Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for dapsone

Proprietary Product Name: Aczone

Sponsor: Allergan Australia Pty Ltd

First round report: March 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviations	Meaning
ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
ASIS	Acne Symptom and Impact Scale
AUC_{0-x}	area under the concentration time curve from time 0 to x hours post dose
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
BD	twice daily
CI	confidence interval
Cmax	maximum concentration in plasma
BID/BD	twice daily
BSA	body surface area
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DGME	diethylene glycol monoethyl ether
DHA	dapsone hydroxylamine
ECG	electrocardiogram
EP	European Pharmacopeia
FDA	Food and Drug Administration (US)
G6PD	glucose 6-phosphate dehydrogenase
GAAS	Global Acne Assessment Score
GCP	Good Clinical Practice
QTc	corrected QT interval
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety

Abbreviations	Meaning
IVRS/IWRS	interactive voice/web response system
ITT	intent-to-treat (analysis population)
LDH	lactate dehydrogenase
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDPE	low density polyethylene
LOCF	last observation carried forward
LS	least-squares
MCII	mean cumulative irritancy index
MED	minimal erythemal dose
MedDRA	Medical Dictionary for Regulatory Activities
NAD	n-acetyl dapsone
NFD	N-formyl dapsone
PI	Product Information
PP	per protocol
PT	preferred term
QD	once daily
QTc	corrected QT interval
QTcB	QTc Bazett's formula
QTcF	QTc Fridericia-correction
RIPT	repeat insult patch test
SE	standard error
SLS	sodium lauryl sulphate
SOC	system organ class
TEAE	treatment-emergent adverse event
TMP/SMX	trimethoprim/sulfamethoxazole
SD	standard deviation

Abbreviations	Meaning
UPT	urine pregnancy test
w/w	weight per weight

1. Introduction

This is a submission to register a new dose form, new route of administration and extension of indications.

1.1. Drug class and therapeutic indication

Dapsone is a synthetic sulfone with antibacterial and anti-inflammatory properties. The product is Aczone"', dapsone, 7.5% w/w, gel, topical, bottle, with integral pump - manual actuated.

Dapsone is currently approved in Australia (to other sponsors) in a tablet dosage form for the following indications:

- ARTG 17608 - ALPHAPHARM DAPSONE 100 dapsone 100mg tablet for leprosy, dermatitis herpetiformis, actinomycotic mycetoma
- ARTG 104483 LINK MEDICAL PRODUCTS DAPSONE dapsone 100mg tablet for dermatitis herpetiformis, leprosy, actinomycotic mycetoma.
- ARTG 104482 LINK MEDICAL PRODUCTS DAPSONE dapsone 25mg tablet for dermatitis herpetiformis, leprosy, actinomycotic mycetoma.

The proposed new indication is:

For the topical treatment of acne vulgaris in patients 12 years of age and older.

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

- Dapsone 25 mg tablet (Link Medical Products)
- Dapsone 100 mg tablet (Alphapharm and Link Medical Products)

The submission proposes registration of the following new dosage form and strength:

- Dapsone gel 7.5% w/w dapsone gel formulation is packaged in an airless pump container closure system - and provided in 30 g, 60 g, 90 g and 100 g fill sizes and 3 g professional sample tube.

1.3. Dosage and administration

The sponsor is requesting a new standalone Product Information (PI), ie it does not include the tablet formulation.

The Dosage and Administration section of the new PI includes the following:

- For dermatological (topical) use only.
- Aczone® 7.5% w/w gel should only be applied to affected areas. For external use only. Not for oral, ophthalmic or intravaginal use. If contact with eyes occurs, rinse thoroughly with water.
- After the skin is gently washed and patted dry, approximately a pea-sized amount of Aczone® 7.5% w/w gel, should be applied in a thin layer to the entire face once daily. In addition, a thin layer may be applied to other affected areas once daily. Aczone® 7.5% w/w gel should be rubbed in gently and completely.
- Patients should be instructed to wash their hands after application of Aczone® 7.5% w/w gel.

- If there is no improvement after 12 weeks, treatment with Aczone® 7.5% w/w gel should be reassessed.

2. Clinical rationale

Acne vulgaris is the most common dermatological disorder in the US where it is estimated to affect approximately 40 to 50 million people. It is most common in adolescents, affecting approximately 80%, but may also occur in 54% of adult women and 40% of adult men. Globally, acne vulgaris is the eighth most prevalent disease (645.5 million patients; Hay et al, 2014). In a study published in 1998, the prevalence was 93% in 16- to 18-year-old students in Victoria, Australia (Kilkenny et al, 1998).

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including 1) hyperkeratinisation, 2) increased sebum production, 3) bacterial proliferation, and 4) inflammation. The face, anterior trunk, and upper back are the most commonly affected areas due to a greater concentration of sebaceous glands in these areas. Clinically, acne is graded according to the number and types of lesions present: open and closed comedones, inflammatory papules, pustules, cysts, nodules, and even scarring may be seen.

A number of topical and systemic products are approved in Australia for treatment of acne vulgaris. The pharmacologic categories of therapies for acne vulgaris include topical retinoids (eg, adapalene, tazarotene, and tretinoin), topical antibiotics (eg, erythromycin and clindamycin), topical benzoyl peroxide, oral retinoids (eg, isotretinoin), and systemic hormonal therapies (eg, ethinyl oestradiol/levonorgestrel). Combination therapy utilising agents with complementary mechanisms (such as an antimicrobial and a topical retinoid) is often prescribed in the management of acne vulgaris, since most anti-acne medications do not act against all of the major pathophysiologic processes or types of lesions of acne vulgaris.

Despite the well-known role of inflammation in acne, no primarily anti-inflammatory topical therapy is currently available in Australia for treatment of acne. Aczone 7.5% provides both the anti-inflammatory and antimicrobial properties of dapsone while greatly limiting the risk of complications associated with systemic exposure from oral administration of dapsone for acne vulgaris.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission is based on the submission in the USA and contains a full clinical development program of pharmacology, efficacy and safety suitable for a topical product.

The submission contained the following clinical information:

- 1 x clinical pharmacology studies, including 1 that provided pharmacokinetic data and none that provided pharmacodynamic data
- 2 x pivotal efficacy/safety studies
- 3 other efficacy/safety studies related to the 7.5% gel
- Studies related to 5% gel
  - 3 x clinical pharmacology studies, including 3 that provided pharmacokinetic data and none that provided pharmacodynamic data
  - 1 x pivotal efficacy/safety studies
  - 3 x other efficacy/safety studies

· 2 x other {Integrated Summary of Efficacy, Integrated Summary of Safety tabulations}

3.2. Paediatric data

The submission included paediatric pharmacokinetic and efficacy and safety data.

3.3. Good clinical practice

The study reports state that all studies were conducted in compliance with Good Clinical Practice (GCP). For subjects under age of 18, written minor assent and/or parental/guardian consent was obtained in accordance with local laws and appropriate ethics committee requirements.

There were a number of GCP compliance issues identified at one centre in the USA in Study 225678-006 and due to resulting concerns over data integrity, it was decided to exclude all 51 patients at that centre from all analysis populations in that study. Sensitivity analyses were performed to evaluate the impact of excluding those patients and the results of sensitivity analyses including patients from the centre were consistent with analyses excluding those patients.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1: Submitted pharmacokinetic studies.

7.5% dapsone gel

PK topic	Subtopic	Study ID	Primary aim
PK in special populations§	Bioequivalence† - Multi-dose	225678-004	Bioequivalence

5% dapsone gel

PK in special populations§	Bioavailability – oral vs topical	DAP110	Bioavailability
	Dose Ranging	DAP9903	Dose range
PK interactions	Trimethoprim/sulfamethoxazole	03-0-182	Interaction

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

Very little information is provided on the pharmacokinetics. The submission relies on the acceptance of the 5% gel formulation overseas. Much of the information on the PK is taken from the

US Approved Package Insert for the 5% Gel and selected literature references. A formal literature based submission was not done.

4.2.1. Physicochemical characteristics of the active substance

Dapsone is a white or slightly yellow-white, crystalline powder with a molecular weight of 248.30 g/mol. The amine groups on the aminobenzene rings have calculated pKa1 at 0.5 and calculated pKa2 at 1.2. Dapsone is very slightly soluble in water, freely soluble in acetone, sparingly soluble in alcohol, and dissolves freely in dilute mineral acids (EP Current edition).

4.2.2. Pharmacokinetics in healthy subjects

All PK studies were conducted in patients with acne vulgaris.

4.2.3. Pharmacokinetics in the target population

4.2.3.1. Absorption

No studies were done which investigated the absorption of Dapsone 7.5% gel.

Study DAP9903 was a phase 1, multicentre; parallel-design trial carried out in 18 patients with acne vulgaris and incorporated a dose-ranging PK component. Both 1% dapsone topical gel and dapsone 5% were administered once daily or twice daily for 28 days in fixed dose (1 g of gel per application) to a defined area of facial skin of approximately 250 cm^2. This resulted in topical dapsone application of 10, 20, 50, and 100 mg/day in the 4 treatment groups. Systemic absorption of dapsone was very low over this range of doses with mean C_{max} values on Day 28 ranging from 5.54 to 15.1 ng/mL.

Dapsone concentrations appeared to reach steady-state by Week 1. Dapsone exposures (C_{max} and AUC) increased less than proportionally over the range of doses studied. Across the treatment groups, T½ was approximately 30 hours.

4.2.4. Bioavailability

4.2.4.1. Bioavailability relative to an oral tablet

Study DAP0110 was conducted in 18 patients with acne vulgaris to assess the maximum potential systemic exposure to dapsone after treatment with dapsone 5% gel compared with oral dapsone. In this study, dapsone 5% was applied twice daily for 14 days to the face, back, chest, and shoulder (approximately 3000 cm^2) at a mean ± standard deviation (SD) product dose of 2.2 ± 1.2 g/day (equivalent to a dapsone dose of 110 mg/day). A subset of patients (N = 10) also received a single dose of oral dapsone (100 mg) after a 14 day washout period in a cross-over design.

Mean C_{max} following dapsone 5% application on Day 0 and Day 14 were 5.43 and 19.7 ng/mL, respectively. The mean plasma dapsone AUC_{0-24} was 88.7 ng·hr/mL on Day 0 and 415 ng·hr/mL on Day 14. Median terminal T½ after the last dapsone 5% dose was 46.3 hours. Following the single 100 mg oral dose of dapsone, exposure with regards to mean C_{max} and mean area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}) were 1,375 ng/mL and 5,2641 ng·hr/mL, respectively. The median terminal T½ for oral dapsone was 19.3 hours.

Exposure after oral dose of dapsone was approximately 100 times greater than the exposure after the topical dose indicating that dapsone is minimally and slowly absorbed following topical application of dapsone 5%.

4.2.4.2. Bioavailability relative to 5% gel

Study 225678-004 compared the 7.5% gel (Formulation 11080X, which was chosen for further development) applied once daily with the 5% gel applied twice daily for 28 days. Mean plasma concentrations of dapsone (including mean peak and trough concentrations) following application of Aczone 7.5% once daily were consistently lower than those following application of dapsone 5% twice daily. Relative to dapsone 5% applied twice daily, the daily systemic exposure of dapsone, as defined by the geometric mean ratio for maximum plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 hours post dose (AUC_{0-24}), was approximately 28.6%

and 28.7% lower for Aczone 7.5%, respectively. Based on the 90% confidence intervals (CI) of the geometric mean ratios for C_{max} and AUC_{0-24}, these differences were statistically significant. In addition, the C_{max} and AUC_{0-24} values for Aczone 7.5% were approximately 49.4% and 48.5% lower for the metabolites N-acetyl dapsone (NAD), and were approximately 22.8% and 25.0% lower for dapsone hydroxylamine (DHA).

Table 2: Study 225678-004: Mean plasma PK parameters of dapsone, N-acetyl dapsone, and dapsone hydroxylamine following once-daily topical dermal administration of Aczone 7.5% and twice-daily topical dermal administration of dapsone 5% for 28 days in patients with acne vulgaris.

Analyte	PK Parameters on Day 28	Dapsone 5% Twice Daily (N = 18)		Aczone 7.5% Once Daily (N = 19)	
		Mean	SD	Mean	SD
Dapsone	T_{max} (hr)	12.7	12.0	10.6	7.5
	C_{max} (ng/mL)	17.6	6.7	13.0	6.8
	C_{trough} (ng/mL)	15.9	5.7	11.1	6.5
	AUC_{0-12} (ng·hr/mL)	186	71	NA	NA
	AUC_{0-24} (ng·hr/mL)	379	142	282	146
	T½ (hr)	51.3	17.1	51.4	12.4
	GMR for C_{max}	NA		71.4 (54.8, 93.1)*	
	GMR for AUC_{0-24}	NA		71.3 (55.5, 91.7)*	
N-acetyl Dapsone	T_{max} (hr)	13.0	12.5	14.0	10.2
	C_{max} (ng/mL)	11.7	8.8	6.47	5.43
	C_{trough} (ng/mL)	8.91	5.6	5.52	4.89
	AUC_{0-12} (ng·hr/mL)	118	88	NA	NA
	AUC_{0-24} (ng·hr/mL)	236	168	135	111
	T½ (hr)	52.2	20.3	49.6	11.2
	GMR for C_{max}	NA		50.6 (32.5, 78.8)*	
	GMR for AUC_{0-24}	NA		51.5 (33.4, 79.3)*	
Dapsone hydroxylamine	T_{max} (hr)	16.1	8.2	12.1	8.0
	C_{max} (ng/mL)	1.47	0.56	1.19	0.76
	C_{trough} (ng/mL)	1.34	0.57	0.860	0.475
	AUC_{0-12} (ng·hr/mL)	15.0	5.7	NA	NA
	AUC_{0-24} (ng·hr/mL)	31.1	11.6	24.5	15.6
	T½ (hr)	54.7	21.4	53.9	25.6
	GMR for C_{max}	NA		77.2 (57.5, 104)	
	GMR for AUC_{0-24}	NA		75.0 (56.0, 100)	

SD = standard deviation; T_{max} = time to maximum plasma concentration; C_{max} = maximum plasma concentration; C_{trough} = trough concentration; AUC_{0-12} = area under the concentration-time curve from 0 to 12 hours post dose; AUC_{0-24} = area under the concentration-time curve from 0 to 24 hours post dose;

T½ = half-life; GMR = geometric mean ratio (relative to Dapsone 5% twice daily); NA = not applicable

* Statistically significant based on 90% confidence interval

4.2.4.3. Influence of food

Not applicable.

4.2.4.4. Dose proportionality

In study DAP9903 dapsone exposures (C_{max} and AUC) increased less than proportionally over the range of doses studied.

4.2.5. Metabolism

Dapsone is metabolised by 2 major pathways to form N-acetyl dapsone (NAD) and dapsone hydroxylamine (DHA).

4.2.5.1. Excretion

Following oral administration, approximately 85% of the administered dapsone is recovered in urine, mainly as soluble metabolites (Dapsone tablets (oral) US package insert, 2011), and only a small fraction (5% to 15%) is excreted as unchanged drug in humans (Tingle et al, 1997).

4.2.6. Pharmacokinetics in other special populations

4.2.6.1. Pharmacokinetics in subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency

Study ACZ ACN 01 was conducted to evaluate the risk of haematological adverse events with dapsone 5% in acne vulgaris patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The study was performed in order to meet the post-approval requirements for dapsone 5% in the US, and the design of the study was based on the recommendation of the US FDA. This was a double-blind, multicentre, randomised, cross-over study with 64 patients applying dapsone 5% or vehicle twice daily in 12-week sequences, with a 2-week washout period between the 2 treatment periods. Dapsone 5% was applied onto the entire face and as required to other acne-affected areas. The mean ± SD product application was 1.06 ± 0.57 g/day, which is equivalent to average topical application of 52.8 mg/day dapsone.

Following 12 weeks of treatment with dapsone 5%, plasma concentrations of dapsone (5.63 ng/mL at 2 weeks and 5.30 ng/mL at 12 weeks) were approximately 2-fold higher than those of the N-acetyl dapsone (2.77 ng/mL at 2 weeks and 2.51 ng/mL at 12 weeks). Plasma concentrations for dapsone were similar following 2 weeks or 12 weeks of dosing with dapsone 5%, which suggested that steady state was reached within 2 weeks of dosing with dapsone 5%.

4.2.7. Pharmacokinetic interactions

Study 03-0-182 was conducted to assess the potential for PK drug-drug interactions between dapsone 5% and combination antibacterial products containing trimethoprim (TMP) and sulfamethoxazole (SMX). This was a 42-day, phase 1, prospective, open-label study administering TMP/SMX tablets (160 mg/800 mg) twice daily for 7 days on Days 1 to 7 followed by a 1-week washout. The next 28 days, patients applied dapsone 5% twice daily to the face, neck, shoulders, upper chest, and upper back (approximately 3000 cm^2) on Days 15 to 42. During the last 7 days of the dapsone 5% application, patients received oral TMP/SMX tablets twice daily on Days 36 to 42. Dapsone plasma concentrations reached steady-state within 7 days. A new steady-state was reached within 5 days after initiation of concomitant dosing with TMP/SMX.

Mean dapsone AUC_{0-12} increased 145% from 292 to 402 ng·hr/mL after dapsone 5% alone treatment compared with co-administration of TMP/SMX. A similar trend was seen in C_{max} values, with a 139% increase during treatment with TMP/SMX, but the dapsone levels remained well below those associated with oral use.

4.3. Evaluator's overall conclusions on pharmacokinetics

It is difficult to assess the PK of dapsone 7.5% gel when so little information is provided on this strength and formulation. The majority of the data presented is for the dapsone 5% gel. There is very minimal systemic absorption of dapsone from 5% gel applied twice daily and as the 7.5% gel provides less dapsone exposure than 5% gel applied twice daily it would appear even less likely to be of any significant systemic absorption of dapsone from the 7.5% gel.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No studies were submitted related to the pharmacodynamic action of dapsone. The information provided comes from selected literature references. A formal literature based submission was not done.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Dapsone is a synthetic sulfone with antimicrobial and anti-inflammatory properties that has been available for over 60 years for the oral treatment of leprosy and dermatitis herpetiformis.

The anti-inflammatory properties of dapsone result from the inhibition of the cytotoxic system in granulocytes. Inhibition of neutrophil myeloperoxidase and eosinophil peroxidase by dapsone suppresses the production of hypochlorous acid that kills bacteria but also damages adjacent tissue (Bozeman et al, 1990). Dapsone also scavenges reactive oxygen species and minimises inflammation associated with the generation of these highly reactive species (Niwa et al, 1984; Theron and Anderson, 1985). Dapsone suppresses neutrophil recruitment and local production of toxic respiratory and secretory products through the inhibition of chemoattractant-induced signal transduction (Debol et al, 1997). Dapsone's antimicrobial activity is unrelated to its anti-inflammatory activity. Dapsone competitively inhibits dihydropteroate synthase, which is the enzyme required for the synthesis of folic acid. Therefore, microorganisms that need to synthesise folic acid are sensitive to this class of compounds (sulfones) (Coleman, 1993).

5.3. Evaluator's overall conclusions on pharmacodynamics

No new information on pharmacodynamics was provided.

6. Dosage selection for the pivotal studies

The pivotal studies evaluated dapsone 7.5% formulation 11080X with once-daily dosing. This dapsone 7.5% formulation was evaluated in a 5-week Phase 1 PK study (Study 225678-004), the results of which indicated that dapsone 7.5% formulation dosed once daily demonstrated systemic exposures 28.6% and 28.7% lower than Aczone 5% dosed twice daily (as defined by the geometric mean ratio for C_{max} and AUC_{0-24}, respectively), and was therefore not expected to raise additional safety concerns. It was anticipated that simplification of the dosing regimen from twice daily to once daily would be more convenient to patients and yield better compliance compared with twice daily dosing with 5% gel.

7. Clinical efficacy

7.1. Treatment of acne vulgaris

7.1.1. Pivotal efficacy studies

7.1.1.1. Study 225678-006: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris

Study design, objectives, locations and dates

A multicentre, randomised, double blind, vehicle controlled, parallel group study conducted at 105 sites (96 in USA and 9 in Canada) from November 2013 to October 2014.

Objective

To assess the safety and efficacy of Dapsone 7.5% versus vehicle control administered topically once daily for 12 weeks in patients with acne vulgaris.

Inclusion and exclusion criteria

Inclusion

Healthy male and female (non-childbearing potential) patients who were 12 years of age or older with acne vulgaris and a minimum of 20 but not more than 50 inflammatory lesions (papules and pustules) on the face; a minimum of 30 but not more than 100 non-inflammatory lesions (open comedones and closed comedones) on the face and with an acne grade of 3 (moderate) using the Global Acne Assessment Score (GAAS) as assessed by the investigator at screening and baseline.

Exclusion

Uncontrolled systemic disease(s); severe cystic acne, acne conglobata, acne fulminans, or secondary acne (chloracne, drug-induced acne, etc); one or more nodule(s) or cyst(s) above the mandibular line; use of phototherapy devices (eg, ClearLight™), energy-based devices, adhesive cleansing strips (eg, Pond's®, Biore®), or cosmetic procedures (eg, facials, peeling, comedo extraction) within the prior1 week; use of topical anti-inflammatory drugs, salicylic acid (eg, Clearasil®, Clean & Clear®); corticosteroids, antibiotics, antibacterials (including benzoyl peroxide-containing products [eg, benzamycin]), retinoids; other topical acne treatments (eg, photodynamic therapy, medicated soaps such as those containing benzoyl peroxide, salicylic acid, sulfur, or sodium sulfacetamide) within the prior 2 weeks; use of systemic anti-inflammatory drugs (used for more than 2 weeks) in the prior2 weeks; use of systemic antibiotics (except penicillins) for the prior 4 weeks; other acne treatments (eg, isotretinoin, anti-androgens such as spironolactone) for the prior 6 months; oral contraceptives solely for the control of acne.

Study treatments

Patients were randomly assigned in a 1:1 ratio to receive dapsone 7.5% or vehicle applied by the patient topically once daily for 12 weeks.

The first dose of study product was administered at the investigational centre on day 1 and was supervised by study staff. Patients were instructed to gently wash and pat their skin dry, and to apply an approximately pea-sized amount of dapsone 7.5% to the entire face in a thin layer once daily. Thereafter, patients administered the assigned drug to their entire face once daily at home. It was recommended to be at the same time of day at the patient's preference.

Acne-affected areas within reach of the patient on their neck, upper chest, upper back, and shoulders were also to be treated.

Efficacy variables and outcomes

There were 2 primary efficacy outcomes: GAAS and lesion count at Week 12.

Other efficacy outcomes included:

- Absolute change from baseline in total lesion counts
- Percentage change from baseline in total, inflammatory and non-inflammatory lesion counts at Week12
- Proportion of patients who reported “very good” or “excellent” in Item 10 (facial appearance) of the Acne Symptom and Impact Scale (ASIS) at Week 12
- Change from baseline at week 12 in ASIS Sign domain (facial acne signs)
- Proportion of patients with at least a 1 grade improvement from baseline at Week 12 in ASIS Item 1 (facial oiliness)
- Proportion of patients with at least a 1 grade improvement from baseline at Week 12 in ASIS Item 8 (facial redness)

Definitions of GAAS, lesion count and ASIS are provided.

Randomisation and blinding methods

Randomisation was carried out using an interactive voice response system (IVRS) or interactive web response system (IWRS) and was stratified by sex (male versus female).

All study treatments were provided in identical 75-mL MegaPump™ containers to maintain blinding in the study. The study product was dispensed by study personnel other than the investigator or other evaluators.

Analysis populations

The intent-to-treat (ITT) population consisted of all randomised patients, excluding patients from 1 investigational centre removed due to GCP issues.

The per-protocol (PP) population included randomised patients with no protocol deviations during the study that might potentially affect the primary efficacy analyses.

The safety population included all patients who were treated with at least 1 application of study treatment, excluding patients from the removed investigational centre.

Table 3: Study 225678-006: Patients enrolled and study populations (All screened patients)

Disposition	Number (%) of Patients		
	Dapsone 7.5%	Vehicle	Total
Total [a]			2557
Screen failure			389
Screen success			2168
Enrolled [b]	1069	1084	2153
ITT [c]	1044 (97.7)	1058 (97.6)	2102 (97.6)
PP [d]	968 (90.6)	962 (88.7)	1930 (89.6)
Safety [e]	1044 (97.7)	1057 (97.5)	2101 (97.6)

ITT = intent-to-treat; PP = per-protocol; a. Includes all screened patients; b. Includes all randomised patients. Three patients were randomised twice. These patients were included in all analyses once, using the first of each respective patient number; c. Includes all randomised patients, excluding patients from 1 investigational centre; d. Includes all randomised patients with no protocol deviations during the study that might potentially affect the primary efficacy analyses. Patients from 1 investigational centre were also excluded. Early discontinuation from treatment was not a reason for exclusion from the PP population; e. Includes all patients who were treated with at least 1 application of study treatment. Patients from 1 investigational centre were also excluded.

Sample size

The study was designed to have adequate statistical power to evaluate the co-primary efficacy variables at Week 12. A sample size of 2182 patients was proposed with a 1:1 randomisation ratio to 1 of the 2 treatment groups (dapsone 7.5% or vehicle). Accounting for an attrition rate of 20%, 1,746 patients were anticipated to complete the study. The power calculation for each primary endpoint, based on a 2-sided alpha of 0.05 and 873 patients per treatment group, is provided below:

- GAAS: the proposed sample size would provide 93.6%, 90.0%, and 85.2% power to detect 7.0, 6.5, and 6.0 percentage difference in success rate (ie, GAAS 0 or 1 at week 12), respectively, in favour of dapsone 7.5%, assuming vehicle success rate to be 19.5%. A treatment effect of 6.5% difference was used in the sample size calculation based on the treatment effect of 8 percentage points from the Aczone 5% phase 3 trials with a discount of 1.5 percentage points
- Lesion counts: power scenarios for each lesion type are provided in the table below. The calculations were based on change from baseline in each lesion type at Week 12, separately, in favour of dapsone 7.5%

Table 4: Lesion counts.

Lesion Type	Treatment difference [a]	Standard Deviation [b]	Power
Inflammatory lesion counts	3.4 [b]	14.22	>99.9%
	3.0		99.3%
	2.5		95.7%
Non-inflammatory lesion counts	5.0 [b]	23.28	99.4%
	4.5		98.1%
	4.0		94.8%

a. Treatment difference is the difference in change from baseline in lesion counts at week 12 between dapsone 7.5% and vehicle; b. Assumptions were based on the Aczone 5% phase 3 trial data

Statistical methods

The analysis of the difference between dapsone 7.5% and its vehicle in the proportion of patients with a score of 0 (none) or 1 (minimal) on the GAAS at Week 12 was performed using a Cochran-Mantel-Haenszel (CMH) test stratified by sex. In addition, 2-sided 95% Wald type confidence intervals (CIs) with CMH weights for the treatment difference in response rates were provided. The Breslow-Day homogeneity of the odd-ratio test was performed to test treatment-by-sex interaction at a significance level of 0.10.

Between-group comparisons of mean change from baseline in inflammatory lesion counts at Week 12 were performed using an ANCOVA model with treatment group, inflammatory and non-inflammatory lesion count at baseline, and sex as covariates. The treatment difference (dapsone 7.5% minus vehicle) and 95% CIs for the treatment difference were provided.

The study results were to be positive if dapsone 7.5% was superior to its vehicle, at a 2-sided alpha of 0.05, with respect to the co-primary efficacy variables (1) proportion of patients with a GAAS score of 0 (none) or 1 (minimal) at Week 12, and (2) mean change from baseline at Week 12 in lesion counts (inflammatory and non-inflammatory).

The absolute change from baseline in total lesion counts and percent change from baseline in lesion counts were analysed using the same statistical methods as the primary outcome. For the proportion of patients who report “Very good” (2) or “Excellent” (1) in Item 10 of the ASIS at Week 12, an analysis of the treatment difference between dapsone 7.5% and its vehicle was performed using the CMH test stratified by sex. In addition, 2-sided 95% CIs for the treatment difference in response rates were provided. The analyses included patients who had an ASIS score of 4 (Fair) or 5 (Bad) at baseline. For the ASIS Sign Domain, between-group comparisons of mean change from baseline at Week 12 were analysed with an ANCOVA model using the rank data, with treatment group and sex as covariates. The treatment difference and 95% CIs were provided based on Hodges-Lehmann method. For the proportion of patients with at least a 1-grade improvement from baseline in item 1 of the ASIS at Week 12 (ie, the patient’s assessment of oiliness on the face), an analysis of the treatment difference between dapsone 7.5% and its vehicle was performed using the CMH test stratified by sex. In addition, 2-sided 95% CIs for the treatment difference in response rates were provided. For the proportion of patients with at least a 1-grade improvement from baseline in item 8 of the ASIS at Week 12 (ie, the patient’s assessment of redness on the face), an analysis of the treatment difference between dapsone 7.5% and its vehicle was performed using the CMH test stratified by sex. In addition, 2-sided 95% CIs for the treatment difference in response rates were provided.

Participant flow

See Table 5.

Table 5: Study 225678-006: Patient disposition and exit status (ITT population).

	Number (%) of Patients		
Disposition	**Dapsone 7.5% (N = 1044)**	**Vehicle (N = 1058)**	**Total (N = 2102)**
Enrolled [a]	1044	1058	2102
Completed [b]	948 (90.8)	976 (92.2)	1924 (91.5)
Discontinued [c]	96 (9.2)	82 (7.8)	178 (8.5)
Adverse event	4 (0.4)	5 (0.5)	9 (0.4)
Lack of efficacy	0 (0.0)	1 (0.1)	1 (0.0)
Pregnancy	3 (0.3)	3 (0.3)	6 (0.3)
Lost to follow-up	38 (3.6)	29 (2.7)	67 (3.2)
Personal reason(s)	21 (2.0)	20 (1.9)	41 (2.0)
Protocol violation	2 (0.2)	6 (0.6)	8 (0.4)
Other	28 (2.7)	18 (1.7)	46 (2.2)

a. Includes all randomized patients in the ITT population; b. Includes patients who completed the study through week 12; c. Only the primary reasons for discontinuation are summarised.

Major protocol violations/deviations

One ninety one (191) patients had significant protocol deviations. The most common deviations were due to significant study procedures performed by site staff that were not on the Authorisation List and/or were not appropriately trained or certified (eg, GAAS, lesion count) and failure to meet inclusion/exclusion criteria.

Serious non-compliance with GCP in the areas of protocol adherence and clinical study management were identified at 1 investigational site in the USA. The site was terminated from the study and all ongoing patients at the centre were discontinued from the study. Due to concerns over data integrity, all patients randomised at the site (51 patients) were excluded from the ITT population and the safety population. Results of sensitivity analyses including patients from the centre were consistent with analyses excluding those patients.

Baseline data

There were no statistically significant differences by treatment group in any of the demographic characteristics (age, sex, race, and skin phototype). Slightly more females (55.8%) than males (44.2%) participated in the study. Adults and adolescents were approximately equally represented (48.7% and 51.3%, respectively). The mean age was 20.0 years (range: 12 to 63 years). The majority of patients were Caucasian (60.4%), followed by black (17.2%) and Hispanic (13.8%).

There were no statistically significant differences by treatment group in GAAS or inflammatory lesion count. The mean inflammatory lesion count at baseline was 29.1. The non-inflammatory lesion count at baseline was significantly lower in the dapsone 7.5% group than in the vehicle group, with means of 46.9 and 48.6, respectively (p=0.020). Similarly, the total lesion count was significantly lower in the dapsone 7.5% group than in the vehicle group, with means of 75.7 and 77.9 and, respectively (p=0.018).

Results for the primary efficacy outcome

Both co-primary endpoints (responder rates in the GAAS and mean change in inflammatory and non-inflammatory lesion counts at Week 12) were statistically superior for dapsone 7.5% compared with the vehicle group. The responder rates were 29.9% and 21.2% ($p < 0.001$) in the dapsone 7.5% group and vehicle group, respectively. LS mean reductions from baseline in

inflammatory and non-inflammatory counts for the dapsone 7.5% versus vehicle groups were -16.1 versus -14.4 (p<0.001) and -21.0 versus -17.9 (p<0.001), respectively.

Table 6: Study 225678-006: Primary efficacy analysis at Week 12 (ITT population).

Measure	Variable	Statistic	Treatment Group		
			Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)	p-value Difference
GAAS	Success [a]		29.9% (27.0%, 32.7%)	21.2% (18.7%, 23.7%)	< 0.001 [b] 8.5% [c] (4.7%, 12.3%)
Inflammatory lesion count	Change from baseline	LS Mean	-16.1	-14.1	< 0.001 [d]
		SE	0.32	0.32	-2.0 (-2.90, -1.11)
Non-inflammatory lesion count	Change from baseline	LS Mean	-20.8	-17.6	< 0.001 [d]
		SE	0.56	0.55	-3.2 (-4.67, -1.63)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; GAAS = Global Acne Assessment Score; LS = least squares; SE = standard error. Inflammatory lesion count is the sum of papules, pustules, and nodules/cysts. Non-inflammatory lesion count is the sum of open and closed comedones. Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). a. Percent (95% CI) of patients with 0 or 1 score; missing data are imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets; b. P-values for the test of general association between the responder and treatment group using a CMH test stratified by sex; c. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex; d. P-value and 95% CIs for between-group comparison are obtained from an analysis of covariance model including treatment, baseline and sex. Estimated differences are based on the LS mean. Missing data are imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets.

Results in the PP population were consistent with those in the ITT population.

Results for other efficacy outcomes

Analyses at visits other than Week 12

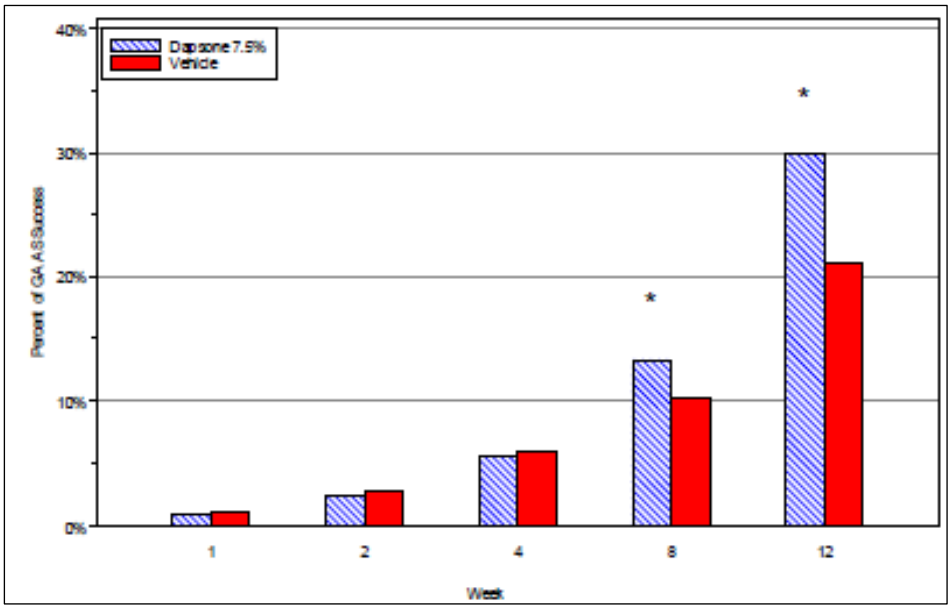
A statistically significant difference in responder rates in the GAAS favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p=0.034) and showed further improvement at Week 12.

Table 7: Study 225678-006: GAAS: Percent of patients with 0 or 1 score at each visit (ITT population).

Visit (Week)	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)	p-value [a]	Difference	95% CI [b]
1	0.9% (0.3%, 1.5%)	1.2% (0.5%, 1.8%)	0.564	-0.3%	-1.1%, 0.6%
2	2.4% (1.5%, 3.4%)	2.8% (1.8%, 3.8%)	0.577	-0.4%	-1.8%, 1.0%
4	5.6% (4.2%, 7.0%)	6.0% (4.5%, 7.4%)	0.667	-0.4%	-2.5%, 1.6%
8	13.3% (11.2%, 15.4%)	10.2% (8.4%, 12.1%)	0.034	3.0%	0.2%, 5.8%
12	29.9% (27.0%, 32.7%)	21.2% (18.7%, 23.7%)	< 0.001	8.5%	4.7%, 12.3%

CI = confidence interval; CMH = Cochran Mantel-Haenszel; GAAS = Global Acne Assessment Score. Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Number and percent of patients with 0 or 1 score; missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets. a. p-values for the test of general association between the responder and treatment group using a CMH test stratified by sex. b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

Figure 1: Study 225678-006: GAAS: Percent of patients with a score of 0 or 1 over the treatment period by treatment group and visit (ITT population).



CMH = Cochran Mantel-Haenszel; GAAS = Global Acne Assessment Score. Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Missing data are imputed using a multiple imputation method. * Indicates the p-value is less than 0.05 for the CMH test between dapsone 7.5% and vehicle stratified by sex.

A statistically significant difference in mean reduction from baseline in inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 2 (p=0.018) and was maintained at the end of the study.

Table 8: Study 225678-006: Inflammatory lesion count: change from baseline at each visit (ITT population).

Visit (Week)	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)	p-value [b]	Difference [b]	95% CI [b]
1	-5.0 (0.26)	-4.9 (0.26)	0.826	-0.1	-0.79, 0.63
2	-7.8 (0.28)	-6.9 (0.28)	0.018	-0.9	-1.72, -0.16
4	-10.9 (0.30)	-9.4 (0.30)	< 0.001	-1.4	-2.26, -0.59
8	-13.7 (0.31)	-12.1 (0.30)	< 0.001	-1.6	-2.44, -0.76
12	-16.1 (0.32)	-14.1 (0.32)	< 0.001	-2.0	-2.90, -1.11

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

A statistically significant difference in mean reduction from baseline in non-inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p = 0.003) and showed further improvement at Week 12.

Table 9: Study 225678-006: Non-inflammatory lesion count: change from baseline at each visit (ITT population).

Visit (Week)	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)	p-value [b]	Difference [b]	95% CI [b]
1	-4.6 (0.36)	-5.6 (0.36)	0.060	1.0	-0.04, 1.97
2	-7.7 (0.47)	-8.3 (0.47)	0.437	0.5	-0.78, 1.81
4	-11.2 (0.48)	-11.1 (0.48)	0.928	-0.1	-1.39, 1.27
8	-16.2 (0.52)	-14.1 (0.51)	0.003	-2.1	-3.57, -0.73
12	-20.8 (0.56)	-17.6 (0.55)	< 0.001	-3.2	-4.67, -1.63

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

For the GAAS, the Breslow-Day homogeneity of the odds-ratio test was performed for the ITT population to test treatment-by-sex interaction. The p-value of Breslow-Day homogeneity of the odds-ratio test for GAAS was not statistically significant, indicating no significant difference in the odd ratios based on patient's sex. For inflammatory and non-inflammatory lesion counts, the p-value for treatment by sex interaction was not statistically significant, indicating no significant difference in the treatment effect between groups. In both female and male patients, dapsone 7.5% was better than vehicle for all efficacy measures.

Subgroup analysis

Analyses of the primary efficacy outcomes based on demographic factors found the following:

- Patients who were 18 and older tended to have greater acne improvement than patients aged 12 to17 years
- Female patients tended to have greater acne improvement than male patients
- Results were generally consistent in Caucasian and non-Caucasian patients
- Results were generally consistent in female patients who used hormonal contraceptives and those who did not use hormonal contraceptive

Change from baseline in total lesion counts at Week 12

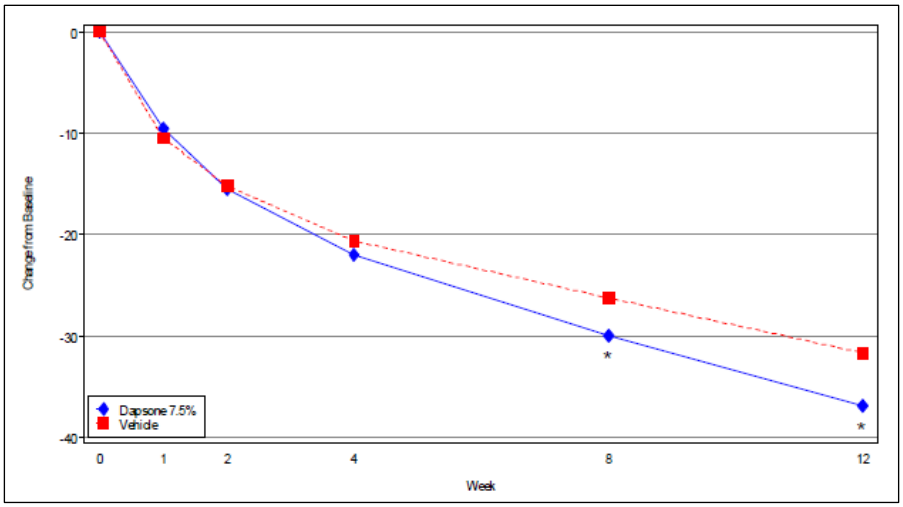
LS mean reductions from baseline in total lesion counts at week 12 for the dapsone 7.5% versus vehicle groups were -36.9 versus -31.7 (p<0.001), respectively. A statistically significant difference in mean reduction from baseline in total lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p<0.001) and was maintained at the end of the study.

Table 10: Study 225678-006: Total lesion count: Change from baseline at each visit (ITT population).

Visit (Week)	Treatment Group [a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)			
1	-9.5 9 (0.48)	-10.5 (0.48)	0.163	1.0	-0.39, 2.29
2	-15.5 (0.61)	-15.2 (0.60)	0.687	-0.3	-2.01, -1.32
4	-22.0 (0.64)	-20.6 (0.63)	0.117	-1.4	-3.17, 0.35
8	-29.9 (0.68)	-26.2 (0.67)	< 0.001	-3.7	-5.58, -1.83
12	-36.9 (0.76)	-31.7 (0.75)	< 0.001	-5.2	-7.26, -3.13

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

Figure 2: Study 225678-006: Total lesion count: Change from baseline at each follow-up visit by treatment group (ITT population).



Total lesion count is the sum of inflammatory lesion counts and non-inflammatory lesion counts. Baseline (day 1) measurement is considered week 0. Missing data were imputed using the multiple imputation method. * Indicates the p-value is less than 0.05 from an analysis of covariance including treatment, baseline, and sex.

Percent change from baseline in lesion counts at Week 12

The analysis of mean percent reduction from baseline in lesion counts at Week 12 was consistent with results of the primary efficacy analysis of mean reduction from baseline at Week 12 for inflammatory and non-inflammatory lesion counts. The LS mean percent reductions from baseline in inflammatory, non-inflammatory and total lesion counts for the dapsone 7.5% versus vehicle groups were -55.5 versus -49.0 (p<0.001), -44.4 versus -38.4 (p<0.001), and -48.7 versus -42.4 (p<0.001), respectively.

Table 11: Study 225678-006: Lesion counts: Percent change from baseline at Week 12 (ITT population)

Lesion Count	Treatment Group [a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)			
Inflammatory	-55.5 (1.10)	-49.0 (1.10)	< 0.001	-6.5	-9.56, -3.43
Non-inflammatory	-44.4 (1.15)	-38.4 (1.10)	< 0.001	-5.9	-9.03, -2.83
Total	-48.7 (0.95)	-42.4 (0.93)	< 0.001	-6.3	-8.91, -3.72

CI = confidence interval; LS = least squares; SD = standard deviation; Total lesion count is the sum of inflammatory lesion counts and non-inflammatory lesion counts; a. LS mean (SE); b. p-value and 95% CI for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets.

In the analysis of mean percent reduction from baseline in lesion counts, results were consistent with respect to onset of action with results of the primary efficacy analysis of mean reduction from baseline for inflammatory and non-inflammatory lesion counts. A statistically significant difference in mean percent reduction from baseline in inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed starting Week 2 (p=0.029) and was maintained at the end of the study. A statistically significant difference in mean percent reduction from baseline in non-inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p=0.012) and was maintained at the end of the study. A statistically significant difference in mean percent reduction from baseline in total lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p<0.001) and was maintained till the end of the study.

Analyses for the Acne Symptom Impact Score (ASIS)

A greater proportion of the dapsone 7.5% group compared with the vehicle group reported “Very good” or “Excellent” in ASIS Item 10 (facial appearance) at each assessment and showed further improvement throughout treatment; at Week 12, the difference between groups was statistically significant in favour of dapsone 7.5% group (23.8%) versus the vehicle group (19.2%) (p=0.015).

Table 12: Study 225678-006: ASIS Item 10: Proportion of patients who reported 'Very good' or 'Excellent' at each follow-up visit (ITT population)

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 910)	Vehicle (N = 913)			
4	83 (9.1)	67 (7.3)	0.153	1.8%	(-0.7%, 4.4%)
8	143 (15.7)	118 (12.9)	0.083	2.8%	(-0.4%, 6.1%)
12	217 (23.8)	175 (19.2)	0.015	4.7%	(0.9%, 8.5%)

ASIS = Acne Symptom and Impact Scale; CI = confidence interval; CMH = Cochran Mantel-Haenszel; LOCF = last observation carried forward; ASIS Item 10: Over the past 7 days, rate how your face looked because of your acne?: 1 = Excellent, 2 = Very good, 3 = Good, 4 = Fair, and 5 = Bad. Missing data were imputed using LOCF; Results presented are for patients with a score of 4 (Fair) or 5 (Bad) on the ASIS at baseline; a. p-values for between-group comparison using a CMH test stratified by sex; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

For the ASIS Sign Domain (facial acne signs), the mean reduction from baseline was not statistically significant.

Table 13: Study 225678-006: ASIS sign domain: Change from baseline at each follow-up visit (ITT population).

Visit (Week)	Mean (SD)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)			
4	-0.48 (0.571)	-0.48 (0.573)	0.906	0.00	(-0.00, 0.00)
8	-0.62 (0.641)	-0.59 (0.633)	0.313	-0.00	(-0.11, 0.00)
12	-0.73 (0.677)	-0.69 (0.678)	0.145	-0.00	(-0.11, 0.00)

ANCOVA = analysis of covariance; ASIS = Acne Symptom and Impact Scale; CI = confidence interval; LOCF = last observation carried forward; ASIS Sign Domain consists of item 1 to 9 from the ASIS questionnaire; each item has a scale from 0 to 4. ASIS Sign domain score = (sum of items 1 through 9)/9. A higher score on the ASIS Sign Domain indicates the presence of more severe symptoms. Missing data were imputed using LOCF. Results presented are for patients with a score of 4 (Fair) or 5 (Bad) on the ASIS at baseline. a. P-values for between-group comparison obtained from an ANCOVA model with the rank data using fixed effects of treatment and sex; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 95% CI based on Hodges-Lehmann method.

At each assessment, a lower proportion of patients in the dapsone 7.5% group compared with the vehicle group had at least a 1-grade improvement in ASIS Item 1 (facial oiliness). A smaller mean reduction from baseline was seen in the dapsone 7.5% group compared with the vehicle group at each assessment.

Table 14: Study 225678-006: ASIS Item 1: Proportion of patients with at least a 1-grade improvement from baseline at each follow-up visit (ITT population).

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)			
4	398 (38.1)	487 (46.0)	< 0.001	-7.9%	(-12.1%, -3.7%)
8	448 (42.9)	505 (47.7)	0.027	-4.8%	(-9.1%, -0.6%)
12	477 (45.7)	548 (51.8)	0.005	-6.1%	(-10.4%, -1.9%)

ASIS = Acne Symptom and Impact Scale; CI = confidence interval; CMH = Cochran Mantel-Haenszel; LOCF = last observation carried forward; ASIS Item 1: How oily is your face right now? 0 = Not at all, 1 = A little, 2 = Somewhat, 3 = Quite a bit, 4 = Very. Missing data were imputed using LOCF; a. p-values for between-group comparison using a CMH test stratified by sex. Since the sign domain was not significant, based on the gatekeeping procedure, the statistical testing stopped at sign domain score and the rest of the endpoints (item 1 and item 8) were not statistically significant even though the p-value was less than 0.05; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

There were no statistically significant differences between groups in terms of the proportion of patients with at least a 1-grade improvement from baseline in ASIS Item 8 (facial redness) or the mean reduction from baseline over the treatment period.

Table 15: Study 225678-006: ASIS Item 8: Proportion of patients with at least a 1-grade improvement from baseline at each follow-up visit (ITT population).

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 1044)	Vehicle (N = 1058)			
4	495 (47.4)	502 (47.4)	0.996	-0.0%	(-4.3%, 4.3%)
8	542 (51.9)	543 (51.3)	0.789	0.6%	(-3.7%, 4.9%)
12	580 (55.6)	561 (53.0)	0.244	2.5%	(-1.7%, 6.8%)

ASIS = Acne Symptom and Impact Scale; CI = confidence interval; CMH = Cochran Mantel-Haenszel; LOCF = last observation carried forward; ASIS Item 8: How much redness do you have on your face right now?: 0 = Not at all, 1 = A little, 2 = Somewhat, 3 = Quite a bit, and 4 = Very. Missing data were imputed using LOCF. a. P-values for between-group comparison using a CMH test stratified by sex. b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

7.1.1.2. Study 225678-007: A Safety and Efficacy Study to Compare Dapsone Dermal Gel with Vehicle Control in Patients with Acne Vulgaris.

Study design, objectives, locations and dates

A multicentre, randomised, double blind, vehicle controlled, parallel group study conducted at 103 centres (93 in the USA and 10 in Canada) from November 2013 to October 2014.

Objective

To assess the safety and efficacy of dapsone 7.5% versus vehicle control administered topically once daily for 12 weeks in patients with acne vulgaris.

Following the baseline visit, patients returned for visits at weeks 1 and 2, then at Weeks 4, 8, and 12.

Inclusion and exclusion criteria

Same as for study 225678-006.

Study treatments

Patients were randomised to 1 of 2 treatment groups – dapsone 7.5% or vehicle control. The treatment period was 12 weeks.

Patients administered study product topically to their entire face once daily for 12 weeks. Patients also topically administered the study product once daily to acne-affected areas within reach on the neck, shoulders, upper back, and/or upper chest, although these non-facial areas were not considered in the analysis of efficacy for this study. The first application of study product was carried out by the patient at the study centre under the supervision of qualified study staff.

Efficacy variables and outcomes

The primary efficacy outcomes were the proportion of patients with a score of 0 (none) or 1 (minimal) on the GAAS at Week 12 and the change from baseline in inflammatory and non-inflammatory lesion counts at Week 12.

Other efficacy outcomes included:

- Absolute change from baseline in total lesion counts (sum of inflammatory lesion counts and non-inflammatory lesion counts) at Week 12
- Percentage change from baseline in lesion counts (total, inflammatory, and non-inflammatory lesion counts):
  - percentage change from baseline in total lesion counts at Week 12
  - percentage change from baseline in inflammatory lesion counts at Week 12
  - percentage change from baseline in non-inflammatory lesion counts at Week 12
- the proportion of patients who reported “Very good” or “Excellent” in ASIS Item 10 (facial appearance) at Week 12
- the change from baseline at Week 12 in ASIS Sign Domain (facial acne signs)
- the proportion of patients with at least a 1-grade improvement from baseline at Week 12 in ASIS Item 1 (facial oiliness)
- the proportion of patients with at least a 1-grade improvement from baseline at Week 12 in ASIS Item 8 (facial redness)

Randomisation and blinding methods

Patients were randomised 1:1 to receive dapsone 7.5% or vehicle. Randomisation was stratified by sex (male versus female) and carried out using an IVRS or IWRS.

Both study treatments were provided in identical 75-mL MegaPump™ containers to maintain masking of the study.

Analysis populations

Intent-to-treat (ITT) population: all randomised patients = 2,238.

Per-protocol (PP) population: all randomised patients with no major protocol deviations that were considered to affect the primary efficacy outcomes = 2,068.

Safety population: all randomised patients who applied study treatment at least once = 2,235.

Sample size

Same as for study 225678-006.

Statistical methods

Same as for study 225678-006.

Participant flow

See Table 16.

Table 16: Study 225678-007: Patient disposition and exit status (ITT population).

Disposition	Number (%) of Patients		
	Dapsone 7.5% (N = 1118)	**Vehicle (N = 1120)**	**Total (N = 2238)**
Total [a]			2576
Screen failure			313 [b]
Enrolled [c]	1118	1120	2238
Completed [d]	1026 (91.8)	1027 (91.7)	2053 (91.7)
Discontinued [e]	92 (8.2)	93 (8.3)	185 (8.3)
Adverse event	2 (0.2)	2 (0.2)	4 (0.2)
Lack of efficacy	1 (0.1)	1 (0.1)	2 (0.1)
Pregnancy	2 (0.2)	1 (0.1)	3 (0.1)
Lost to follow-up	45 (4.0)	40 (3.6)	85 (3.8)
Personal reason(s)	15 (1.3)	19 (1.7)	34 (1.5)
Protocol violation	2 (0.2)	2 (0.2)	4 (0.2)
Other [f]	25 (2.2)	28 (2.5)	53 (2.4)

ITT = intent-to-treat; PP = per-protocol; a. Includes all screened patients, including 4 who were reported post-database lock as having been screened at 1site (1 patient qualified for enrolment but did not participate in the study); b. Includes 3 patients reported post-database lock as having been screened at 1site, who did not qualify for enrolment; c. Includes all randomised patients in the ITT population; d. Includes patients who completed the study through Week 12; e. Only the primary reasons for discontinuation are summarised. f. Other reasons are provided.

Major protocol violations/deviations

Overall 170 (7.6%) patients had major protocol deviations, with similar numbers between the treatment groups. The most common deviations were study procedures performed by site staff that was not on the Authorisation List and/or was not appropriately trained or certified (eg, GAAS, lesion count) or failure to meet the inclusion criteria on lesion counts. Most deviations were considered minor and did not affect the study conduct or interpretation of the study results.

Post-database lock, it was determined that 4 patients screened at 1 site in the USA were not entered into the database (including the IVRS and eCRF). One patient qualified for enrolment but decided not to participate while the remaining 3 patients did not qualify. This deviation was considered not to impact data quality or the overall conclusions of the study and these 4 patients are included in the patient disposition analysis.

Baseline data

There were no statistically significant differences by treatment group in any of the demographic characteristics (age, sex, race, and skin phototype). Slightly more females (55.8%) than males (44.2%) participated in the study. Adults and adolescents were approximately equally represented

(47.9% and 52.1%, respectively). The mean age was 20.4 years (range: 12 to 61 years). The majority of patients were Caucasian (54.5%), followed by black (20.1%) and Hispanic (18.0%).

There were statistically significant differences (p<0.05) between the treatment groups for several medical history findings but these were not considered to be clinically meaningful or to affect the efficacy or safety conclusions. These findings, with the percentage of patients in the dapsone 7.5% group versus the vehicle group, were migraine (2.4% versus 4.1%), arthralgia (1.1% versus 0.4%), diabetes mellitus (0.8%versus < 0.1%), inguinal hernia (0.7% versus < 0.1%), irregular menstruation (0.6% versus 1.9%), joint injury (0.4% versus 0.0%), and cardiac murmur (0.0% versus 0.7%). Tabulated demographic details are provided.

Results for the primary efficacy outcome

All co-primary endpoints (responder rates in the GAAS and mean change in inflammatory and non-inflammatory lesion counts at week 12) were statistically superior for dapsone 7.5% compared with the vehicle group. The responder rates were 29.8% and 20.9% (p<0.001) in the dapsone 7.5% group and vehicle group, respectively. LS mean reductions from baseline in inflammatory and non-inflammatory counts for the dapsone 7.5% versus vehicle groups were -15.6 versus -13.8 (p<0.001) and -20.7 versus -18.5 (p=0.004), respectively.

Table 17: Study 225678-007: Primary efficacy analysis at week 12 (ITT Population).

Measure	Variable	Statistic	Treatment Group		p-value Difference 95% CI
			Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)	
GAAS	Success [a]		29.8% (27.0%, 32.6%)	20.9% (18.5%, 23.4%)	< 0.001 [b]
					8.9% (5.2%, 12.7%)
Inflammatory lesion count	Change from baseline	LS Mean	-15.6	-13.8	< 0.001 [c]
		SE	(0.35)	(0.35)	-1.7 (-2.73, -0.76)
Non-inflammatory lesion count	Change from baseline	LS Mean	-20.7	-18.5	0.004 [c]
		SE	(0.55)	(0.55)	-2.2 (-3.72, -0.70)

CI = confidence interval; CMH = Cochran Mantel-Haenszel; GAAS = Global Acne Assessment Score; LS = least square; SE = standard error; Inflammatory lesion count is the sum of papules, pustules, and nodules/cysts. Non-inflammatory lesion count is the sum of open and closed comedones. Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe); a. Percent (95% CI) of patients with 0 or 1 score; missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets; b. P-values for the test of general association between the responder and treatment group using a CMH test stratified by sex. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex. Missing data were imputed using a multiple imputation method; c. p-value and 95% CI for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

Results in the PP population were consistent with those in the ITT population.

Analyses at Visits Other Than Week 12

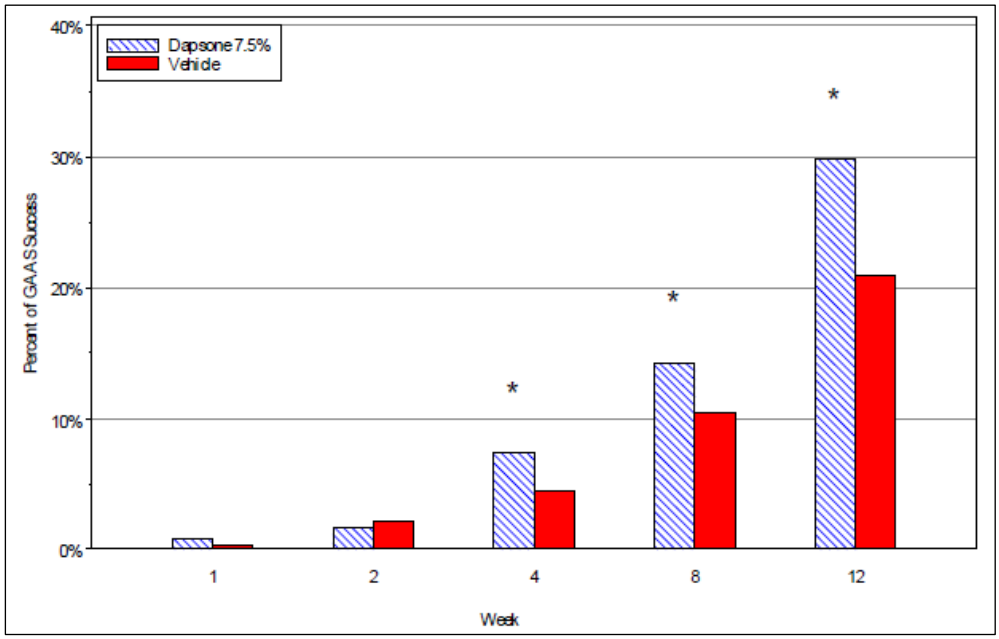
A statistically significant difference in responder rates in the GAAS favouring dapsone 7.5% compared with the vehicle group was observed at week 4 (p=0.004) and was maintained at the end of the study.

Table 18: Study 225678-007: GAAS: Percent of patients with 0 or 1 score at each visit (ITT population).

Visit (Week)	Treatment Group		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
1	0.8% (0.3%, 1.3%)	0.4% (0.0%, 0.8%)	0.197	0.4%	-0.2%, 1.1%
2	1.6% (0.9%, 2.4%)	2.1% (1.2%, 2.9%)	0.468	-0.4%	-1.6%, 0.7%
4	7.3% (5.8%, 8.9%)	4.4% (3.2%, 5.6%)	0.004	3.0%	1.0%, 4.9%
8	14.2% (12.1%, 16.3%)	10.5% (8.6%, 12.3%)	0.008	3.8%	1.0%, 6.6%
12	29.8% (27.0%, 32.6%)	20.9% (18.5%, 23.4%)	< 0.001	8.9%	5.2%, 12.7%

CI = confidence interval; CMH = Cochran Mantel-Haenszel; GAAS = Global Acne Assessment Score; Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Number and percent of patients with 0 or 1 score; missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets. a. p-values for the test of general association between the responder and treatment group using a CMH test stratified by sex. b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

Figure 3: Study 225678-007: GAAS: Percent of patients with a score of 0 or 1 over the treatment period by treatment group and visit (ITT population).



CMH = Cochran Mantel-Haenszel; GAAS = Global Acne Assessment Score; Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe); Missing data were imputed using a multiple imputation method; * Indicates the p-value is less than 0.05 for the CMH test between dapsone 7.5% and vehicle stratified by sex.

A statistically significant difference in mean reduction from baseline in inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 4 (p=0.004) and was maintained at the end of the study.

Table 19: Study 225678-007: Inflammatory lesion count: Change from baseline at each visit (ITT population).

Visit (Week)	Treatment Group[a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
1	-4.5 (0.25)	-4.4 (0.25)	0.800	-0.1	-0.77, 0.59
2	-7.7 (0.28)	-7.0 (0.28)	0.060	-0.7	-1.51, 0.03
4	-11.0 (0.30)	-9.8 (0.30)	0.004	-1.2	-2.07, -0.39
8	-13.5 (0.31)	-12.3 (0.32)	0.011	-1.1	-2.00, -0.26
12	-15.6 (0.35)	-13.8 (0.35)	< 0.001	-1.7	-2.73, -0.76

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

A statistically significant difference in mean reduction from baseline in non-inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p=0.047) and showed further improvement at Week 12.

Table 20: Study 225678-007: Non-inflammatory lesion count: Change from baseline at each visit (ITT population).

Visit (Week)	Treatment Group[a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
1	-5.2 (0.38)	-5.3 (0.38)	0.934	0.0	-1.00, 1.09
2	-8.8 (0.44)	-9.1 (0.44)	0.632	0.3	-0.92, 1.52
4	-12.5 (0.49)	-12.4 (0.48)	0.904	-0.1	-1.42, 1.26
8	-16.8 (0.54)	-15.3 (0.53)	0.047	-1.5	-2.96, -0.02
12	-20.7 (0.55)	-18.5 (0.55)	0.004	-2.2	-3.72, -0.70

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

Analyses of efficacy outcomes based on demographic factors:

- Patients who were 18 and older tended to have greater acne improvement than patients 12 to 17 years old
- Female patients tended to have greater acne improvement than male patients
- Results were generally consistent in Caucasian and non-Caucasian patients
- Results were generally consistent in female patients who used hormonal contraceptives and those who did not use hormonal contraceptives

Tabulated results for outcomes based on age, sex and race are provided.

Change from baseline in total lesion counts at Week 12

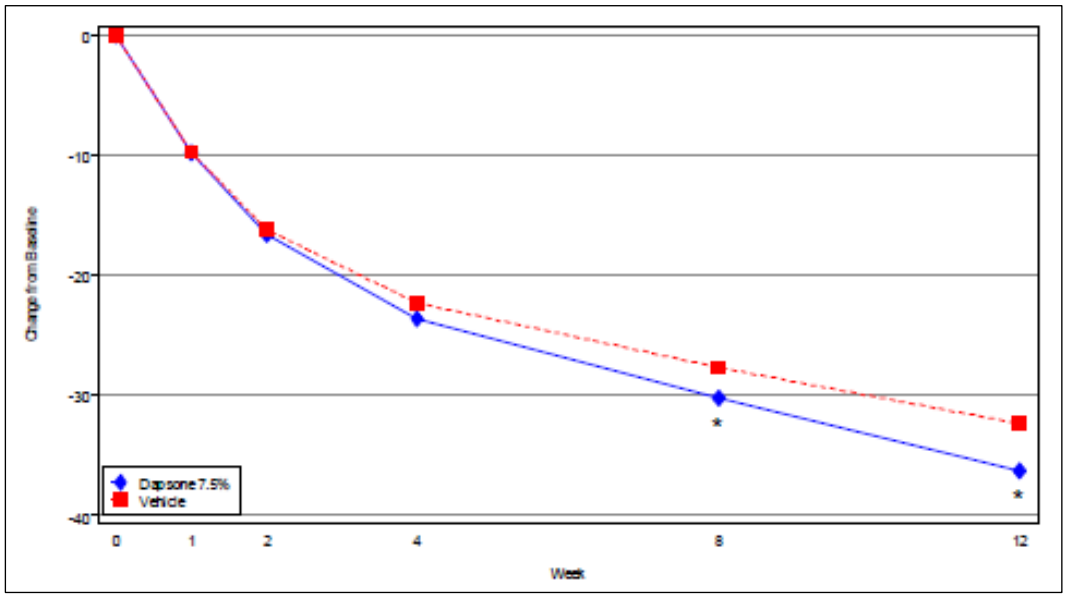
LS mean reduction from baseline in total lesion counts at Week 12 for the dapsone 7.5% versus vehicle group was -36.2, compared to -32.3 (p<0.001).. A statistically significant difference in mean reduction from baseline in total lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at week 8 (p=0.010) and was maintained till the end of the study.

Table 21: Study 225678-007: Total lesion count: change from baseline at each visit (ITT population)

Visit (Week)	Treatment Group[a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
1	-9.7 (0.49)	-9.7 (0.49)	0.973	-0.0	-1.38, 1.33
2	-16.6 (0.58)	-16.2 (0.58)	0.619	-0.4	-2.02, 1.20
4	-23.5 (0.65)	-22.3 (0.65)	0.165	-1.3	-3.07, 0.52
8	-30.2 (0.71)	-27.6 (0.71)	0.010	-2.6	-4.53, -0.63
12	-36.2 (0.76)	-32.3 (0.75)	< 0.001	-3.9	-6.00, -1.83

CI = confidence interval; LS = least square; SE = standard error; a. LS mean (SE); b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method.

Figure 4: Study 225678-007: Total lesion count: change from baseline at each follow-up visit by treatment group (ITT population).



Total lesion count is the sum of inflammatory lesion counts and non-inflammatory lesion counts; Baseline (day 1) measurement is considered week 0; Missing data were imputed using the multiple imputation method; * Indicates the p-value is less than 0.05 from an analysis of covariance including treatment, baseline, and sex.

Percent change from baseline in lesion counts at Week 12

The analysis of mean percent reduction from baseline in lesion counts at Week 12 was consistent with results of the primary efficacy analysis of mean reduction from baseline at Week 12 for inflammatory and non-inflammatory lesion counts. The LS mean percent reduction from baseline in inflammatory, non-inflammatory and total lesion counts at Week 12 for the dapsone 7.5% versus

vehicle groups were -53.8 versus -47.3 (p<0.001), -45.9 versus -40.4 (p<0.001), and -48.9 versus -43.2 (p<0.001), respectively.

Table 22: Study 225678-007: Lesion counts: Percent change from baseline at Week 12 (ITT population).

Lesion Count	Treatment Group [a]		p-value [b]	Difference [b]	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
Inflammatory	-53.8 (1.10)	-47.3 (1.12)	< 0.001	-6.4	-9.53, -3.29
Non-inflammatory	-45.9 (1.18)	-40.4 (1.18)	< 0.001	-5.5	-8.76, -2.23
Total	-48.9 (0.97)	-43.2 (0.97)	< 0.001	-5.7	-8.34, -2.97

CI = confidence interval; LS = least squares; SD = standard deviation; Total lesion count is the sum of inflammatory lesion counts and non-inflammatory lesion counts; a. LS mean (SE); b. p-value and 95% confidence intervals for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex. Estimated differences were based on the LS mean. Missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets.

A statistically significant difference in mean percent reduction from baseline in inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed starting Week 2 (p=0.048) and was maintained till the end of the study.

A statistically significant difference in mean percent reduction from baseline in non-inflammatory lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p=0.015) and was maintained till the end of the study.

A statistically significant difference in mean percent reduction from baseline in total lesion counts favouring dapsone 7.5% compared with the vehicle group was observed at Week 8 (p=0.002) and was maintained till the end of the study.

Acne Symptom and Impact Scale (ASIS) Item 10 at week 12

At week 12 the mean reduction from baseline for dapsone 7.5% compared with the vehicle group in the ASIS Sign Domain score was not statistically significant.

Table 23: Study 225678-007: Analysis of ASIS at week 12 (ITT population).

Variable	Treatment Group		p-value	Difference 95% CI
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)		
Proportion of patients who reported "Very good" or "Excellent" in ASIS Item 10 (based on patients who had an ASIS score of 4 [Fair] or 5 [Bad] at baseline)	224/926 (24.2%)	211/961 (22.0%)	0.252 [a]	2.2% [b] (-1.6%, 6.0%)
Change from baseline in ASIS Sign Domain score N	1118	1120	0.057 [c]	0.00 [d]
Mean (SD)	-0.74 (0.700)	-0.68 (0.675)		(-0.11, 0.00)
Median	-0.67	-0.67		
Min to max	-3.2 to 1.4	-2.8 to 2.3		
Proportion of patients with at least a 1-grade improvement from baseline in ASIS Item 1	542/1118 (48.5%)	552/1120 (49.3%)	0.711 [a]	-0.8% [b] (-4.9%, 3.4%)
Proportion of patients with at least a 1- grade improvement from baseline in ASIS Item 8	601/1118 (53.8%)	592/1120 (52.9%)	0.647 [a]	1.0% [b] (-3.2%, 5.1%)

ASIS = Acne Symptom and Impact Scale; CI = confidence interval; CMH = Cochran Mantel-Haenszel; LS = least squares; SD = standard deviation; ASIS Item 10: Over the past 7 days, rate how your face looked because of your acne? 1 = Excellent, 2 = Very good, 3 = Good, 4 = Fair, and 5 = Bad; ASIS Item 1: How oily is your face right now? 0 = Not at all, 1 = A little, 2 = Somewhat, 3 = Quite a bit, and 4 = Very; ASIS Item 8: How much redness do you have on your face right now?: 0 = Not at all, 1 = A little, 2 = Somewhat, 3 = Quite a bit, and 4 = Very; The ASIS Sign Domain consists of Items 1 to 9 from the ASIS; each item has a scale from 0 to 4. ASIS Sign Domain score = (sum of items 1 through 9) / 9. A higher score on the ASIS Sign Domain indicates the presence of more severe signs of acne; Missing data were imputed using the last observation carried forward method: a. Between-group comparisons were performed using a CMH test stratified by sex; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex; c. p-value for between-group comparison were obtained from an analysis of covariance model using the rank data with treatment and sex as covariates; d. The estimated difference (dapsone 7.5% minus vehicle) and its 95% CI were obtained based on the Hodges-Lehmann method.

Analyses of ASIS at visits other than Week 12

At each assessment, the number of subjects reporting "Very good" or "Excellent" in the ASIS Item 10 (facial appearance) in the dapsone 7.5% group compared with the vehicle group was not statistically significant.

Table 24: Study 225678-007: ASIS Item 10: Proportion of patients who reported 'Very good' or 'Excellent' at each follow-up visit (ITT population)

Visit (Week)	Number (%)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 926)	Vehicle (N = 961)			
4	93 (10.0)	84 (8.7)	0.336	1.3%	(-1.3%, 3.9%)
8	151 (16.3)	128 (13.3)	0.069	3.0%	(-0.2%, 6.2%)
12	224 (24.2)	211 (22.0)	0.252	2.2%	(-1.6%, 6.0%)

ASIS = Acne Symptom and Impact Scale; CI = confidence interval; CMH = Cochran Mantel-Haenszel; LOCF = last observation carried forward; ASIS Item 10: Over the past 7 days, rate how your face looked because of your acne?: 1 = Excellent, 2 = Very good, 3 = Good, 4 = Fair, and 5 = Bad. Missing data were imputed using LOCF; Results presented are for patients with a score of 4 (Fair) or 5 (Bad) on the ASIS at baseline; a. p-values for between-group comparison using a CMH test stratified by sex; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex.

The mean improvement from baseline in the ASIS Item 10 (facial appearance) over the treatment period was statistically significant in favour of dapsone 7.5% over the vehicle group at Week 12 (p=0.048).

For the ASIS Sign Domain (facial acne signs), a mean reduction from baseline was seen at each assessment in both groups but was not statistically significant.

Table 25: Study 225678-007: ASIS sign domain: Change from baseline at each follow-up visit (ITT population).

Visit (Week)	Mean (SD)		p-value [a]	Difference	95% CI [b]
	Dapsone 7.5% (N = 1118)	Vehicle (N = 1120)			
4	-0.51 (0.573)	-0.48 (0.568)	0.274	0.00	(-0.11, 0.00)
8	-0.64 (0.628)	-0.59 (0.632)	0.093	-0.00	(-0.11, 0.00)
12	-0.74 (0.700)	-0.68 (0.675)	0.057	-0.00	(-0.11, 0.00)

ANCOVA = analysis of covariance; ASIS = Acne Symptom and Impact Scale; CI = confidence interval; LOCF = last observation carried forward; ASIS Sign Domain consists of item 1 to 9 from the ASIS questionnaire; each item has a scale from 0 to 4. ASIS Sign domain score = (sum of items 1 through 9)/9. A higher score on the ASIS Sign Domain indicates the presence of more severe symptoms. Missing data were imputed using LOCF; Results presented are for patients with a score of 4 (Fair) or 5 (Bad) on the ASIS at baseline: a. p-values for between-group comparison obtained from an ANCOVA model with the rank data using fixed effects of treatment and sex; b. Estimated treatment difference (dapsone 7.5% minus vehicle) and 95% CI based on Hodges-Lehmann method.

There were no statistically significant differences between groups in the proportion of patients with at least a 1-grade improvement from baseline in ASIS Item 1 (facial oiliness) or the mean reduction from baseline over the treatment period.

There were no statistically significant differences between groups in the proportion of patients with at least a 1-grade improvement from baseline in ASIS Item 8 (facial redness) or the mean reduction from baseline over the treatment period.

7.1.2. Other efficacy studies

The sponsor provided 5 additional studies conducted using dapsone 5% gel which had a different formulation and was applied twice daily.

7.1.3. Analyses performed across trials (pooled & meta-analyses)

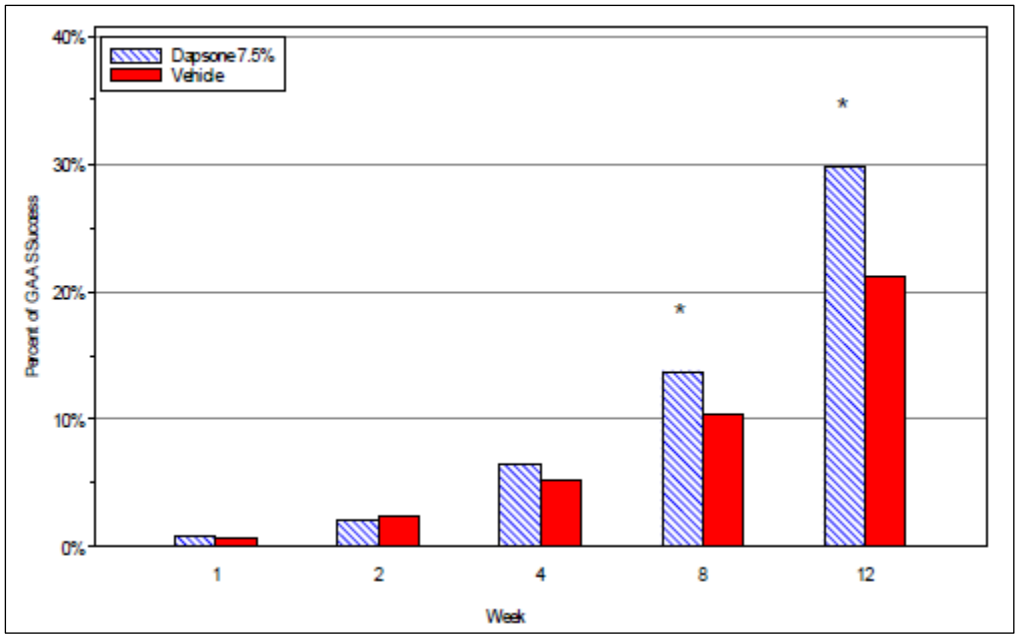
The Sponsor has provided analyses for the pooled results from studies 225678-006 and 225678-007.

Table 26: Primary efficacy analysis at Week 12 – Pooled studies 225678-006 and 225678-007 (ITT population).

Measure	Variable	Statistic	Treatment Group		P-value Difference 95% CI
			Aczone 7.5% (N = 2162)	Vehicle (N = 2178)	
GAAS	Success [a]		29.8% (27.9%, 31.8%)	21.1% (19.3%, 22.8%)	< 0.001 [b] 8.8% [c] (6.1%, 11.4%)
Inflammatory lesion count	Change from baseline	LS Mean [d]	-15.8	-13.9	< 0.001 [e]
		SE	0.24	0.24	-1.9 (-2.55, -1.20)
Non-inflammatory lesion count	Change from baseline	LS Mean [d]	-20.7	-18.0	< 0.001 [e]
		SE	0.39	0.39	-2.7 (-3.74, -1.59)

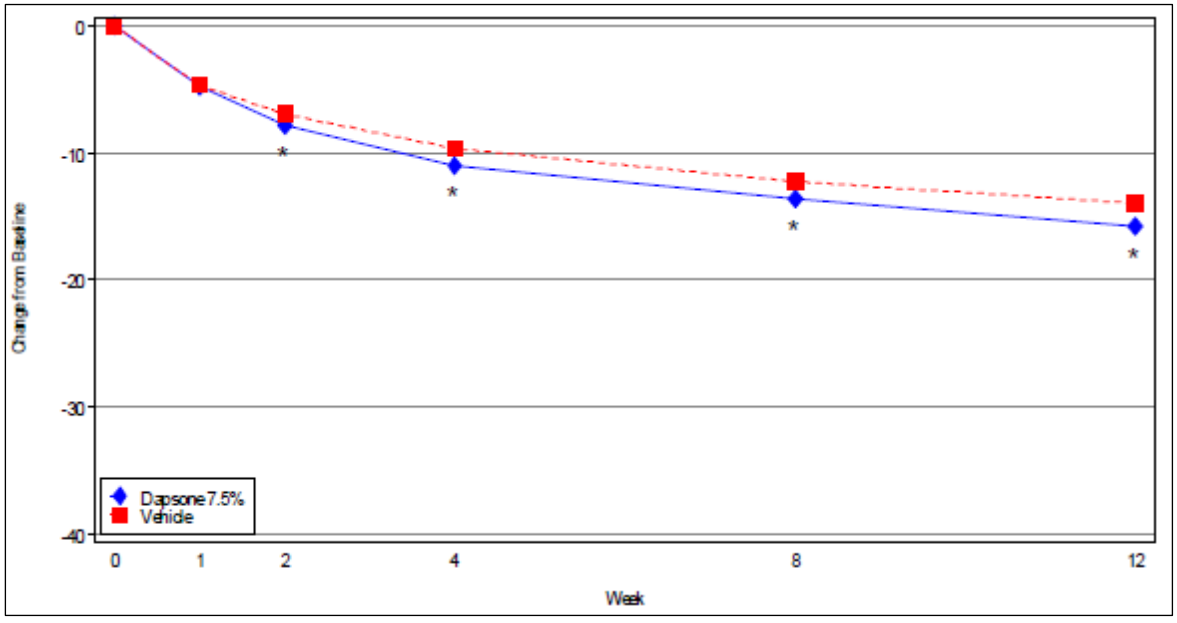
CI = confidence interval; GAAS = Global Acne Assessment Score; LS = least-squares; SE = standard error; Inflammatory lesion count is the sum of papules, pustules, and nodules/cysts. Non-inflammatory lesion count is the sum of open and closed comedones. Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe); a. Percentage of patients with 0 or 1 score (95% CI of success rate); missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets; b. p-values for the test of general association between the responder and treatment group using a Cochran Mantel-Haenszel test stratified by sex; c. Estimated treatment difference (Aczone 7.5% minus vehicle) and 2-sided 95% Wald CI for treatment difference with adjustment for sex; d. Missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets using PROC MIANALYZE. Estimated difference was based on the LS mean. The combined estimate of LS mean and standard error for LS means are reported; e. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex.

Figure 5: GAAS: Percent of patients with a score of 0 or 1 over the treatment period by treatment group and visit – Pooled studies 225678-006 and 225678-007 (ITT population).



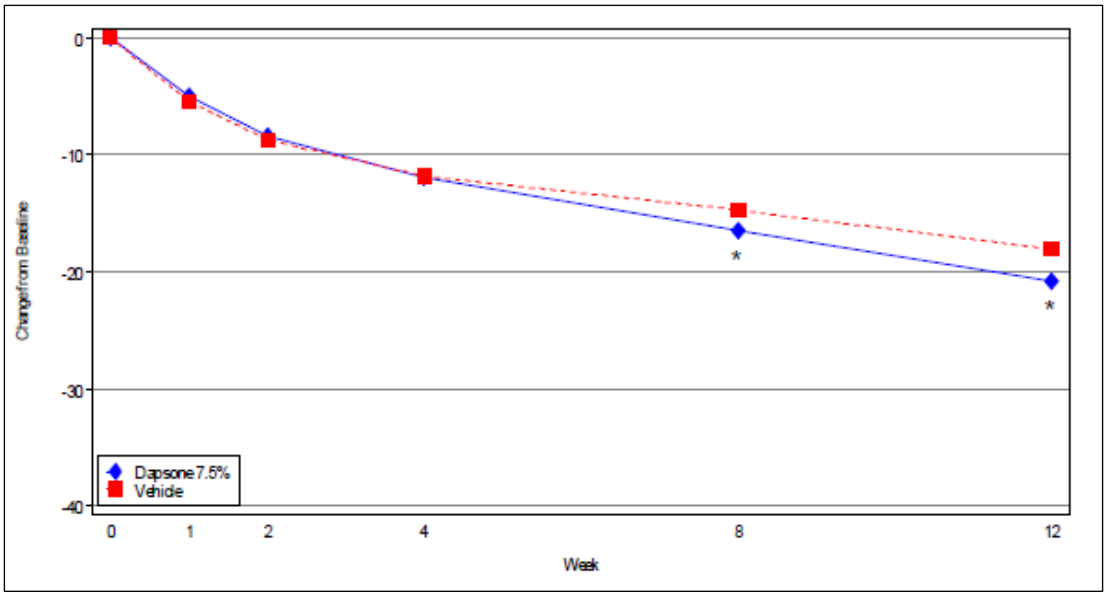
Dapsone 7.5% = Aczone 7.5%; GAAS = Global Acne Assessment Score; Patient's acne severity was evaluated by the investigator using a 5-point GAAS scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe). Missing data were imputed using a multiple imputation method; * indicates the p-value was < 0.05 for the Cochran Mantel-Haenszel test between Aczone 7.5% and vehicle stratified by sex.

Figure 6: Inflammatory lesion count: change from baseline at each follow-up visit by treatment group – Pooled studies 225678-006 and 225678-007 (ITT population).



Dapsone 7.5% = Aczone 7.5%; Inflammatory lesion count was the sum of papules, pustules, and nodules/cysts. Baseline (week 0) was the measurement on day 1. Missing data were imputed using the multiple imputation method; * indicates the p-value was< 0.05 from an analysis of covariance including treatment, baseline, and sex.

Figure 7: Non-inflammatory lesion count: change from baseline at each follow-up visit by treatment group – Pooled studies 225678-006 and 225678-007 (ITT population).



Dapsone 7.5% = Aczone 7.5%; Non-inflammatory lesion count was the sum of open and closed comedones. Baseline (week 0) was the measurement on day 1; Missing data were imputed using the multiple imputation method; * indicates the p-value was < 0.05 from an analysis of covariance including treatment, baseline, and sex.

Table 27: Secondary efficacy analysis of lesion counts at Week 12 – Pooled studies 225678-006 and 225678-007 (ITT population).

Measure	Variable	Statistic	Treatment Group		P-value Difference 95% CI
			Aczone 7.5% (N = 2162)	Vehicle (N = 2178)	
Total lesion count	Absolute change from baseline	LS Mean [a]	-36.5	-32.0	< 0.001 [b]
		SE	0.54	0.53	-4.5 (-5.98, -3.02)
	% Change from baseline	LS Mean [a]	-48.8	-42.8	< 0.001 [b]
		SE	0.69	0.67	-5.9 (-7.83, -4.06)
Inflammatory lesion count	% Change from baseline	LS Mean [a]	-54.6	-48.1	< 0.001 [b]
		SE	0.79	0.79	-6.5 (-8.69, -4.26)
Non-inflammatory lesion count	% Change from baseline	LS Mean [a]	-45.1	-39.4	< 0.001 [b]
		SE	0.83	0.81	-5.7 (-7.98, -3.42)

CI = confidence interval; LS = least-squares SE = standard error; Total lesion count is the sum of inflammatory lesion counts and non-inflammatory lesion counts; a. Missing data were imputed using a multiple imputation method. Inferential statistics were produced by combining the results from the imputed datasets using PROC MIANALYZE. Estimated difference was based on the LS mean. The combined estimate of LS mean and standard error for LS means are reported; b. p-value and 95% CIs for between-group comparison were obtained from an analysis of covariance model including treatment, baseline, and sex.

7.2. Evaluator's conclusions on clinical efficacy

The Sponsor has claimed this submission is a proposed extension of indication but the Sponsor does not have an existing approved product to which this is an extension. Further, in addition to a proposed extension of indication, this submission is also for a proposed new dosage from and a new route of administration. The submission is clearly based on the US application where the product is a new strength and dose regimen as a 5% gel formulation is approved for the treatment of acne and has been marketed for many years.

Also, the whole application is premised on the efficacy of the 5% gel which is not approved in Australia. The reformulation of the product resulted in a 7.5% gel which can be applied once per day, rather than the twice per day of the 5% gel. The once a day application of 7.5% gel results in lower systemic absorption.

Only 1 study is provided which compares the 5% gel applied twice day and the 7.5% gel applied once per day and efficacy was not 1 of the primary objectives of the study. Study 225678-004 was a PK and safety study of 28 days treatment duration. Efficacy measures were only an exploratory objective and while all efficacy measures were comparable between treatment groups, the 28 days treatment period was really too short to evaluate efficacy effectively.

The efficacy then rests on 2 placebo (vehicle) controlled trials of similar design in which treatment was assessed after 12 weeks of treatment. The trials are of significant size with a total of 4,340 patients treated (2,162 on active and 2,178 on vehicle) and the results of the trial are consistent, demonstrating that the 7.5% gel was statistically significantly better than vehicle in global acne scale (GAAS) and both inflammatory and non-inflammatory lesion counts.

To support the efficacy studies the Sponsor provided 3 studies using the 5% gel applied twice daily. While the 5% gel is a different formulation the results indicate that the 5% gel was statistically significantly better than vehicle in global acne scale (GAAS) and both inflammatory and non-inflammatory lesion counts.

The studies show that twice a day therapy with 5% gel is effective and once a day therapy with 7.5% gel is acceptable. The real clinical question is – is 7.5% once a day therapy better or at least equal to 5% twice a day therapy? Is the 7.5% gel better because of the lower systemic exposure? No data is presented that the 5% gel poses any safety issues. Should the sponsor have submitted the twice daily 5% gel rather than the 7.5% gel?

This cannot be answered from the data in this submission as there is no comparative study. Why this was not done is unclear. Can the 7.5% gel be approved rather than the 5%? The sole reason for the 7.5% appears to be compliance and yet no data is presented to state that there is a problem with compliance in the proposed patient population.

While it is difficult to compare results from different studies the following table compares the results for the primary and secondary results collated from the studies of the 2 formulations.

Table 28: Comparison of results from dapsone 7.5% and dapsone 5% clinical studies.

Measure	Variable	Aczone 7.5%	Vehicle	P-value Difference
Dapsone 7.5% gel (pooled studies)				
	N	2162	2178	
GAAS	Success [a] (%)	29.8	21.1	< 0.001
Total lesion count	Mean reduction from baseline	36.5	32.0	< 0.001
	% Change from baseline	48.8	42.8	< 0.001
Inflammatory lesion count	Mean reduction from baseline	15.8	13.9	<0.001
	% Change from baseline	54.6	48.1	< 0.001
Non-inflammatory lesion count	Mean reduction from baseline	20.7	18.0	<0.001
	% Change from baseline	45.1	39.4	< 0.001
Dapsone 5% gel				
Study DAP004	N	330	166	
GAAS	Success [a]	26.7	18.7	0.042
Total lesion count	Mean reduction from baseline	28.5	18.3	<0.001
	% Change from baseline	32.0	21.9	0.001
Inflammatory lesion count	Mean reduction from baseline	12.8	9.3	0.003
	% Change from baseline	37.2	26.6	0.001
Non-inflammatory lesion count	Mean reduction from baseline	15.7	9.2	0.004
	% Change from baseline	27.5	16.8	0.001
Study DAP0203	N	745	7400	
GAAS	Success [a]	44.2	35.9	0.0003
Total lesion count	Mean reduction from baseline	30.4	24.6	0.0001
	% Change from baseline	38.3	32.0	0.0004
Inflammatory lesion count	Mean reduction from baseline	113.7	12.3	0.0265
	% Change from baseline	45.9	41.7	0.0302
Non-inflammatory lesion count	Mean reduction from baseline	16.4	12.1	0.0001
	% Change from baseline	31.1	23.9	0.0022
DAP0204	N	761	764	
GAAS	Success [a]	36.9	29.8	0.0017
Total lesion count	Mean reduction from baseline	28.4	21.7	0.0001
	% Change from baseline	37.4	29.3	<0.0001
Inflammatory lesion count	Mean reduction from baseline	14.3	12.0	0.0001
	% Change from baseline	47.6	40.3	<0.0001
Non-inflammatory lesion count	Mean reduction from baseline	13.9	9.7	0.0001
	% Change from baseline	29.6	21.1	<0.0001

a. Percentage of patients with 0 or 1 score

While comparisons across studies is not ideal, the results for the studies appear to be comparable.

In the long term (12 months) study with the 5% gel (DAP0114) efficacy was observed as early as Month 1 and showed further improvement throughout the 12-month treatment period. The mean percent reduction from Baseline to Month 12 was -58.2% for inflammatory lesions, -19.5% for non-inflammatory lesions and -49.0% for total lesions.

8. Clinical safety

The Aczone 7.5% safety profile is based on analyses from 6 clinical studies conducted in 4,741 subjects/patients (328 healthy subjects and 4,413 patients with acne vulgaris), of whom 2,547 subjects/patients received at least one dose of Aczone 7.5%. In the 2 pivotal phase 3 studies, Aczone 7.5% and vehicle were applied once daily for up to 12 weeks in 4,336 patients with acne vulgaris. Across the 4 phase 1 studies, Aczone 7.5% was applied topically for up to 6 weeks.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by examining and interviewing the patient at each study visit
- Laboratory tests were not done in the pivotal studies.
- Local tolerability (face only) was assessed based on patient-rated stinging/burning, and investigator or trained evaluator assessments of dryness, scaling, and erythema. Dryness, scaling, and erythema were to be assessed by the same person throughout the study whenever possible.

Stinging and burning on the face was defined as a prickling pain sensation within 5 minutes after dosing for post baseline visits and was rated by the patient as follows:

- None (0) = No stinging/burning
- Mild (1) = Slight warm, tingling/stinging sensation; not really bothersome
- Moderate (2) = Definite warm, tingling/stinging sensation that was somewhat bothersome
- Severe (3) = Hot, tingling/stinging sensation that had caused definite discomfort

Dryness was defined as brittle or tight sensation and rated by the investigator/trained designee as follows:

- None (0) = No dryness
- Mild (1) = Slight but definite roughness
- Moderate (2) = Moderate roughness
- Severe (3) = Marked roughness

Scaling was defined as abnormal shedding of the stratum corneum and rated by the investigator/ trained designee as follows:

- None (0) = No scaling
- Mild (1) = Barely perceptible shedding, noticeable only on light scratching or rubbing
- Moderate (2) = Obvious but not profuse shedding
- Severe (3) = Heavy scale production

Erythema was defined as abnormal redness of the skin and rated by the investigator/trained designee as follows:

- None (0) = No erythema
- Mild (1) = Slight pinkness present

- Moderate (2) = Definite redness, easily recognised
- Severe (3) = Intense redness

Vital signs - including heart rate, systolic/diastolic blood pressure, and body temperature were recorded at each study visit.

- Physical examination was done at each study visit

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.3. Dose-response and non-pivotal efficacy studies

Laboratory testing was done in the Phase 1 studies for the 7.5% gel and in the 5% gel studies. The test included haematology (white blood cell count [WBC] with differential, red blood cell count [RBC], red blood cell morphology/blood film, haemoglobin concentration [Hg], haematocrit value [HCT], mean corpuscular volume, mean corpuscular haemoglobin. and platelet count); serum chemistry (glucose, urea nitrogen creatinine, total protein, albumin. calcium, phosphorus, electrolytes [Na, K, CI, bicarbonate [HCO_3]]. total cholesterol. triglycerides, total bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, creatinine kinase, and lactate dehydrogenase).

8.1.4. Other studies evaluable for safety

8.1.4.1. Clinical pharmacology studies

Individual study summaries including safety are provided. No new safety issues were identified.

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.3. Patient exposure

See Table 29-32.

Table 29: Exposure in the clinical development programme for Aczone 7.5%

Study Number	Duration	Regimen	Test Product	Number of Evaluable Subjects/Patients [a]	
				Safety Population	Receiving Aczone 7.5%
Phase III studies					
225678-006	12 weeks	Applied topically to the face and acne-affected areas once daily	Aczone 7.5% gel	2101	104 4
225678-007	12 weeks	Applied topically to the face and acne-affected areas once daily	Aczone 7.5% gel	2235	111 7
Total in pooled safety analysis (Studies 225678-006 and 225678-007):				4336	216
Phase I studies					
225678-004	28 days	2 grams of 3 dapsone 7.5% gel formulations (dosed once daily) or dapsone 5% gel (dosed twice daily) applied topically	Aczone 7.5% gel	77	5 8
225678-009	~6 weeks	200 µL per occlusive patch applied to the left upper back (up to 22 patches per subject)	Aczone 7.5% gel	237	23 7
225678-010 [b]	1 day	0.2 g per occlusive patch applied to the upper back (2 patches per subject)	Aczone 7.5% gel	33	3 3
225678-011	~6 weeks	200 µL per occlusive patch applied to the upper back (14 patches per subject)	Aczone 7.5% gel	58	5 8
Total in all studies:				**4741**	**254**

a. Subjects/patients who were enrolled in the studies (excluding study centre 16078 in Study 225678-006) and who received a dose of study product (safety population); b. Due to an equivocal phototoxicity finding on day 4, one subject had a retest, receiving an additional application of Aczone 7.5% at 2 sites. This subject received a total dose of 0.8 g of Aczone 7.5%.

Table 30: Exposure to study treatment (Safety population) – Pooled studies 225678-006 and 225678-007.

Duration	Statistic	Treatment Group	
		Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
Study duration (days) [a]	N	2161	2175
	Mean (SD)	82.6 (13.64)	82.6 (12.77)
	Median	85.0	85.0
	Min to max	6 to 168	6 to 160
Treatment duration (days) [b]	N	2161	2175
	Mean (SD)	79.4 (17.05)	79.7 (16.54)
	Median	84.0	84.0
	Min to max	1 to 147	1 to 124
Cumulative exposure (N [%])	At least 1 day	2161 (100.0)	2175 (100.0)
	At least 4 weeks	2083 (96.4)	2093 (96.2)
	At least 8 weeks	2013 (93.2)	2036 (93.6)
	At least 12 weeks	1296 (60.0)	1302 (59.9)

Max = maximum; Min = minimum; SD = standard deviation

a. Study duration is defined as date of study exit minus date of first dose plus 1. If the date of exit is missing, the date of the last visit was used; b. Treatment duration is defined as date of last dose minus date of first dose plus 1.

Table 31: Clinical study exposure to Aczone 7.5% w/w by age group and gender: All studies.

Total population				
Age group	Persons		Person-Years	
Gender	Male	Female	Male	Female
12-17 years	634	454	138	100
≥ 18 years	416	1043	76	169
Total	1050	1497	214	268

Table 32: Clinical study exposure to Aczone 7.5% w/w by ethnic or racial origin: All studies.

Ethnic/racial origin	Persons	Person-Years
Caucasian	1468	282
Black	468	87
Asian	87	18
Hispanic	430	76
Other	94	19
Total	2547	482

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies - 7.5%

The incidences of treatment emergent AEs (TEAEs) were similar between Aczone 7.5%-treated and vehicle-treated patients. TEAEs were reported in 18.3% (396/2161) of patients in the Aczone 7.5% group and 18.8% (409/2175) of patients in the vehicle group. The most common TEAEs were: nasopharyngitis, headache, upper respiratory tract infection, application site dryness, application site pruritus, and application site pain.

Table 33: TEAEs that occurred in ≥ 1% of patients in any treatment group by System Organ Class (Safety Population) – Pooled studies 225678-006 and 225678-007

System Organ Class	Adverse Event (Preferred Term)	Number (%) of Patients	
		Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
Overall		396 (18.3)	409 (18.8)
General disorders and administration site conditions	Overall	95 (4.4)	92 (4.2)
	Application site dryness	26 (1.2)	22 (1.0)
	Application site pruritus	23 (1.1)	14 (0.6)
	Application site pain	11 (0.5)	33 (1.5)
Infections and infestations	Overall	160 (7.4)	157 (7.2)
	Nasopharyngitis	40 (1.9)	48 (2.2)
	Upper respiratory tract infection	32 (1.5)	34 (1.6)
Nervous system disorders	Overall	45 (2.1)	32 (1.5)
	Headache	34 (1.6)	26 (1.2)

All treatment-emergent adverse events that occurred in ≥ 1% of patients in any treatment group across the pooled studies are represented, regardless of relationship to treatment. Within each system organ class, preferred terms are sorted by descending frequencies of treatment groups from left to right. Within each preferred term, a patient is counted at most once.

The incidence of application site TEAEs was similar between Aczone 7.5%-treated and vehicle-treated patients. The most common application site TEAEs were: application site dryness application site pruritus and application site pain.

Table 34: Application site TEAEs by MedDRA Preferred Term (Safety population) – Pooled studies 225678-006 and 225678-007.

Adverse Event (Preferred Term)	Number (%) of Patients	
	Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
Application site dryness	26 (1.2)	22 (1.0)
Application site pruritus	23 (1.1)	14 (0.6)
Application site erythema	16 (0.7)	13 (0.6)
Application site exfoliation	12 (0.6)	14 (0.6)
Application site pain	11 (0.5)	33 (1.5)
Application site paraesthesia	5 (0.2)	7 (0.3)
Application site dermatitis	4 (0.2)	2 (0.1)
Skin tightness	3 (0.1)	1 (<0.1)
Application site irritation	3 (0.1)	0 (0.0)
Application site acne	2 (0.1)	4 (0.2)
Skin irritation	2 (0.1)	3 (0.1)
Acne	2 (0.1)	2 (0.1)
Seborrhoea	2 (0.1)	2 (0.1)
Impetigo	2 (0.1)	0 (0.0)
Application site bruise	1 (<0.1)	2 (0.1)
Application site erosion	1 (<0.1)	1 (<0.1)
Application site papules	1 (<0.1)	1 (<0.1)
Application site photosensitivity reaction	1 (<0.1)	1 (<0.1)
Application site rash	1 (<0.1)	1 (<0.1)
Application site discolouration	1 (<0.1)	0 (0.0)
Application site discomfort	1 (<0.1)	0 (0.0)
Application site eczema	1 (<0.1)	0 (0.0)
Application site reaction	1 (<0.1)	0 (0.0)
Application site swelling	1 (<0.1)	0 (0.0)
Application site vesicles	1 (<0.1)	0 (0.0)
Burning sensation	1 (<0.1)	0 (0.0)
Hair growth abnormal	1 (<0.1)	0 (0.0)
Solar dermatitis	0 (0.0)	2 (0.1)
Application site warmth	0 (0.0)	1 (<0.1)
Inappropriate schedule of drug administration	0 (0.0)	1 (<0.1)
Sticky skin	0 (0.0)	1 (<0.1)

MedDRA = Medical Dictionary for Regulatory Activities; All application site treatment-emergent adverse events are represented, regardless of relationship to treatment. Preferred terms are sorted by descending frequencies of treatment groups from left to right; Within each preferred term, a patient is counted at most once.

8.4.1.2. Other studies – 7.5%

- Study 225678-004: similar safety profiles with respect to AEs were demonstrated with all 3 dapsone 7.5% formulations administered once daily and dapsone 5% administered twice daily following 28 days of administration. TEAEs occurred in 23/58 (39.7%) across all 7.5% formulations. The most frequent TEAEs across the 3 dapsone 7.5% formulations were headache and cough. In the dapsone 5% group, no individual TEAE was reported in more than 1 patient.
- Study 225678-009: 4.6% (11/237) of subjects reported a total of 16 TEAEs. Pyrexia, tremor, and skin discolouration were the most commonly-reported TEAEs, each occurring in 0.8% (2/237) of subjects. No other TEAE was reported in more than 1 subject.
- Study 225678-010: No AEs were reported.

- Study 225678-011: 19.0% (11/58) of subjects reported a total of 17 TEAEs. Application site reaction, reported in 3 subjects, was the most commonly-reported TEAE. No other TEAE occurred in more than 1 subject.

8.4.1.3. Other studies – 5%

In the 12-week controlled studies DAP0203 and DAP0204 the incidence of application site TEAEs was similar between the dapsone 5% and vehicle groups in these studies. The only systemic TEAE reported for more than 5% of patients in either treatment group was nasopharyngitis, which had a similar incidence in both treatment groups.

Table 35: Systemic TEAEs reported by ≥1.0% of patients in any treatment group in dapsone 5% studies DAP0203 and DAP0204.

System Organ Class Preferred Term	Number (%) of Patients			
	DAP0203		DAP0204	
	Dapsone 5% (N = 730)	Vehicle (N = 726)	Dapsone 5% (N = 736)	Vehicle (N = 741)
Infections and infestations				
Nasopharyngitis	37 (5.1)	44 (6.1)	35 (4.8)	49 (6.6)
Upper respiratory tract infection NOS	35 (4.8)	34 (4.7)	13 (1.8)	8 (1.1)
Sinusitis NOS	11 (1.5)	12 (1.7)	17 (2.3)	7 (0.9)
Influenza	6 (0.8)	7 (1.0)	8 (1.1)	12 (1.6)
Respiratory, thoracic and mediastinal disorders				
Pharyngitis	22 (3.0)	23 (3.2)	15 (2.0)	15 (2.0)
Cough	21 (2.9)	21 (2.9)	10 (1.4)	8 (1.1)
Rhinitis NOS	9 (1.2)	6 (0.8)	3 (0.4)	1 (0.1)
Sinus congestion	8 (1.1)	7 (1.0)	2 (0.3)	2 (0.3)
Nasal congestion	4 (0.5)	10 (1.4)	4 (0.5)	4 (0.5)
Nervous system disorders				
Headache NOS	33 (4.5)	32 (4.4)	13 (1.8)	17 (2.3)
Injury, poisoning and procedural complications				
Joint sprain	9 (1.2)	9 (1.2)	4 (0.5)	4 (0.5)
Sunburn	8 (1.1)	3 (0.4)	2 (0.3)	8 (1.1)
Gastrointestinal disorders				
Nausea	10 (1.4)	6 (0.8)	4 (0.5)	6 (0.8)
Vomiting NOS	9 (1.2)	5 (0.7)	3 (0.4)	4 (0.5)
Abdominal pain upper	8 (1.1)	5 (0.7)	0	3 (0.4)
Investigations				
Blood creatine phosphokinase increased	6 (0.8)	9 (1.2)	5 (0.7)	2 (0.3)

NOS = not otherwise specified; Note: In these studies the investigator questioned the patient regarding potential application site adverse events at each visit.

Table 36: Application Site TEAEs in dapsone 5% studies DAP0203 and DAP0204.

System Organ Class Preferred Term	Number (%) of Patients			
	DAP0203		DAP0204	
	Dapsone 5% (N = 730)	Vehicle (N = 726)	Dapsone 5% (N = 736)	Vehicle (N = 741)
General disorders and administration site conditions				
Application site reaction NOS	187 (26.6)	192 (26.4)	139 (18.9)	152 (20.5)
Application site dryness	159 (21.8)	145 (20.0)	142 (19.3)	134 (18.1)
Application site erythema	139 (19.0)	124 (17.1)	103 (14.0)	111 (15.0)
Application site burning	16 (2.2)	25 (3.4)	18 (2.4)	17 (2.3)
Application site pruritus	11 (1.5)	12 (1.7)	10 (1.4)	24 (3.2)
Application site rash	0	2 (0.2)	0	5 (0.7)
Application site irritation	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Application site papules	0	0	1 (0.1)	1 (0.1)
Application site pigmentation changes	0	0	2 (0.3)	0
Application site pain	0	1 (0.1)	0	0
Application site paraesthesia	0	0	1 (0.1)	0
Skin and subcutaneous tissue disorders				
Photosensitivity reaction NOS	1 (0.1)	0	0	0

NOS = not otherwise specified; Note: In these studies the investigator questioned the patient regarding potential application site adverse events at each visit.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies – 7.5%

Treatment-related TEAEs were reported in 3.5% (75/2161) of patients in the Aczone 7.5% group and 3.4% (73/2175) of patients in the vehicle group. The most common treatment-related TEAEs (those occurring in ≥ 1% of patients in any treatment group) were application site events: application site dryness and application site pain. The treatment related TEAEs which occurred in more than one patient were all application site reactions.

8.4.2.2. Other studies – 7.5%

- Study 225678-004: no treatment-related TEAEs were reported for any of the 3 dapsone 7.5% once-daily formulations. One treatment-related TEAE of mild pruritus was reported in 1 patient in the dapsone 5% group.
- Study 225678-009: 3.0% (7/237) of subjects had TEAEs that were considered to be treatment-related: skin discolouration and tremor in 2 subjects; application site dermatitis in 1 subject; application site paraesthesia and application site pruritus in 1 subject; application site reaction and pyrexia in 1 subject; pyrexia in 1 subject; and myalgia and dyspnoea in 1 subject.
- Study 225678-011: 8.6% (5/58) of subjects had TEAEs that were considered to be treatment-related: application site reactions in 3 subjects, urticarial patches in 1 subject, and rash on the dorsal aspect of the feet and bilaterally on the legs in 1 subject.
- Study 225678-010: there were no treatment-related TEAEs reported.

8.4.2.3. Other studies – 5%

Study DAP004: The most frequently reported treatment related TEAEs were application site burning (0.9% dapsone, 2.4% vehicle), application site pruritus (1.2% dapsone, 1.2% vehicle), and application site reaction NOS (stinging; 0.9% dapsone, 1.2% vehicle).

8.4.3. Deaths and other serious adverse events (SAEs)

8.4.3.1. Pivotal studies – 7.5%

There were no deaths reported in the phase 3 studies.

The incidence of SAEs in the pooled safety population was 0.3% (7/2,161) in the Aczone 7.5% group and 0.4% (9/2,175) in the vehicle group. The SAEs reported in 7 patients treated with Aczone 7.5% across both studies were: application site dermatitis (33 days after treatment); appendicitis (46 days after treatment); tibia fracture (34 days after treatment); acute myeloid leukaemia (42 days after treatment); helicobacter infection (19 days after treatment); appendicitis and peritoneal haematoma (50 and 53 days, respectively, after treatment); and alcoholism (28 days after treatment). None of these SAEs were considered treatment related. SAEs were reported in 9 patients treated with vehicle across both studies of which only 1 SAE (depression) in a vehicle-treated patient was considered to be related to study product.

8.4.3.2. Other studies – 7.5%

There were no deaths reported in any of the phase 1 studies.

- Studies 225678-004 and 225678-010: there were no other SAEs reported.
- Study 225678-009: 1 SAE (positive urine pregnancy test) was reported at the end of the study (patient had elective termination).
- Study 225678-011: 1 SAE occurred: subject was hospitalised with chest pain approximately 2 days after application of her third set of study product patches. Subject was diagnosed with stress cardiomyopathy ("Takotsubo" cardiomyopathy) which was considered not related to the study drugs.

8.4.3.3. Other studies – 5%

No deaths were reported during the dapsone 5% studies.

No SAEs were reported in Studies DAP9903, DAP0110, 03-0-182, and ACZ ACN 01.

The incidence of SAEs was 0.4% (7/1796) in the dapsone 5% groups and 0.4% (6/1633) in the vehicle groups in the 3 12-week controlled studies (DAP0203, DAP0204 and DAP 004), and 1.0% (5/506) of patients treated with dapsone 5% in the long-term safety study (DAP0114). No SAE was considered treatment-related by the investigator.

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies – 7.5%

Discontinuations due to TEAEs occurred in 0.3% (6/2161) of patients in the Aczone 7.5% group and 0.3% (7/2175) of patients in the vehicle group.

The TEAEs leading to the discontinuation of 6 patients in the Aczone 7.5% group across both studies were: acute myeloid leukaemia (42 days after treatment); application site papules and application site discolouration (both 8 days after treatment); application site acne and application site dermatitis (both 8 days after treatment); rash erythematous and rash pruritic (both 26 days after treatment); application site vesicles, application site swelling, application site pruritus, and pruritus (2, 1, 2, and 2 days after treatment, respectively); and application site discomfort (1 day after treatment). Of the TEAEs that led to discontinuation in patients in the Aczone 7.5% group, 7 that occurred in 3 patients were considered to be treatment related by the investigator: application site acne and application site dermatitis in 1 patient; application site vesicles, application site swelling, application site pruritus, and pruritus in 1 patient and application site discomfort in 1 patient.

8.4.4.2. Other studies – 7.5%

- Studies 225678-004 and 225678-010: there were no discontinuations due to AEs.

- Study 225678-009: 6 subjects were discontinued as a result of non-serious TEAEs including skin discolouration and tremor in 2 subjects (treatment-related), application site pruritus and paraesthesia in 1 subject (treatment-related), application site dermatitis in 1 subject (treatment-related), myalgia and dyspnoea in 1 subject (non-treatment-related), and contact dermatitis ("tape reaction") in 1 subject.
- Study 225678-011: 5 of the 58 subjects were discontinued as a result of TEAEs: application site irritation in 2 subjects (treatment-related), application site reaction in 1 subject (treatment-related); urticaria in 1 subject (treatment-related); and stress cardiomyopathy in 1 subject.

8.4.4.3. Other studies – 5%

- Study DAP0110: No patients discontinued due to AEs.
- Study ACZ ACN 01: 1 patient discontinued due to a TEAE of contact dermatitis during treatment with dapsone 5%, which was considered treatment-related and subsequently resolved.
- Study DAP9903: 1 patient treated with dapsone 1% twice daily discontinued due to facial swelling that was considered to be treatment-related and later resolved.
- Study 03-0-182: 3 patients discontinued due to TEAEs related to TMP/SMX (paraesthesia and dysarthria, urticaria, and hypersensitivity to TMP/SMX); all 3 patients fully recovered.
- Discontinuations due to TEAEs occurred in 0.5% (9/1796) of patients in the dapsone 5% group and 0.6% (10/1633) of patients in the vehicle group in the three 12-week controlled studies (DAP0203, DAP0204 and DAP 004), and 2.2% (11/506) of patients treated with dapsone 5% in the long-term safety study (DAP0114).

8.4.5. Laboratory tests

8.4.5.1. Pivotal studies – 7.5%

No protocol stipulated laboratory assessments were done in the pivotal Phase 3 studies 225678-006 and 225678-007. Laboratory assessments were not deemed necessary as the C_{max} and AUC_{0-24} of dapsone for the Aczone 7.5% applied once daily were 28.6% and 28.7% (lower), respectively, relative to dapsone 5% applied twice daily in Study 225678-004.

8.4.5.2. Other studies – 7.5%

No laboratory data were collected in Studies 225678-009, 225678-010, and 225678-011.

Unscheduled blood tests that were performed for 2 subjects who both reported the TEAEs of skin discolouration ("blue hands") and tremor ("shaking"). These subjects had follow-up procedures performed because the investigator suspected an episode of dapsone-induced methaemoglobinaemia. However, additional investigations did not reveal any findings relevant to these TEAEs, including the finding that methaemoglobin levels in both of these subjects were normal (0.60% and 0.90%).

Study 225678-004: no clinically significant effects on laboratory (chemistry, haematology, and urinalysis) and methaemoglobin findings were observed in any of the groups using dapsone 7.5% or dapsone 5%.

Mean methaemoglobin levels at baseline were 0.78%, 0.81%, 0.76%, and 0.74% in the 3 7.5% dapsone formulations and dapsone 5% groups, respectively, and at day 28 mean change from baseline was 0.00, -0.10, -0.02, and -0.02 in each group, respectively.

8.4.5.3. Other studies – 5%

Safety laboratory evaluations (haematology and serum chemistry) were performed at screening/baseline and week 12 in the dapsone 5% 12-week controlled studies (DAP0004, DAP0203, and DAP0204), and at baseline and months 1, 3, 6, 9, and 12/early termination in the long-term safety study (DAP0114).

No clinically important differences between the treatment groups were identified in Studies DAP0004, DAP0203, and DAP0204. No notable changes in laboratory data were observed over the 12-month treatment period in the long-term safety study.

8.4.6. Vital signs and physical findings

8.4.6.1. Pivotal studies – 7.5%

For both phase 3 studies, vital sign measurements were similar across the Aczone 7.5% and vehicle treatment groups and were within acceptable ranges for each time point. Physical examination findings were similar between treatment groups.

8.4.6.2. Other studies – 7.5%

Study 225678-004: the topical application of any formulation of dapsone 7.5% for 28 days did not result in any clinically significant changes in vital sign data and physical findings. No vital signs data were reported as a TEAE.

Vital signs were not collected in Studies 225678-009, 225678-010, and 225678-011.

8.4.6.3. Other studies – 5%

Vital sign measurements were similar between the treatment groups in the dapsone 5% 12-week controlled studies (DAP004, DAP0203 and DAP0204) with no unusual deviations or changes in those studies or in the long-term safety study. Physical examination abnormalities were generally minor and, in the controlled studies, similarly distributed between treatment groups.

8.4.7. Electrocardiographs (ECGs)

8.4.7.1. Pivotal studies – 7.5%

ECGs were not done.

8.4.7.2. Other studies – 7.5%

Study 225678-004: time-matched ECGs were collected in triplicate on days -1 and 28 at 0 (predose), 1, 2, 4, 8, and 12 hours post dose. Mean changes from baseline in QTc (both QTcB and QTcF) interval were noted for all treatment groups but these were small indicating no clinically significant effect on the QTc interval by any of the dapsone 7.5% formulations. An independent cardiologist review of changes from baseline to day 28 in heart rate, PR interval, QRS interval, and QTcF interval indicated that none of the 4 treatments (3 7.5% formulations and dapsone 5%) was associated with a large or clinically significant mean change from baseline in QTc at any time point, and it was concluded that an electrocardiographic or proarrhythmic effect of any of the dapsone formulations is extremely unlikely.

8.4.7.3. Other studies – 5%

ECGs were not done.

8.4.8. Dermal tolerability

8.4.8.1. Pivotal studies – 7.5%

Overall, Aczone 7.5% and vehicle were well tolerated. At any post baseline visit, for patients with increases in scores for dermal tolerability assessments, the most frequently reported increase in severity was from “none” to “mild” for each of the assessments of stinging/burning, dryness, scaling, and erythema. At any post baseline visit, the percentage of patients with increases in scores post baseline to “severe” was low (≤ 1% of Aczone 7.5%-treated patients and ≤ 2.2% of vehicle-treated patients). Across all time points for all 4 assessments (stinging/burning, dryness, scaling, and erythema), a majority (> 50%) of patients in both treatment groups had a severity rating of “none.” The incidences of stinging/burning, dryness, scaling, and erythema were similar before treatment (baseline visit) and at each post baseline study visit during the 12 weeks of Aczone 7.5% treatment.

Table 37: Dermal tolerability by treatment group: final assessment and maximum severity worsening from baseline (Safety population) – Pooled studies 225678-006 and 225678-007.

Variable	Visit/time point	Response	Number (%) of Patients	
			Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
Stinging/burning [c]	Baseline (Day 1)	0	1688 (78.1)	1708 (78.5)
		1	323 (14.9)	326 (15.0)
		2	103 (4.8)	104 (4.8)
		3	21 (1.0)	11 (0.5)
		Not reported	26 (1.2)	26 (1.2)
	Final response [a]	0	1683 (77.9)	1386 (63.7)
		1	392 (18.1)	635 (29.2)
		2	43 (2.0)	113 (5.2)
		3	7 (0.3)	17 (0.8)
		Not reported	36 (1.7)	24 (1.1)
	Maximum severity [b]	1	507 (23.5)	686 (31.5)
		2	121 (5.6)	249 (11.4)
		3	21 (1.0)	48 (2.2)
Dryness [d]	Baseline (Day 1)	0	1842 (85.2)	1855 (85.3)
		1	270 (12.5)	259 (11.9)
		2	41 (1.9)	55 (2.5)
		3	3 (0.1)	1 (< 0.1)
		Not reported	5 (0.2)	5 (0.2)
	Final response [a]	0	1904 (88.1)	1872 (86.1)
		1	208 (9.6)	261 (12.0)
		2	10 (0.5)	12 (0.6)
		3	1 (<0.1)	0 (0.0)
		Not reported	38 (1.8)	30 (1.4)
	Maximum severity [b]	1	383 (17.7)	412 (18.9)
		2	44 (2.0)	52 (2.4)
		3	4 (0.2)	0 (0.0)
Scaling [d]	Baseline (Day 1)	0	1935 (89.5)	1952 (89.7)
		1	197 (9.1)	196 (9.0)
		2	23 (1.1)	22 (1.0)
		3	1 (< 0.1)	0 (0.0)
		Not reported	5 (0.2)	5 (1.0)
	Final response [a]	0	1983 (91.8)	1969 (90.5)
		1	128 (5.9)	168 (7.7)
		2	10 (0.5)	7 (0.3)
		3	2 (<0.1)	1 (<0.1)
		Not reported	38 (1.8)	30 (1.4)
	Maximum severity [b]	1	269 (12.4)	324 (14.9)
		2	29 (1.3)	44 (2.0)
		3	4 (0.2)	2 (< 0.1)
Erythema [d]	Baseline (Day 1)	0	1515 (70.1)	1544 (71.0)
		1	468 (21.7)	476 (21.9)
		2	163 (7.5)	145 (6.7)
		3	10 (0.5)	5 (0.2)
		Not reported	5 (0.2)	5 (0.2)
	Final response [a]	0	1734 (80.2)	1703 (78.3)
		1	341 (15.8)	374 (17.2)
		2	47 (2.2)	68 (3.1)
		3	1 (<0.1)	0 (0.0)
		Not reported	38 (1.8)	30 (1.4)

Variable	Visit/time point	Response	Number (%) of Patients	
			Aczone 7.5% (N = 2161)	Vehicle (N = 2175)
	Maximum severity [b]	1	210 (9.7)	246 (11.3)
		2	58 (2.7)	79 (3.6)
		3	4 (0.2)	2 (< 0.1)

Severity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe; a. Final is the last available data observed during the post baseline period; b. Maximum severity is the data observed with the highest severity during the post baseline period in those patients whose severity score increased from baseline. The rows for each treatment group do not add up to 100% because the proportions of patients who had no worsening in severity scores from baseline are not displayed; c. Assessed by the patient; d. Assessed by the investigator

8.4.8.2. Other studies – 7.5%

Study 225678-004: all formulations were well tolerated. Dermal tolerability assessments were performed daily through Day 28 allowing calculation of the mean cumulative irritancy index (MCII) for each treatment group for dryness, scaling, and erythema, both separately and combined. MCII for each assessment was low (combined range 0.01 to 0.03) and not clinically significantly different for any 7.5% gel formulation compared with dapsone 5%.

Table 38: Study 225678-004: Dermal tolerability by treatment group: maximum severity during treatment period (Safety population).

Tolerability	Response	Dapsone 7.5% Formulations			
		DAP-11078 (N = 20)	DAP-11079 (N = 19)	DAP-11080 (N = 19)	Dapsone 5% (N = 19)
Dermatologist's or Designee's Assessment					
Dryness	1-Mild	6/20 (30.0%)	2/19 (10.5%)	8/19 (42.1%)	5/19 (26.3%)
Scaling	1-Mild	4/20 (20.0%)	6/19 (31.6%)	6/19 (31.6%)	9/19 (47.4%)
	2-Moderate	1/20 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema	1-Mild	2/20 (10.0%)	0 (0.0%)	1/19 (5.3%)	0 (0.0%)
	2-Moderate	1/20 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient's Self-Assessment					
Stinging/ Burning	1-Mild	5/20 (25.0%)	8/19 (42.1%)	7/19 (36.8%)	6/19 (31.6%)
	2-Moderate	3/20 (15.0%)	2/19 (10.5%)	3/19 (15.8%)	1/19 (5.3%)

Note: For each tolerability assessment, patients who reported "none" are not shown in this table.

Study 225678-009

Under the conditions of study 225678-009, Aczone 7.5% gel and vehicle did not show any potential for sensitisation or cumulative irritation. For the sensitisation analysis (N = 203 in subsets 1 and 2), the primary challenge test results were negative for both Aczone 7.5% gel and vehicle for 99.0% (201/203) of skin sites.

Study 225678-010

Under the conditions of study 225678-010, Aczone 7.5% and vehicle did not show any potential for phototoxicity in healthy subjects. At end of the study (day 4), results of phototoxicity testing were

negative for 97.0% (31/32) of subjects, as assessed by a dermatologist. One subject was considered to have an equivocal phototoxic reaction to Aczone 7.5% (score of 1) but a retest yielded a negative phototoxic reaction (score of 0). Therefore, no subject was considered to have had a phototoxic reaction to Aczone 7.5% gel or to its vehicle.

Study 225678-011

Under the conditions of study 225678-011, Aczone 7.5% and vehicle did not show any potential for photoallergy in healthy subjects. At the last reading of the challenge phase, 98.0% (49/50) of subjects were considered to have a negative photosensitisation reaction at the irradiated sites, as assessed by a dermatologist. One subject was considered to have an equivocal photosensitisation reaction on challenge (1 site for Aczone 7.5% and 1 site for vehicle). This subject was lost to follow-up and no rechallenge could be performed.

8.4.8.3. Other studies – 5%

Not discussed in summaries. The individual CSRs only report dermal tolerability by events reported as AEs.

8.5. Post-marketing experience

There is no post marketing data with Aczone 7.5%.

A post-marketing review of safety information was reported through 31 December 2014 for dapsone 5% gel. The AEs showed no pattern as to the nature or severity of the events to indicate a change to the benefit-risk profile of dapsone 5%. However, methaemoglobinaemia is included in both the US approved Package Inserts for the 5% gel and the 7.5% gel based on 2 post-marketing cases of methaemoglobinaemia (1 spontaneous and 1 literature report [Swartzentruber et al, 2014]).

8.5.1. Safety issues with the potential for major regulatory impact

Not applicable.

8.5.2. Other safety issues

8.5.2.1. Safety in special populations

In the Aczone 7.5% phase 3 studies (225678-006 and 225678-007), subgroup analyses were performed for all TEAEs regardless of causality using the pooled safety population. The following subgroups were analysed: age group (age 12 to 17 years versus ≥ 18 years), sex (male versus female), and race (Caucasian versus non-Caucasian). In the analyses of the pooled studies, the overall incidence of TEAEs was similar among the subgroups of age, sex, and race. Within each subgroup, the overall incidence of TEAEs was similar between the treatment groups.

No subgroup safety analyses were conducted in Studies 225678-009, 225678-010, and 225678-011. The patient numbers in Study 225678-004 were too small to allow for meaningful analysis.

The CSRs for the dapsone 5% studies do not include subgroup analyses for TEAEs.

8.5.2.2. Safety in patients with G6PD deficiency

A phase 4 study ACZ ACN 01 was conducted as a post approval commitment requested by the US FDA to further evaluate the safety of topical 5% dapsone gel in patients with G6PD deficiency, who are at greater risk of developing haemolysis and haemolytic anaemia than those with normal G6PD activity. This crossover study in 64 patients was requested as the original 5% dapsone submission had only included 25 patients with low G6PD activity.

Haemolysis is characterised by decreases in haemoglobin with the following concomitant changes: an increase in bilirubin, as the breakdown product of haemoglobin accumulates; a decrease in haptoglobin, as this haemoglobin-binding protein is quickly consumed; an increase in reticulocytes as a compensatory measure to increase production of new red blood cells; and an increase in LDH.

Week 2 is the primary time point of interest since any changes that would occur are expected to be observed within this timeframe. The analyses were performed using the safety evaluable data set, which included 56 subjects who applied at least 50% of the treatment applications in the first treatment period and had clinical laboratory results available from week 2.

After 2 weeks of treatment, there was a small decrease from baseline in haemoglobin of -0.32 g/dL with dapsone 5% treatment and no change from baseline with vehicle treatment (0.01 g/dL). The magnitude of the mean change in the dapsone 5% group was small and not clinically significant. After 12 weeks of treatment, there were no differences in haemoglobin or changes from baseline between dapsone and vehicle treatments. No changes in haemoglobin were considered clinically significant.

Changes from baseline in bilirubin were small and similar between the treatments at both 2 and 12 weeks, with changes of 0.06 and 0.01 mg/dL, respectively, for dapsone and 0.01 and 0.06 mg/dL for vehicle. Changes from baseline in haptoglobin were small and similar between the treatments at both 2 and 12 weeks, with changes of -0.2 and 5.0 mg/dL, respectively, for dapsone and 4.8 and 1.6 mg/dL for vehicle. At 2 weeks, the mean change in reticulocyte proportion was 0.22% with dapsone and 0.04% with vehicle treatment, and at 12 weeks, the mean change was 0.19% with dapsone and 0.08% with vehicle. The changes from baseline during dapsone treatment are marginal and not considered clinically relevant. Changes from baseline in LDH were small and similar between the treatments at both 2 and 12 weeks, with changes of -3.3 and 1.6 IU/L with dapsone and 1.1 and 2.3 IU/L with vehicle.

8.5.2.3. Safety related to drug-drug interactions and other interactions

No formal drug interaction studies were conducted with Aczone 7.5% gel.

Study 03-0-182 was an interaction study that evaluated the effect of dapsone 5% in combination with double strength (160 mg/800 mg) TMP/SMX. During co-administration, systemic levels of TMP and SMX were essentially unchanged, however, levels of dapsone and its metabolites increased in the presence of TMP/SMX. The systemic exposure from Aczone 7.5% gel is expected to be about 1% of that from the 100 mg oral dose, even when co-administered with TMP/SMX.

8.5.3. Pregnancy

No studies in pregnancy have been conducted.

Dapsone has been shown to have an embryocidal effect in rats and rabbits when administered orally in doses of 75 and 150 mg/kg/day (approximately 1200 and 360 times the systemic exposure observed in human females under maximal topical use conditions, based on area under the curve [AUC] comparisons), respectively. These effects were probably secondary to maternal toxicity.

In the pivotal studies, there were 21 patients with positive urine pregnancy tests, all occurring at the week 12 or early exit visit: 10 patients in the Aczone 7.5% group and 10 patients in the vehicle group. Of these patients, 5 patients discontinued the study early due to pregnancy and the other 5 patients were found to have positive pregnancy test results at their study exit visit (excluding 1 patients who was incorrected coded as positive).

The outcomes for only 2 patients who discontinued early are known. One subject who discontinued after 66 days of treatment delivered at healthy baby and 1 patient who discontinued after 34 days of treatment had an elective termination. The outcomes of the subjects who tested positive at end of study were not reported.

One subject in the Phase 1 7.5% studies had a positive pregnancy test at the end of the study and reported that she had had an elective termination.

In the 5% dapsone gel studies 9 subjects receiving dapsone were reported to have become pregnant while on study drug. Of these 9, 6 had a known outcome: 1 had an elective termination, 4 had healthy children and 1 delivered a healthy female with 1 extra digit on each hand, which was removed (there was a family history of such abnormalities).

8.6. Evaluator's overall conclusions on clinical safety

It is stated that based on the lower systemic exposure with Aczone 7.5% compared with dapsone 5%, the results of the dapsone 5% studies, including the long-term, open-label Study DAP0114 that demonstrated safety and continued efficacy of dapsone 5% over 12 months an agreement was made with the US FDA that the Sponsor (Allergan) was not required to conduct a long-term safety study or a thorough QT/QTc study with Aczone 7.5%, and did not have to include an assessment of systemic safety (eg, laboratory analyses or ECG monitoring) in the phase 3 studies of Aczone 7.5%.

The safety is therefore based on only 2 studies of 12 weeks duration plus 4 phase 1 studies of duration of 1 dose to ~6 weeks.

In phase 1 dermal tolerability studies (Studies 225678-009, 225678-010, and 225678-011), Aczone 7.5% did not show any potential for cumulative irritation, sensitisation, phototoxicity, or photoallergy under the conditions employed in the studies.

No new safety issues have been identified in the clinical studies with the 7.5% gel.

Application site reactions were common but appear to be similar to that seen with the 5% gel although this is hard to assess. A good summary of the local adverse reactions for 5% gel is provided in the approved US Package Insert as it is not addressed in the *Clinical Summaries*.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Aczone 7.5% gel in the proposed usage are:

- Consistent results in 2 identical randomised, vehicle controlled studies
- Combined results in the 2 pivotal studies demonstrated a benefit in both the primary outcomes – global acne score and lesion counts
- The combined results in the 2 pivotal studies showed on average, a 55% reduction in inflammatory lesions and a 45% reduction in non-inflammatory lesions over a 12 week treatment period which was statistically significantly better ($p<0.0001$) than results for vehicle
- Results were sustained through 12 weeks (results with 5% gel twice daily demonstrated continued efficacy through 52 weeks)
- Incidence of skin reactions was low and no indication of sensitisation or phototoxicity
- No new safety issues were identified in the clinical studies

9.2. First round assessment of risks

The risks of Aczone 7.5% gel in the proposed usage are:

- Skin reactions particularly skin dryness and application site pruritus are most common
- Methaemoglobinaemia has been reported for oral dapsone and in post-marketing experience with topical dapsone 5%
- Concomitant treatment with dapsone and TMP/SMX may increase the likelihood of haemolysis in patients with G6PD deficiency

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Aczone 7.5% gel, given the proposed usage, is favourable.

The efficacy results are consistent in the clinical studies and appear comparable to the 5% gel applied twice daily.

The results of phase 4 Study ACZ ACN 01 showed no evidence of haemolytic anaemia in G6PD-deficient patients with acne who were treated with dapsone 5%, and any minor changes in haemoglobin were not associated with any other evidence of haemolysis. In the pivotal studies with Aczone 7.5% applied once daily there was no clinical evidence of haemolysis or haemolytic anaemia. Concomitant treatment with dapsone and TMP/SMX may increase the likelihood of haemolysis in patients with G6PD deficiency. Methaemoglobinaemia has been reported for oral dapsone and in post marketing experience with topical dapsone 5% and so remains a risk for the 7.5% gel.

10. First round recommendation regarding authorisation

Based on the data presented, it is recommended that the application be approved for the indication requested.

11. Clinical questions

None

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