1. Title Page

STATISTICAL ANALYSIS PLAN

An Open-Label Phase 4 Safety and Efficacy Trial of ACZONE (Dapsone) Gel, 7.5% in 9 to 11 Year-Old Patients With Acne Vulgaris

Version 2.0: 2018-05-10

Protocol Number:	1679-401-006
Development Phase:	4
Product Name:	ACZONE (Dapsone, AGN-225678) Gel, 7.5%
Study Statistician:	PPD
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California 92612 +1-714-246-4500 +1-800-347-4500

2. Table of Contents

2.1 List of Tables

2.2 List of Figures

Not applicable.

3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
AE	adverse event
ATC	Anatomical Therapeutic Chemical
CFB	change from baseline
DHA	dapsone hydroxylamine
eCRF	electronic case report form
IGA	Investigator's Global Assessment
MedDRA	Medication Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NAD	N-acetyl dapsone
PK	pharmacokinetic
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study 1679-401-006 dated 23-Jun-2016. Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic (PK) data will be prepared separately.

This document is organized into 3 main sections:

1. Study Overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

4.1 Study Design Summary

Structure: Multicenter, open-label, non-comparative trial

Duration: Patient participation is up to approximately 16 weeks from screening to trial exit; treatment duration is up to 12 weeks

Study Treatment Groups: ACZONE 7.5%

Controls: No control group

Dosage/Dose Regimen: All patients will receive treatment with ACZONE 7.5% once-daily

Pharmacokinetic (PK) Cohort (at least 16 evaluable PK patients): For the first 8 days (+ 2 days), study drug will be administered once-daily under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders as instructed by the study site. The study drug should be rubbed in gently and completely. On Day 1, the study drug will be administered on site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on site in the morning. After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer during the final 11 weeks. Evaluable PK patients are defined as those that are administered at least 8 days of study drug under maximal use conditions, and provided PK samples for analysis without any major protocol deviations.

Non-PK Cohort (approximately 84 patients): Patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face

once-daily for 12 weeks as instructed by the study site. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer.

Randomization/Stratification: No randomization; all patients will receive ACZONE 7.5%. Assignment to PK or Non-PK Cohort will be based on patient/legally authorized representative choice and investigator's judgment.

Visit Schedule: up to 7 scheduled study visits (see Table 4-2 for further details):

- Visit 1: Screening (-30 to day -1)
- Visit 2: Day 1 (Baseline)[a]
- Visit 3: Week 1 (Day 8 + 2 days)
- Visit 4: Week 2 (±3 days)
- Visits 5 and 6: Weeks 4 and 8 (±7 days)
- Visit 7: Week 12 / Early Exit (±7 days)

[a] *Can be combined with the screening visit if no washout period is required.*

Number of Participants: For the PK Cohort, at least 16 patients will be enrolled to ensure 16 evaluable PK subjects at the Week 1 visit. For the Non-PK Cohort, approximately 84 additional patients will be enrolled in the study for a total of approximately 100 patients.

4.2 Study Objectives and Endpoints

Each study objective is presented with corresponding endpoint(s) below:

Table 4-1 Study Objectives and Corresponding Endpoints

Objectives	Endpoints

• To evaluate the safety and tolerability of ACZONE 7.5% administered topically once-daily for 12 weeks in 9 to 11 year-olds with acne vulgaris.	**Safety Assessments**
	• Adverse events (AE)
	• Vital signs
	  ○ Heart rate
	  ○ Blood pressure
	  ○ Respiratory rate
	  ○ Body temperature
	• Local dermal tolerability (face only)
	  ○ Dryness
	  ○ Scaling
	  ○ Erythema
	  ○ Stinging/burning

• To evaluate the peak and trough plasma drug concentrations in 9 to 11 year-olds with acne vulgaris following once-daily dosing of	**Pharmacokinetic Assessments** • Peak and trough plasma concentrations of dapsone, N-acetyl dapsone (NAD), dapsone hydroxylamine

Objectives	Endpoints
ACZONE 7.5% under maximal use conditions for the first 8 days (+ 2 days).	(DHA), and other metabolites or analytes (if warranted) at Week 1/Visit 3
• To explore the efficacy of ACZONE 7.5% administered topically once-daily in 9 to 11 year-olds with acne vulgaris.	**Efficacy Assessments** • Lesion counts (face only) o Change and percent change from baseline in inflammatory lesion counts o Change and percent change from baseline in noninflammatory lesion counts o Change and percent change from baseline in total lesion counts (Total lesion counts will be the sum of inflammatory lesion counts and noninflammatory lesion counts.) • Investigator's Global Assessment (IGA) (face only) o Proportion of patients with none (0) or minimal (1) score on the IGA at each visit o Proportion of patients with none (0) or minimal (1) score plus at least a 2-grade improvement on the IGA at each visit

4.3 Schedule of Activities

Table 4-2 Schedule of Activities

Study Period	**Screening[a]**	**Baseline/Day 1[a]**	**Week 1**	**Week 2**	**Weeks 4 and 8**	**Week 12/ Early Exit**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5 and Visit 6**	**Visit 7**
Visit Windows	**Day -30 to Day -1**	**N/A**	**Day 8 (+ 2 days)**	**Day 15 (± 3 days)**	**Day 29 (± 7 days) and Day 57 (± 7 days)**	**Day 85 (± 7 days)**
Informed consent/authorization and minor assent[b]	X					
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Demographics	X					
Skin phototype assessment	X					
Physical examination includes vital signs, height and weight[c]	X					X
Pregnancy test (urine)[d]	X	X			X	X
IGA	X	X	X	X	X	X
Lesion count	X	X	X	X	X	X
Enrollment		X				
PK Cohort: Dispense study drug, training on application/return[e]		D	R/D		R/D	R
Non-PK Cohort: Dispense study drug, training on application/return[f]		D			R/D	R
Standardized photographs[g]		X				X
Local tolerability[h]		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X

Study Period	**Screening[a]**	**Baseline/Day 1[a]**	**Week 1**	**Week 2**	**Weeks 4 and 8**	**Week 12/ Early Exit**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5 and Visit 6**	**Visit 7**
Visit Windows	**Day -30 to Day -1**	**N/A**	**Day 8 (+ 2 days)**	**Day 15 (± 3 days)**	**Day 29 (± 7 days) and Day 57 (± 7 days)**	**Day 85 (± 7 days)**
Adverse events	X	X	X	X	X	X
PK sampling[i]			X			

D = dispense; IGA = Investigator's Global Assessment; N/A = not applicable; R = return; PK= pharmacokinetic

[a] If a washout period is not required, then screening and baseline visits can occur on the same day, and the procedures required to be repeated at both visits should be performed once.

[b] Consent for photography is included in the informed consent process at select centers.

[c] Physical examination and vital signs are to be performed if inclusion/exclusion criteria are met at screening; not required for screen failures. Vital signs include heart rate, blood pressure, respiratory rate, and body temperature.

[d] Female patients only. The urine pregnancy test can also be performed at any timepoint during the course of the trial at the investigator's discretion. If a patient misses a menstrual cycle, a urine pregnancy test must be performed.

[e] Patients in the PK cohort will be dispensed 1 kit with 14 tubes on Baseline/Day 1 (Visit 2). All patients in the PK cohort will start dosing on Day 1 using the 2.0 gram tubes dispensed for individual application.PK Cohort patients will return used study drug at Week 1/Visit 3. At Week 1/Visit 3, Week 4 (Visit 5) and Week 8 (Visit 6) the patients in the PK Cohort are dispensed 60-gram pumps. Dispensed and returned study drug will be weighed at the study center.

[f] All patients will start dosing on day 1. The patients in the Non-PK Cohort are dispensed 60-gram pumps on Baseline/Day 1 (Visit 2), Week 4 (Visit 5) and Week 8 (Visit 6). Dispensed and returned study drug will be weighed at the study center.

[g] At select centers, patients may have photographs taken of their face for illustration or presentation purposes. Patients who consent to being photographed will be required to remove any make-up at least 20 minutes prior to having photographs taken.

[h] Local tolerability will be assessed prior to drug administration on day 1, as well as postdose on the face only.

[i] Only applies to patients in the PK Cohort at the Week 1/Visit 3. Blood samples will be collected within 30 minutes prior to dosing in clinic in the morning and at approximately 10 hours post dose (± 3 hour) (patients are allowed to leave and come back if needed) under maximal use conditions to determine the peak and trough plasma drug concentrations.

5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This SAP will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9. Information on the PK analyses can be found in the PK data analysis plan.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5-1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who sign informed consent.	—
Safety	All participants who received at least one application of study drug.	Actual received
Modified Intent-to-Treat (mITT)	All enrolled participants who have a baseline assessment and at least one post-baseline assessment.	Actual received

5.1.1.1.2 Study Treatments

The following treatment group is defined for this study:

- ACZONE 7.5%

5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP.

Table 5-2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of participants in individual categories
	  ○ Participants with ≥ 1qualifying event counted once per individual category
	• N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator)
	  ○ N1 = participants with non-missing baseline value

Methodology	Description
Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = participants with non-missing value
CFB[1] descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit

[1] CFB = change from baseline

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.4 Missing Data

No imputation of missing efficacy data for this study is specified for methodologies in Section 5.1.1.1.3.

5.1.1.1.5 Site Pooling

Unless specifically detailed, data will be pooled over sites for the summary analyses.

5.1.1.2 Demographics

The Screened Population, Safety, and mITT Populations will be used to summarize in this section.

5.1.1.2.1 Participant Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Participant disposition will be summarized as follows:

Table 5-3 Participant Disposition Summaries

Parameter	Description	Timing	Methodology

Screening and disposition	Distribution in the screened population in total and by screen failure/screen success
	• Age
	• Sex
	• Ethnicity
	• Race group 1
	  ○ White
	  ○ Black or African American
	  ○ Asian
	  ○ American Indian or Alaska Native
	  ○ Native Hawaiian or Other Pacific Islander
	• Race group 2
	  ○ White
		Screening Period	Continuous descriptives and categorical descriptives

Parameter	Description	Timing	Methodology
	○ Non-white • Reasons for screen failure in the screened population ○ eCRF categories		
Study disposition	• Distribution in the safety population in total and by cohort (PK and Non-PK cohorts)	Treatment Period	Categorical descriptives

5.1.1.2.2 Protocol Deviations

Protocol deviations will be listed as follows:

Table 5-4 Protocol Deviations

Parameter	Description	Timing	Methodology
Important protocol deviations	Protocol deviations are defined as any variation from the protocol, including enrollment of a participant who did not meet all inclusion criteria and/or met any exclusion criteria and failure to perform the assessments and procedures within the required time frame.	—	Listing

5.1.1.2.3 Demographics

Demographics will be summarized in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population, as follows:

Table 5-5 Demographic Summaries

Parameter	Description	Timing	Methodology
Age	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Sex, ethnicity and race	• Sex • Ethnicity • Race group 1 ○ White ○ Black or African American ○ Asian ○ American Indian or Alaska Native ○ Native Hawaiian or Other Pacific Islander • Race group 2 ○ White ○ Non-white	Screening Period	Categorical descriptives

5.1.1.2.4 Baseline Characteristics

Baseline characteristics will be summarized in total and by cohort (PK cohort and Non-PK cohort) for mITT or Safety Populations as follows:

Table 5-6 Baseline Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics	For Safety Population only: • Height (m) • Weight (kg) • Body mass index (BMI) o Weight (kg) / height $(m)^2$	Latest assessment in Screening Period	Continuous descriptives
Baseline characteristics	For Safety Population only: • Skin phototype assessment o I: Always burns easily; never tans (sensitive) o II: Always burns easily; tans minimally (sensitive) o III: Burns moderately; tans gradually (light brown) (normal) o IV: Burns minimally; always tans well (moderate brown) (normal) o V: Rarely burns; tans profusely (dark brown) (insensitive) o VI: Never burns; deeply pigmented (insensitive)	Latest assessment in Screening Period	Categorical descriptives
Disease characteristics	For mITT Population only: • Investigator's Global Assessment (IGA) (face only)	Latest assessment in Screening Period	Categorical descriptives
Disease characteristics	For mITT Population only: • Total lesion counts (face only) • Inflammatory lesion counts (face only) • Non-inflammatory lesion counts (face only)	Latest assessment in Screening Period	Continuous descriptives

5.1.1.2.5 Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or newer. Unique participants who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population as follows:

Table 5-7 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the total group.

5.1.1.2.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced (DDE), version MAR2016 or newer. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population as follows:

Table 5-8 Medication Summaries

Parameter	Description	Timing	Methodology
Prior medications[1]	Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date	Screening Period	Categorical descriptives
Concomitant medications[1]	Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date	Treatment Period	Categorical descriptives

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the total group.
[1] If the available date information is not sufficient for classification, the medication will be classified as both a prior medication and a concomitant medication.

5.1.1.3 Efficacy Analyses

Efficacy analyses are to be considered exploratory and no inferential statistics will be presented for this study. Efficacy analyses will be based on the mITT Population.

The following efficacy assessments and terms are defined:

Table 5-9 Efficacy Assessments

Assessment/Term	Description
Investigator's Global Assessment (IGA)	Overall severity of acne vulgaris evaluated using a 5-point IGA (face only): • Clear (0) o No comedones, papules or pustules o Residual hyperpigmentation and erythema may be present • Almost clear (1) o Rare comedones o No more than a few small papules and pustules • Mild (2) o Easily recognizable comedones in limited numbers o +/- Presence of small papules and pustules • Moderate (3) o Many comedones o +/- Easily recognizable small and medium-sized papules o No nodules or cysts. • Severe (4) o Widespread and numerous comedones o Many small, medium-sized and large papules and pustules o Nodules or cysts may or may not be present.
Inflammatory lesion counts	Inflammatory lesion counts will be the sum of counts of the following lesion types (face only): • Papule – a small, red, solid elevation less than 1.0 cm in diameter • Pustule – a small, circumscribed elevation of the skin that contains yellow-white exudate • Nodule – a circumscribed, elevated, solid lesion generally more than 1.0 cm in diameter with palpable depth • Cyst – a smooth, dome-shaped, elevated, freely moveable, skin colored, round to ovoid lesion greater than 0.7 cm in diameter
Noninflammatory lesion counts	Noninflammatory lesion counts will be the sum of counts of the following lesion type (face only): • Open Comedone – a pigmented dilated pilosebaceous orifice (blackhead) • Closed Comedone – a tiny white papule (whitehead)
Total lesion counts	Total lesion counts will be the sum of inflammatory lesion counts and noninflammatory lesion counts (face only).

Baseline assessments for IGA and lesion count will be the latest assessment pre-treatment on or before day 1 (visit 2).

The efficacy endpoints will be summarized in total (both study cohorts combined) as follows:

Table 5-10 Efficacy Analyses

Endpoint	Description	Timing	Methodology
IGA	Summary by analysis visit: • Proportion of patients with none (0) or minimal (1) score • Proportion of patients with none (0) or minimal (1) score plus at least a 2-grade improvement from baseline	Baseline (day 1), and Weeks 1, 2, 4, 8, and 12/early exit	Categorical descriptives
Inflammatory lesion counts[1]	Summary by analysis visit: • Change from baseline	Baseline (day 1), and Weeks 1, 2, 4,	CFB descriptives

Endpoint	Description	Timing	Methodology
	• Percent change from baseline	8, and 12/early exit	
Noninflammatory lesion counts[1]	Summary by analysis visit: • Change from baseline • Percent change from baseline	Baseline (day 1), and Weeks 1, 2, 4, 8, and 12/early exit	CFB descriptives
Total lesion counts	Summary by analysis visit: • Change from baseline • Percent change from baseline	Baseline (day 1), and Weeks 1, 2, 4, 8, and 12/early exit	CFB descriptives

[1] If a number of patients have fewer than 5 inflammatory or noninflammatory lesions at baseline, an additional analysis may be conducted for that lesion type including only those patients with at least 5 lesions of that type at baseline.

5.1.1.4 Pharmacokinetic Analyses

The PK analysis plan is beyond the scope of this document and will be outlined in a separate document.

5.1.1.5 Safety Analyses

Safety analyses will be based on the Safety Population.

5.1.1.5.1 Study Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population as follows:

Table 5-11 Study Treatment Summaries

Parameter	Description	Timing	Methodology
Study treatment exposure (days)	Treatment end date - treatment start date + 1	Treatment Period	Continuous descriptives
Mean daily dose for PK cohort	For PK cohort only, summary by visit interval: $\frac{\text{Weight of study drug dispensed - Weight of study drug returned}}{\text{Interval duration}^1}$	Baseline (day 1)-Week 1 (visit 2-3); Week 1–4 (visit 3-5); Week 4–8 (visit 5-6); Week 8–12 (visit 6-7) Treatment Period	Continuous descriptives
Mean daily dose for non-PK cohort	For Non-PK cohort only, summary by visit interval: $\frac{\text{Weight of study drug dispensed - Weight of study drug returned}}{\text{Interval duration}^1}$	Baseline (day 1)-Week 4 (visit 2-5); Week 4–8 (visit 5-6); Week 8–12 (visit 6-7) Treatment Period	Continuous descriptives
Study treatment compliance (%)	Summary by visit interval and by cohort (PK cohort and Non-PK cohort): $100 \times \frac{\text{Number of days treatment taken as prescribed}^2}{\text{Interval duration}^1}$	Baseline (day 1)-Week 1 (visit 2-3), Week 1–2 (visit 3-4), Week 2–4 (visit 4-5), Week 4–8 (visit 5-6), Week 8–12 (visit 6-7) Treatment Period	Continuous descriptives

[1] Interval duration=Interval end date – interval start date + 1, for the visit interval starting from baseline (day 1).
[2] An individual usage tube containing 2 grams of study drug is expected for PK cohort in the first 8 (+2) days; otherwise, an approximately pea-sized amount of study drug is expected. Number of days treatment taken as prescribed = interval duration – number missed – number extra during interval.

5.1.1.5.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5-12 AE Terms

Term	Description
Treatment-emergent adverse event (TEAE)	An adverse event recorded on the eCRF would be considered treatment-emergent if either of the following conditions are met: AE onset date ≥ first study treatment date; or AE onset date < first study treatment date and either: • the severity of the event worsened on or after the first study treatment date, or • the event became serious on or after the first study treatment date
Serious Treatment-emergent adverse event (TEAE)	An event identified as TEAE that further meets serious adverse event (SAE) criteria at any time would be a treatment-emergent SAE.

AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA version 19.0 or newer. Unique participants reporting AEs in the following AE categories will be summarized in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population as follows:

Table 5-13 AE Summaries

Parameter	Description	Timing	Methodology
Overall summary	Overall summary only for the following categories: • TEAEs • Treatment-related TEAEs • Serious TEAEs • TEAEs leading to study discontinuation • Deaths	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
TEAEs	Overall summary and by SOC and PT	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
TEAEs by severity	Overall summary and by SOC, PT and worst severity *The worst severity is defined as the greater of the onset severity and maximum severity following onset recorded on the eCRF. If the same TEAE term has been reported more than once for a subject with different severity grades, the worst severity grade will be used in the tabulation.*	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
Treatment-related TEAEs	Overall summary and by SOC and PT	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives

Parameter	Description	Timing	Methodology
Treatment-related TEAEs by severity	Overall summary and by SOC, PT and worst severity *The worst severity is defined as the greater of the onset severity and maximum severity following onset recorded on the eCRF. If the same TEAE term has been reported more than once for a subject with different severity grades, the worst severity grade will be used in the tabulation.*	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
Serious TEAEs	Overall summary and by SOC and PT	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
TEAEs leading to study discontinuation	Overall summary and by SOC and PT	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives
Common TEAEs	Summary by SOC and PT • Includes TEAEs occurring in ≥ 5% of participants in either PK cohort or Non-PK cohort	From treatment start date until Week 12 or early termination date, whichever comes first	Categorical descriptives

SOCs will be sorted alphabetically; PTs will be sorted by descending proportions in the total group.

5.1.1.5.3 Vital Signs

Vital signs will be summarized in total for the Safety Population as follows:

Table 5-14 Vital Signs Summaries

Endpoint	Description	Timing	Methodology
Descriptives	Summary by parameter and analysis visit • Parameters specified in Table 6-7	Screening (visit 1), Week 12/early exit	CFB[1] descriptives

[1] The measurement at the screening (visit 1) will be determined using the latest pre-dose measurement on or before day 1.

5.1.1.5.4 Local Dermal Tolerability

The local tolerability examination of the face is to be performed by the investigator (or appropriately trained designee), who will assess dryness, scaling, and erythema, and the patient will assess stinging/burning. The assessor will examine the skin area where study drug is applied in comparison to the surrounding skin from day 1 to week 12. The same assessor will rate dryness, scaling, and erythema at each visit, where possible. Local tolerability signs and symptoms will be rated using a severity scoring of 0 (none), 1 (mild), 2 (moderate), or 3 (severe), as further defined in Table 6-8.

Local dermal tolerability data will be summarized in total and by cohort (PK cohort and Non-PK cohort) for the Safety Population as follows:

Table 5-15 Local Dermal Tolerability Summaries

Endpoint	Description	Timing	Methodology
Descriptives[1]	Summary by parameter and analysis visit • Parameters specified in Table 6-8.	Pre-dose on baseline (day1), post-dose on baseline (day 1), Weeks 1, 2, 4, 8, and 12/early exit	Categorical Descriptives

[1] All local dermal tolerability data will be listed.

5.1.1.5.5 Urine Pregnancy Test

All patients with positive pregnancy test results will be listed.

5.1.1.6 Subgroup Analyses

No subgroup analyses are planned for this study.

5.1.1.7 Interim Analyses

No interim analyses are planned for this study.

5.1.2 Determination of Sample Size

The sample size for the trial was determined empirically, and is consistent with that requested by the FDA in the post-marketing requirement for ACZONE 7.5%.

5.2 Changes in the Conduct of the Study or Planned Analyses

5.2.1 Changes in the Conduct of the Study

Not applicable.

5.2.2 Changes to Analyses Prior to Database Lock

Not applicable.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment days are defined as follows:

Table 6-1 Analysis Day Definitions

Term	Description

Treatment Day	Relative to treatment start date
	If analysis date ≥ treatment start date:
	• Day = analysis date – treatment start date + 1
	  o Day 1 = treatment start date
	If analysis date < treatment start date:
	• Day = analysis date – treatment start date
	  o Day -1 = day before treatment start date
	  o There is no Day 0

6.2 Analysis Visit Windows

Unless otherwise specified, if there are multiple valid measurements within the same analysis window, the one closest to the target day of the visit will be used. If multiple valid scores are equidistant from the target day of the visit, the latter observation will be used to represent the analysis window. All assessments will be included in respective listings.

6.2.1 Efficacy

The analysis visit windows for efficacy endpoints are defined as follows:

Table 6-2 Efficacy Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Target/Study Visit (eCRF)	Window
Pretreatment	Baseline	Day 1/Visit 2	Treatment Day ≤ 1, pre-dose
Treatment	Week 1	Day 8/Visit 3	Treatment Day [6, 11]
	Week 2	Day 15/Visit 4	Treatment Day [12, 21]
	Week 4	Day 29/Visit 5	Treatment Day [22, 42]
	Week 8	Day 57/Visit 6	Treatment Day [43, 70]
	Week 12	Day 85/Visit 7	Treatment Day [71, last dose + 14 days]

6.2.2 Safety

The analysis visit windows for safety endpoints are defined as follows (note that not all safety endpoints are collected at each visit):

Table 6-3 Safety Analysis Visit Definitions

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Window
Pretreatment	Baseline	Day 1/Visit 2	Treatment Day ≤ 1

Analysis Phase	Analysis Visit (Derived)	Study Visit (eCRF)	Window
Treatment	Week 1	Day 8/Visit 3	Treatment Day [6, 11]
	Week 2	Day 15/Visit 4	Treatment Day [12, 21]
	Week 4	Day 29/Visit 5	Treatment Day [22, 42]
	Week 8	Day 57/Visit 6	Treatment Day [43, 70]
	Week 12	Day 85/Visit 7	Treatment Day [71, last dose + 14 days]

Local dermal tolerability data will be collected both pre-dose and post-dose at day 1 (visit 2)

6.3 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6-4 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[1]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	Yes

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6-5 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

YYYY = available start date year; MM = available start date month; LD = last day of the month.

6.3.1 Missing/Incomplete AE Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

6.3.2 Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

6.3.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment end date + 28
- Death date

6.4 Safety Endpoint Conventions

6.4.1 Adverse Events

6.4.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6-6 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Screening Period, Pretreatment Period
	Severe	Treatment Period
Relationship	—	Screening Period, Pretreatment Period
	Related	Treatment Period

6.4.2 Vital Signs

6.4.2.1 Continuous Descriptives Parameters

The following vital sign parameters will be summarized:

Table 6-7 Vital Sign Descriptive Parameters

Parameters		
Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)
Respiratory Rate (bpm)	Body temperature (°C)	Weight (kg)
Height (cm)		

6.4.3 Local Dermal Tolerability

The following local dermal tolerability parameters will be summarized:

Table 6-8 Local Dermal Tolerability Parameters

Parameter	Grade
Stinging/burning	Prickling pain sensation immediately after (within 5 minutes of dosing, except baseline; patient-rated): • None (0) = No stinging/burning • Mild (1) = Slight warm, tingling/stinging sensation; not really bothersome • Moderate (2) = Definite warm, tingling/stinging sensation that is somewhat bothersome • Severe (3) = Hot, tingling/stinging sensation that has caused definite discomfort
Dryness	Brittle and/or tight sensation (investigator- or designee rated): • None (0) = No dryness • Mild (1) = Slight but definite roughness • Moderate (2) = Moderate roughness • Severe (3) = Marked roughness
Scaling	Abnormal shedding of the stratum corneum (investigator- or designee rated): • 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	Abnormal redness of the skin (investigator- or designee rated): • None (0) = No erythema • Mild (1) = Slight pinkness present • Moderate (2) = Definite redness, easily recognized • Severe (3) = Intense redness

6.5 Imputed Value Listing Conventions

Missing data will not be imputed and listings will present the actual partial or missing values as they appear on the eCRFs.

7. References

No references are cited in this document.

8. Amendment(s)

The following changes have been made and comprise Amendment 1 of this document:

Changes:

- Section 5.1.1.1.1: The PK analysis population has been removed as this will be defined and discussed in a separate PK analysis plan.
- Section 6.4.2.1: Weight (kg) and height (cm) have been added as vital signs parameters to be analyzed. As this is a pediatric study, it is important to review these parameters and any changes from baseline to Week 12.
- Throughout the document, undefined link errors have been corrected.

ALLERGAN

16.1.9 Analysis Plan Prior to Database Lock 1679-401-006

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
10-May-2018 12:56 GMT-07	PPD	PPD Approval
10-May-2018 14:54 GMT-07	PPD	PPD Approval
10-May-2018 15:47 GMT-07	PPD	PPD Approval
10-May-2018 16:00 GMT-07	PPD	PPD Approval

NON-CLINICAL AND TRANSLATIONAL SCIENCES

CLINICAL PHARMACOLOGY

A Pharmacokinetic Data Analysis Plan (DAP) for Study 1679-401-006 Entitled "An Open-Label Phase 4 Safety and Efficacy Trial of ACZONE (Dapsone) Gel, 7.5% in 9 to 11 Year-Old Patients With Acne Vulgaris"

Document Number	1679-401-006 -DAP
Project Name and Number:	ACZONE (Dapsone, AGN-225678) Gel, 7.5% / 1679
Protocol Number:	1679-401-006
Phase:	4
Clinic Start Date:	October 27, 2016
Study Clinical Pharmacologist:	PPD
Sponsor:	Allergan plc

1 Table of Contents

2 List of Abbreviations

ADaM	Analysis Data Model
BLQ	Below Limit of Quantitation
CRF	Case Report Form
CSR	Clinical Study Report
DAP	Data Analysis Plan
DHA	Dapsone Hydroxylamine
NAD	N-acetyl Dapsone
PD	Pharmacodynamic
PK	Pharmacokinetic
SDTM	Study Data Tabulation Model
sFTP	secure File Transfer Protocol

3 Introduction

The data analyses outlined in this document are to support clinical study 1679-401-006.

In this study, measurements will be made for plasma concentrations of dapsone, N-acetyl dapsone (NAD), and dapsone hydroxylamine (DHA). This data analysis plan (DAP) outlines how data analysis of these measurements will be conducted. Additional analyses may be conducted if necessary.

4 Objectives

The objectives of this study are:

- To evaluate the safety and tolerability of ACZONE 7.5% administered topically once-daily for 12 weeks in 9 to 11 year-olds with acne vulgaris.
- To evaluate the peak and trough plasma drug concentrations in 9 to 11 year-olds with acne vulgaris following once-daily dosing of ACZONE 7.5% under maximal use conditions for the first 8 days (+ 2 days).
- To explore the efficacy of ACZONE 7.5% administered topically once-daily in 9 to 11 year-olds with acne vulgaris.

5 Methods

5.1 Study Design

This study is a multicenter, open label, non-comparative, 12-week trial to evaluate the safety, tolerability, pharmacokinetics, and efficacy of ACZONE 7.5% in 9 to 11 year-old patients with mild, moderate, or severe acne vulgaris.

Patient participation is up to approximately 16 weeks. Patients will attend up to the following 7 visits: Screening, Baseline/Day 1 (Screening and Baseline/Day 1 may be combined if no washout is needed), and Weeks 1, 2, 4, 8, and 12/early exit. The total treatment duration of trial participation for each patient is up to 12 weeks. Safety measures include adverse events, physical examination, and vital signs. Efficacy measures include the Investigator's Global Assessment (IGA) and lesion counts in the face.

The 2 cohorts will enroll concurrently; the PK cohort and the non-PK Cohort.

The PK Cohort will include at least 16 evaluable PK patients. Evaluable PK patients are defined as those that are administered at least 8 applications of study drug under maximal use conditions, and have provided evaluable PK samples for analysis without any major protocol deviations. For the first 8 days, study drug will be administered once-daily under maximal use condition (~2 grams/day) to the entire face, neck, upper chest, upper back and shoulders as instructed by the study site. The study drug should be rubbed in gently and completely. On Day 1, the study drug will be administered on-site. From Day 2 through Day 7, the study drug will be administered in the morning at home by the patient's legally authorized representative. At the Week 1/Visit 3 [Day 8 (+2 days)], the study drug will be administered on-site in the morning. Also at the Week 1/Visit 3 visit, blood samples will be collected at 2 timepoints 1) prior to dosing, and 2) approximately 10 hours post dose (± 3 hours). This collection scheme is designed to minimize the number of blood draws in this challenging patient population while still being able to determine the peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted) for steady-state pharmacokinetic assessment. This limited blood collection scheme is appropriate as the systemic drug concentrations of dapsone at steady state were reached after 7 days and appeared to be relatively constant in male and female acne patients 11 years of age or older following once daily topical administration of Dapsone 7.5% Gel under maximal use conditions for 28 days (Study 225678-004). Similarly, steady-state systemic concentrations of dapsone metabolites were also relatively constant.

After the Week 1/Visit 3, patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face, once-daily, at home for the remaining 11 weeks, the same as the dose regimen for the Non-PK Cohort. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer during the final 11 weeks.

For the Non-PK Cohort (approximately 84 patients), patients or the patient's legally authorized representative will apply a pea-sized amount of study drug in a thin layer to the patient's face once-daily at home for 12 weeks as instructed by the study site. Acne-affected areas on the upper chest, upper back, and shoulders should also be treated with a thin layer.

Study Period	**Screening** [a]	**Baseline/Day 1**[a]	**Week 1**	**Week 2**	**Weeks 4 and 8**	**Week 12/ Early Exit**
Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5 and Visit 6**	**Visit 7**
Visit Windows	**Day -30 to Day -1**	**N/A**	**Day 8 (+ 2 days)**	**Day 15 (± 3 days)**	**Day 29 (± 7 days) and Day 57 (± 7 days)**	**Day 85 (± 7 days)**
Informed consent/authorization and minor assent[b]	X					
Inclusion/exclusion criteria	X	X				
Medical/surgical history	X					
Demographics	X					
Skin phototype assessment	X					
Physical examination includes vital signs, height and weight[c]	X					X
Pregnancy test (urine)[d]	X	X			X	X
IGA	X	X	X	X	X	X
Lesion count	X	X	X	X	X	X
Enrollment		X				
PK Cohort: Dispense study drug, training on application/return[e]		D	R/D		R/D	R
Non-PK Cohort: Dispense study drug, training on application/return[f]		D			R/D	R
Standardized photographs[g]		X				X
Local tolerability[h]		X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Concomitant procedures	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
PK sampling[i]			X			

D = dispense; IGA = Investigator's Global Assessment; N/A = not applicable; R = return; PK= pharmacokinetic

[a] If a washout period is not required, then screening and baseline visits can occur on the same day, and the procedures required to be repeated at both visits should be performed once.

[b] Consent for photography is included in the informed consent process at select centers.

[c] Physical examination and vital signs are to be performed if inclusion/exclusion criteria are met at screening; not required for screen failures. Vital signs include heart rate, blood pressure, respiratory rate, and body temperature.

[d] Female patients only. The urine pregnancy test can also be performed at any timepoint during the course of the trial at the investigator's discretion. If a patient misses a menstrual cycle, a urine pregnancy test must be performed.

[e] Patients in the PK cohort will be dispensed 1 kit with 14 tubes on Baseline/Day 1 (Visit 2). All patients in the PK cohort will start dosing on Day 1 using the 2.0 gram tubes dispensed for individual application.PK Cohort patients will return used study drug at Week 1/Visit 3. At Week 1/Visit 3, Week 4 (Visit 5) and Week 8 (Visit 6) the patients in the PK Cohort are dispensed 60-gram pumps. Dispensed and returned study drug will be weighed at the study center.

[f] All patients will start dosing on day 1. The patients in the Non-PK Cohort are dispensed 60-gram pumps on Baseline/Day 1 (Visit 2), Week 4 (Visit 5) and Week 8 (Visit 6). Dispensed and returned study drug will be weighed at the study center.

[g] At select centers, patients may have photographs taken of their face for illustration or presentation purposes. Patients who consent to being photographed will be required to remove any make-up at least 20 minutes prior to having photographs taken.

[h] Local tolerability will be assessed prior to drug administration on day 1, as well as postdose on the face only.

[i] Only applies to patients in the PK Cohort at the Week 1/Visit 3. Blood samples will be collected within 30 minutes prior to dosing in clinic in the morning and at approximately 10 hours post dose (± 3 hour) (patients are allowed to leave and come back if needed) under maximal use conditions to determine the peak and trough plasma drug concentrations.

5.2 Analysis Populations

The following 3 analysis populations will be utilized:

1. The safety population includes all patients who are treated with at least one application of study drug.

2. The modified intent-to-treat (mITT) population includes all enrolled patients who have a baseline assessment and at least one post-baseline assessment.

3. The PK population will be defined as all patients who received applications of study drug for at least 8 days under maximal use conditions and have evaluable blood samples for PK analysis.

Safety analyses will be based on the safety population. Efficacy analyses will be based on the mITT population. PK analyses will be based on the PK population.

5.3 Sample Size Considerations

The FDA approval of ACZONE 7.5% included a post-marketing requirement (PMR 3017-1) to assess the product in patients 9 to 11 years of age, including pharmacokinetic (PK) evaluation in a subset of patients. The sample size for the trial was determined empirically, and is consistent with that requested by the FDA in the postmarketing requirement for ACZONE 7.5% (FDA Letter, 2016).

5.4 Software

Descriptive statistics of plasma concentrations will be calculated with the software program Phoenix® WinNonlin® (version 6.3 or newer)

5.5 Methodology of Measurements

5.5.1 Pharmacokinetic Methodology

For patients in the PK Cohort who will be dosed under maximal use conditions for the first 8 days, blood samples will be collected within 30 minutes prior to dosing (in the clinic in the morning) and at approximately 10 hours post dose (± 3 hours) at the Week 1/Visit 3 [Day 8 (+ 2 days)] to determine the peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted). Blood will be collected in 2 mL prechilled K3EDTA tubes, chilled for 20-30 minutes in an ice water bath and centrifuged within 30

minutes of blood draw at no less than 2000g for 10 minutes. For sites with a refrigerated centrifuge, centrifugation will occur at approximately 4°C; for sites without a refrigerated centrifuge, rotors or buckets will be chilled in a refrigerator overnight. After centrifugation, the plasma samples will be harvested and transferred into 2 prechilled, coded polypropylene tubes. The samples will then be flash-frozen in a dry ice and alcohol bath and stored at approximately –20°C until shipment to PPD. Details on PK collection, processing and storage can be found in the laboratory manual.

Plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted) will be determined using a validated liquid chromatography-tandem mass spectrometry method.

5.6 Data Handling and Storage

PPD will transfer the samples to PPD, which will determine plasma concentrations of dapsone, DHA, and NAD. A source data file from PPD will be transferred to Allergan Clinical Data Management group's server via secure File Transfer Protocol (sFTP). Allergan Data Management will use the data for reconciliation against case report form (CRF) data and general cleaning. Allergan Statistical Science and Programming and PPD will generate SDTM and ADaM PK datasets per SDTM and ADaM specifications. Allergan Statistical Science and Programming group will provide the ADaM PK dataset to Allergan Global Clinical Pharmacology group via a shared folder such as BOX.

Pharmacokinetic analysis and statistical analysis of pharmacokinetic data will be performed using Pharsight Phoenix WinNonlin (version 6.3 or newer), SAS® (version 9.3 or newer), or other appropriate software. Electronic data will be archived on a secure computer server.

Unless otherwise specified in subsequent sections, the general data handling include the following:

- All measured data will be used in analysis initially unless it may be excluded in accordance to regulatory guidances. Measured data not used and the reasons for its exclusion from the final analysis will be documented in the clinical study report (CSR).
- Nominal sample times will be used in the categorization of descriptive statistics.

- All postdose time points for which no sample is collected will be treated as missing. No value will be imputed for these missing values.

- Concentration data below the lower limit of quantitation (BLQ) will be defaulted to 0.00.

6 Data Analysis

6.1 Pharmacokinetics

No PK parameters will be calculated in the PK analysis of this study.

7 Statistical Analysis

7.1 Statistical Summarization

No formal inferential statistics will be performed with the PK data. Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, median, minimum) will be reported for peak and trough plasma concentrations of dapsone, NAD, DHA, and other metabolites or analytes (if warranted).

If warranted, graphical methods may be used to examine the relationships between systemic drug concentrations and the changes in lesion counts and safety parameters. Also, as appropriate, additional pharmacokinetic analysis by gender may be included in the final report.

8 Presentation of Final Results

All summarization will be done using Phoenix® WinNonlin® (version 6.3 or newer). Tabulations may be exported into Word 2010 (or newer) for formatting or exported to pdf.

9 References

FDA Letter 2016:
http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/207154Orig1s000ltr.pdf.

ALLERGAN

PK DAP 1679-401-006

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
29-Jan-2018 16:27 GMT-080	PPD	PPD Approval
30-Jan-2018 10:08 GMT-080	PPD	PPD Approval