years-old subjects with acne vulgaris

Primary Objectives:

- To evaluate the safety and tolerability of ACZONE 7.5% administered topically once daily (QD) for 12 weeks in 9 to 11 year-olds with acne vulgaris
- To evaluate the peak and trough plasma drug concentrations in 9 to 11 year-olds with acne vulgaris following QD dosing of ACZONE 7.5% under maximal use conditions for the first 8 days
- To explore the efficacy of ACZONE 7.5% administered topically QD in 9 to 11 year-olds with acne vulgaris

Study Design: This study was a multi-center, non-comparative study in 9 to 11 year-old subjects with mild, moderate, or severe acne vulgaris. The study assessed the safety, tolerability, PK, and efficacy of Aczone 7.5% applied QD for up to 12 weeks. Subjects were enrolled into 1 of 2 cohorts:

- PK cohort (N = 17): Subjects received topical QD application of Aczone 7.5% on the entire face, neck, upper chest, upper back and shoulders for 8 days. The treatment area and a total amount of drug of approximately 2 g/day were considered under maximal use conditions. Plasma samples were collected to evaluate plasma concentrations of dapsone and its metabolites at pre-dose and 10 hours post-dose (i.e., peak) at the Week 1 visit. After the Week 1 visit, subjects received the topical QD treatment on the face for 11 weeks. Additionally, acne-affected areas on the upper chest, upper back, and shoulders were also treated with a thin layer of Aczone 7.5% during the 11 week treatment.

- Non-PK cohort (N = 83): Subjects received topical QD application of Aczone 7.5% in a thin layer on the face. Acne-affected areas on the upper chest, upper back, and shoulders were also treated with a thin layer of Aczone 7.5%.

  Subjects returned to the study center at Weeks 1, 2, 4, 8, and 12/early exit) for a total of up to 7 visits.

Results:

Demographics: In general, demographic characteristics were comparable between PK and non-PK cohorts (Table 1). The mean age was 10.4 years, and the number of female subjects appeared to be higher (74.0%, 74/100; Table 1). The majority of subjects was White (62.0%, 62/100) and had a

Reference ID: 4474773

baseline Investigator Global Assessment (IGA) of moderate severity (53.1%, 52/98). Assessment of baseline IGA and inflammation was conducted on the face only (N = 98).

Pharmacokinetics: Topical QD treatment of Aczone 7.5% for 8 days under maximal use conditions resulted in quantifiable systemic levels of dapsone and its metabolites (i.e., DHA and NAD) in pediatric subjects (N = 16) 9 to 11 years of age with acne vulgaris. At the 1 Week visit, mean ± SD trough level of plasma dapsone, DHA, and NDA concentrations were 17.2 ± 14.0 ng/mL, 1.05 ± 0.98 ng/mL, and 7.02 ± 5.28 ng/mL, respectively (Table 2). Mean ± SD of plasma dapsone concentration at the 10-hour post-dose was 20.0 ± 12.5 ng/mL (Table 2). Mean ± SD of plasma DHA and NAD concentration at the 10-hour post-dose on Week 1 visit was 1.40 ± 1.10 ng/mL and 9.01 ± 7.37 ng/mL, respectively (Table 2). The lower limit of quantification (LLOQ) for dapsone and NAD was 0.05 ng/mL. For DHA, the LLOQ was 0.1 ng/mL.

Safety: Treatment-emergent adverse events (TEAEs) were reported in 21.0% of subject; 5/17 (29.4%) in the PK cohort and 16/83 (19.3%) subjects in the Non-PK cohort (Table 3). All TEAEs were mild or moderate in severity. In two cohorts together, most common TEAEs were upper respiratory tract infection (3/100), nasopharyngitis (2/100), and pharyngitis streptococcal (2/100). There were 3 subjects developed dermatitis contact in the study: One subject in PK cohort discontinued the treatment due to dermatitis contact (Table 3) resulting in 16 subjects completing PK assessments. There was no death or serious TEAEs reported during the study.

Reviewer comments: *See Clinical review for further information on safety assessment.*

Efficacy: At the end of the study, 46.7% of subjects achieved success (none or minimal disease at the end of 12-week treatment) based on the IGA. Mean ± SD reductions from baseline in inflammatory and noninflammatory lesion counts were -6.2 ± 9.3 (-56.38% change from baseline) and -17.8 ± 17.0 (-46.45%) change from baseline), respectively.

Reviewer comments: *This was an open label trial and efficacy assessment is considered as exploratory. See Clinical review for further information on efficacy assessment.*

Table 1. Demographics and baseline characteristics *(Source: Table 10 - 3 in Study report CSR 1679-401-006)*

Reference ID: 4474773

Characteristic	Statistic	PK Cohort (N = 17)	Non-PK Cohort (N = 83)	Total (N =100)
Age (years)	N	17	83	100
	Mean (SD)	10.1 (0.9)	10.4 (0.7)	10.4 (0.8)
	Median	10.0	11.0	11.0
	Min to max	9, 11	9, 11	9, 11
Sex (N [%])	Male	2 (11.8)	24 (28.9)	26 (26.0)
	Female	15 (88.2)	59 (71.1)	74 (74.0)
Race (N [%])	N	17	83	100
	White	9 (52.9)	53 (63.9)	62 (62.0)
	Black or African American	5 (29.4)	19 (22.9)	24 (24.0)
	Asian	1 (5.9)	9 (10.8)	10 (10.0)
	American Indian or Alaska Native	0	0	0
	Native Hawaiian or other Pacific Islander	0	0	0
	Other[a]	2 (11.8)	2 (2.4)	4 (4.0)
BMI (kg/m^2)	N	17	83	100
	Mean (SD)	21.51 (4.29)	21.74 (5.76)	21.70 (5.52)
	Median	21.50	20.40	20.45
	Min to max	15.4, 29.0	13.8, 45.2	13.8, 45.2
Skin phototype (N [%])	N	17	83	100
	I	0	2 (2.4)	2 (2.0)
	II	2 (11.8)	11 (13.3)	13 (13.0)
	III	6 (35.3)	34 (41.0)	40 (40.0)
	IV	4 (23.5)	17 (20.5)	21 (21.0)
	V	4 (23.5)	6 (7.2)	10 (10.0)
	VI	1 (5.9)	13 (15.7)	14 (14.0)
IGA (N [%])[b]	0 = Clear	0	0	0
	1 = Almost clear	0	0	0
	2 = Mild	9 (52.9)	35 (43.2)	44 (44.9)
	3 = Moderate	8 (47.1)	44 (54.3)	52 (53.1)
	4 = Severe	0	2 (2.5)	2 (2.0)
Inflammatory lesion count[b]	N	17	81	98
	Mean (SD)	9.6 (5.8)	12.8 (14.3)	12.3 (13.3)
	Median	11.0	9.0	10.0
	Min to max	0, 18	0, 79	0, 79
Noninflammatory lesion count[b]	N	17	81	98
	Mean (SD)	39.4 (21.6)	36.8 (23.7)	37.2 (23.2)
	Median	30.0	27.0	28.5
	M in to max	16, 89	5, 150	5, 150
Total lesion count[b]	N	17	81	98
	Mean (SD)	49.0 (23.7)	49.6 (32.6)	49.5 (31.1)
	Median	42.0	38.0	38.5
	Min to max	23, 100	20, 229	20, 229

BMI = body mass index; IGA = Investigator Global Assessment; Max = maximum; Min = minimum; mITT = modified intent-to-treat; Non-PK = nonpharmacokinetic; PK = pharmacokinetic

Skin phototype I: always burns easily; never tans (sensitive), II: always burns easily; tans minimally (sensitive), III: burns moderately; tans gradually (light brown) (normal), IV: burns minimally; always tans well (moderate brown) (normal), V: rarely burns; tans profusely (dark brown) (insensitive), VI: never burns; deeply pigmented (insensitive).

Inflammatory, noninflammatory, and total lesion counts are the total lesion counts on the face assessed on Day 1.

[a] Includes patients with multiple races (Listing 16.2.4-1.1)

[b] IGA and lesion counts were based on evaluation of the face only, using the mITT population.

Source: Tables 14.1-2.1 and 14.1-2.2

Reference ID: 4474773

Table 2. Summary results of pre-dose and 10-hour post-dose plasma concentrations of dapsone and its metabolites in PK cohort at the Week 1 visit *(Data source: Table 11-2 in Study report CSR 1679-401-006)*

Analyte Statistic	Predose Concentration (ng/mL) N = 16	10-hour Postdose Concentration (ng/mL) N = 16
Dapsone		
Mean (SD)	17.2 (14.0)	20.0 (12.5)
Median	13.5	17.2
Min, Max	0.919, 55.5	4.07, 51.9
Dapsone hydroxylamine (DHA)		
Mean (SD)	1.05 (0.979)	1.40 (1.10)
Median	0.783	1.02
Min, Max	0.00, 3.35	0.407, 4.14
N-acetyl dapsone (NAD)		
Mean (SD)	7.02 (5.28)	9.01 (7.37)
Median	5.42	5.33
Min, Max	0.395, 18.0	1.59, 23.2

Max = maximum; Min = minimum
Source: Table 14.6.2-1

Table 3. Summary of adverse event *(Data source: Table 12-2 in Study report CSR 1679-401-006)*

	Number (%) of Patients		
	PK Cohort (N = 17)	Non-PK Cohort (N = 83)	Total (N = 100)
All TEAEs	5 (29.4)	16 (19.3)	21 (21.0)
Treatment-related TEAEs	1 (5.9)	0	1 (1.0)
Serious TEAEs	0	0	0
Deaths	0	0	0
AEs leading to study discontinuation	1 (5.9)	0	1 (1.0)

AE = adverse event; TEAE = treatment-emergent adverse event
Within each type of relationship, a patient is counted at most once. All TEAEs include all reported events, regardless of relationship to treatment.
Treatment-related TEAEs include those that in the investigator's opinion may have been caused by the study treatment with reasonable possibility.
Source: Table 14.3.1-1.1

Conclusions: *The Applicant stated that the pediatric study results demonstrated that topical QD treatment of dapsone 7.5% gel for 12 weeks is a safe and effective treatment for acne vulgaris in subjects 9 to 11 years of age. Plasma concentrations of dapsone and its metabolites in subjects 9 to 11 years of age following QD application under maximal use conditions were low and appeared to reach steady state at the Week 1 visit following 8 days of treatment.*

Reviewer's comments: *The PK cohort had 6/17 subjects at age of 9 years and the Non-PK cohort had 12/83 subjects at age of 9 years, which were reasonable number of pediatric subjects for the*

Reference ID: 4474773

study. The PK cohort had 15/17 (88.2%) completed subjects through 12-week treatment as 1 subject discontinued treatment due to adverse event (i.e. dermatitis contact) and lost to follow-up. Non-PK cohort has 76/83 (91.6%) completed subjects.
A total mean ± SD amount of product applied was 1.81 ± 0.87 g/day during 1st week in the PK cohort, while in the non-PK cohort it was approximately 0.63 g/day. Based on this information, the dose applied in the maximal use cohort is considered as reasonable.
The Applicant selected 10-hour post-dose timepoint to assess the peak plasma concentrations of dapsone and its metabolites based on T_{max} observed in a previous study conducted in subjects 12 years of age and older (Study 225678-004). Study 225678-004 was a Phase 1 study to evaluate different formulations of dapsone in subjects with acne vulgaris. The Applicant reported that mean ± SD T_{max} of plasma dapsone following topical application of dapsone 7.5% gel was 10.8 ± 7.3 hours. Therefore, the selection of 10-hour post-dose was reasonable to measure the peak plasma level of dapsone in the pediatric study.
Per current label, Subjects 16 years of age or older with acne vulgaris receiving dapsone 7.5% gel QD for 28 days showed that the mean ± SD systemic dapsone C_{max} and AUC_{0-24} post-dose on Day 28 were 13.0 ± 6.8 ng/mL and 282 ± 146 ng.h/mL, respectively. Steady state for dapsone was reached within 7 days of dosing. Dapsone exposures in pediatric subjects (12 – 15 years of age) were approximately the same as those in subjects 16 years of age or older in a long-term clinical study of dapsone gel 5% twice daily treatment.
The current pediatric study results in subjects 9 to 11 years of age showed a small increase (16% higher) in plasma dapsone concentrations between pre-dose and 10-hours post-dose suggesting the systemic dapsone concentrations were at or near steady state on Day 8. From Clinical pharmacology perspective, the Applicant's pediatric study results support the proposed labeling change to include intended treatment patient age down to 9 years of age.

Summary of Bioanalytical Method validation:

The plasma levels of dapsone and 2 metabolites were determine using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS). The linear concentration range was 0.05 ng/mL to 25 ng/mL for dapsone and NAD, 0.1 ng/mL to 25 ng/mL for DHA with performance characteristics shown as Table 3. The dapsone standard in human plasma was stable for at least 18 months at – 70 ^{o}C, and this long-term stability duration was adequate to support the storage stability of the PK plasma samples.

Table 3. Precision and accuracy of dapsone bioanalytical method *(Source: Validation report for quantitation of dapsone)*

Reference ID: 4474773

Human Plasma Intraday and Interday Precision and Accuracy				
Dapsone				
	Intraday		Interday	
Nominal Conc. (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)
0.05 (LLOQ)	0.733	3.72	-3.36	4.83
0.15 (LQC)	4.89	4.01	2.96	3.38
10 (MQC)	4.33	1.44	0.783	3.47
20 (HQC)	2.67	0.907	-0.833	3.92

Human Plasma Intraday and Interday Precision and Accuracy				
N-Acetyl Dapsone				
	Intraday		Interday	
Nominal Conc. (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)
0.05 (LLOQ)	-7.67	7.32	-4.81	5.45
0.15 (LQC)	-0.111	3.47	0.148	4.44
10 (MQC)	-0.683	0.602	0.500	1.68
20 (HQC)	-1.83	1.32	-0.833	2.97
Dapsone Hydroxylamine				
	Intraday		Interday	
Nominal Conc. (ng/mL)	Accuracy (% Bias)	Precision (% CV)	Accuracy (% Bias)	Precision (% CV)
0.1 (LLOQ)	-5.90	7.24	-5.39	6.07
0.3 (LQC)	-7.78	4.06	-5.76	3.73
10 (MQC)	-1.68	2.16	-2.92	1.98
20 (HQC)	-3.33	0.534	-3.33	0.939

Reference ID: 4474773

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LUKE Y OH
08/08/2019 03:37:40 PM

CHINMAY SHUKLA
08/08/2019 03:44:50 PM