

A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group
Study to Compare Padagis Israel Pharmaceuticals, Ltd.'s Roflumilast Cream 0.3%
to Arcutis Biotherapeutics, Inc's Zoryve™ (Roflumilast Cream 0.3%) and Both
Active Treatments to a Vehicle Control in the Treatment of Plaque Psoriasis

Protocol No.: PAD-NY-22-05

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STATISTICAL ANALYSIS PLAN

PAD-NY-22-05: Roflumilast Cream 0.3%



A Multi-Center, Double-Blind, Randomized, Vehicle-Controlled, Parallel-Group Study to Compare Padagis Israel Pharmaceuticals, Ltd.'s Roflumilast Cream 0.3% to Arcutis Biotherapeutics, Inc's Zoryve™ (Roflumilast Cream 0.3%) Cream and Both Active Treatments to a Vehicle Control in the Treatment of Plaque Psoriasis

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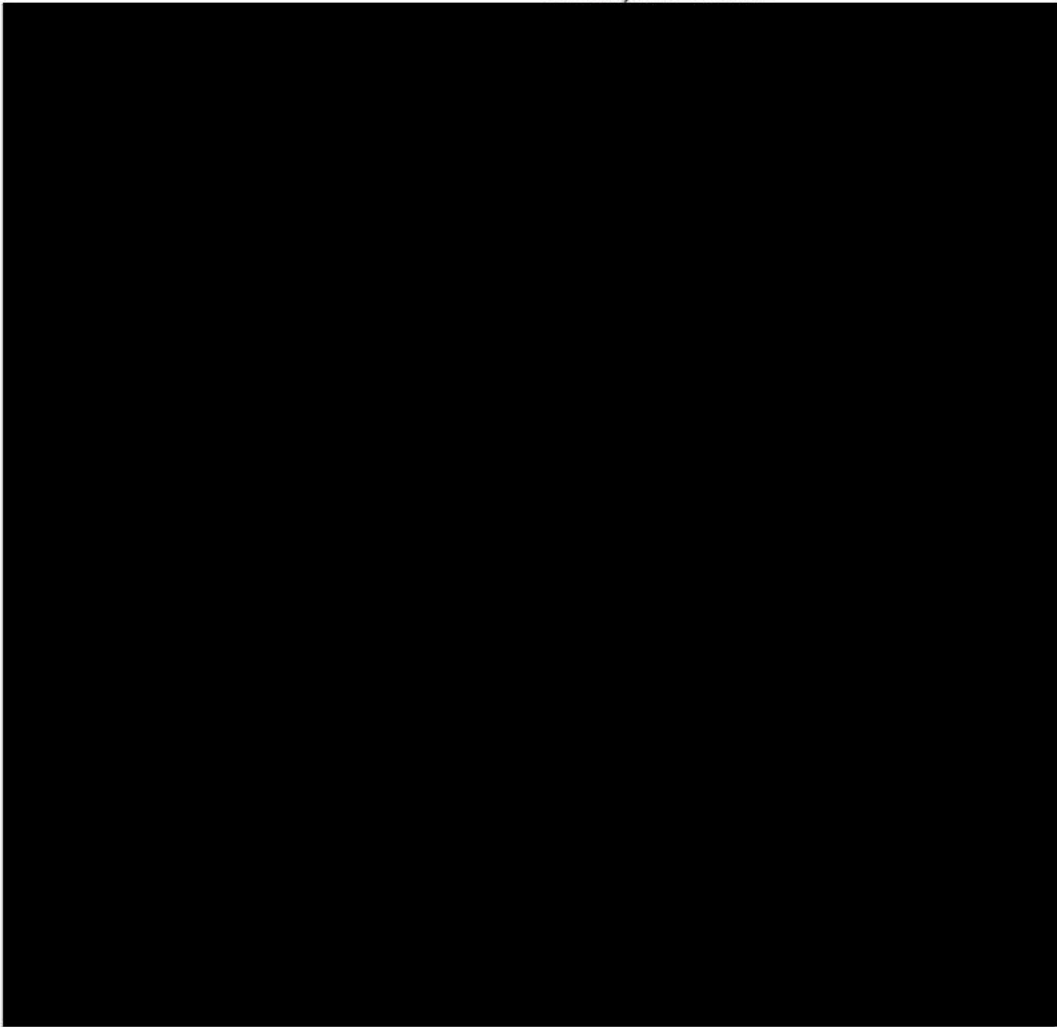


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List of Abbreviations

AE	Adverse Event
BSA	Body Surface Area
CI	Confidence Interval
IGA	Investigator's Global Assessment
ITT	Intent-to-Treat (Population)
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mantel–Haenszel Test
mITT	Modified Intent-to-Treat (Population)
PASI	Psoriasis Area Severity Index
PD	Protocol Deviation
PP	Per-Protocol (Population)
PV	Protocol Violation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
WHO Drug	World Health Organization Drug Dictionary

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol PAD-NY-22-05 [REDACTED]

In the event the protocol is further amended and that amendment has no impact on the statistical analysis methodology, this SAP will not require an amendment.

This SAP has been developed and finalized prior to database lock of the clinical database for Protocol PAD-NY-22-05.

2 Study Objectives

To compare the safety and efficacy of Padagis's Roflumilast Cream 0.3% to Arcutis Biotherapeutics, Inc's Zoryve™ (Roflumilast Cream 0.3%) Cream and demonstrate the superior efficacy of the two active treatments to a vehicle in the treatment of plaque psoriasis.

3 Study Design and Sample Size

3.1 Study Design

To exploring the above objectives, the study will be conducted as a double-blind, randomized, parallel-group, vehicle-controlled, multicenter trial.

Each subject will be randomly assigned to one of the following treatment groups [REDACTED]:

(1) Test: Roflumilast Cream 0.3%, Padagis [REDACTED]
[REDACTED]

(2) Reference: Zoryve™ Cream 0.3%, Arcutis Biotherapeutics, Inc., [REDACTED]
[REDACTED]

(3) Vehicle of test product, Padagis [REDACTED]
[REDACTED]

Subjects will be admitted into the study only after written informed consent has been obtained and all of the inclusion and none of the exclusion criteria have been met. Male and female subjects, 12 to 75 years of age, inclusive, with moderate plaque psoriasis (score of 3) on the Investigator's Global Assessment (IGA), BSA between 2%-20%, and moderate (score of 3) for plaque elevation at the Target (most severe) Lesion will be eligible for enrollment. Randomization will be performed according to a computer-generated randomization scheme where the treatment group designation has been assigned to the subject number. The treatment designation will remain blinded until the final database is closed. An independent third party will hold the randomization code throughout the study. Randomized subjects will apply [REDACTED] study medication to the designated treatment area and rub the cream completely on the skin until the cream is no longer visible once daily for 56 days.

Subjects will come to the study site for clinical evaluations Visit 1/Day 1 (Baseline), Visit 2/Week 4/Day 28 (± 4 days) (Interim) and Visit 3/Week 8/Day 56 (± 4 days) (End of Treatment/Early Termination).

Safety will be assessed by monitoring adverse events at each visit and at the Week 2/Day 14 (± 4 days) Telephone Contact.

3.2 Sample Size

Approximately [REDACTED] subjects will be randomized in ratio [REDACTED] to obtain [REDACTED] Modified Intent-to-Treat (mITT) subjects and [REDACTED] Per-Protocol (PP) subjects.

[REDACTED]

[REDACTED]

4 Analysis Populations

The analysis populations are defined as follows:

- (1) Intent-to-Treat (ITT) population: any subject who was randomized, received at least one application of study medication.
 - (2) Modified Intent-to-Treat (mITT) population: any subject, who met the inclusion/exclusion criteria, was randomized, received at least one application of study medication, and returned for at least one post-baseline efficacy assessment.
 - (3) Per Protocol (PP) population: any subject who (a) met all inclusion/exclusion criteria; (b) was randomized, received and used study medication; (c) met the protocol criteria for compliance (treatment application compliance [REDACTED]
[REDACTED] (d) completed Visit 3/Week 8/Day 56 (End of Treatment/Early Termination Visit) efficacy evaluations within the designated window (± 4 days) OR was discontinued from the study due to treatment failure, and (e) had no protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.
- [REDACTED]
- [REDACTED]

5 Planned Analyses

5.1 Methodological Considerations

The study will be conducted under the same protocol across all the sites. No formal statistical analyses are planned to evaluate the consistency of efficacy results across the multiple clinical sites. These results, however, will be tabulated and if a site's efficacy data are obviously inconsistent with the results across all sites, this will be explored and addressed in the final study report.

All randomized subjects who received study medication will be evaluated for safety using ITT population. The efficacy analysis will be conducted on both the PP and mITT populations.

Tables will have columns corresponding to or be stratified by the treatment groups.

All data will be listed by treatment group, subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of non-missing values, mean, standard deviation, minimum, median and maximum. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

Categorical variables will be summarized by frequency (n) and percentage (%). Percentage will be obtained as $(n/N) \times 100$. Unless otherwise stated, all percentages will be expressed to one decimal place.

Study days will be calculated as follows:

- For events or findings on or after the date of the first study treatment:
 - o Study Day = Date of the event or finding – Date of the first treatment + 1
- For events or findings prior to the date of the first study treatment:
 - o Study Day = Date of the event or finding – Date of the first treatment
- All dates will be displayed in DDMMYYYY format.

Two-sided hypothesis testing will be conducted for all the tests. P-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned.

All statistical analysis will be conducted using SAS® version 9.4 or later (SAS® Institute, Cary, North Carolina).



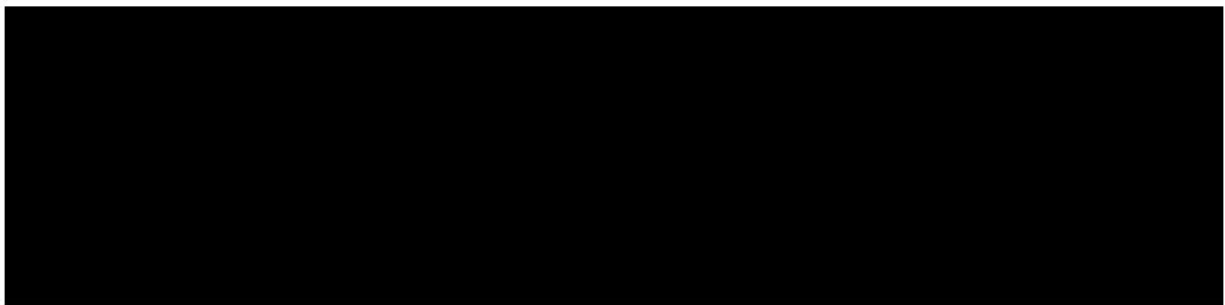
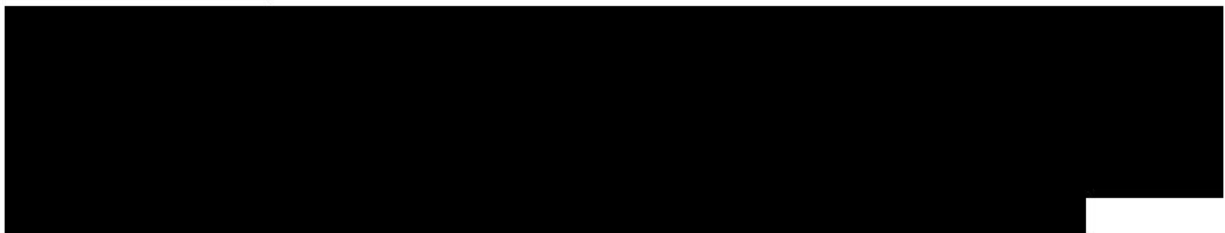
5.3 Demographics and Baseline Characteristics

Baseline variables (e.g., sex, age, ethnic origin) will be summarized descriptively by treatment group.

5.4 Subject Disposition

The numbers of subjects enrolled, treated, discontinued from treatment (by reason) will be presented by treatment group.

A summary of subject disposition will be provided for all subjects. Descriptive summaries of subject disposition, reason for discontinuation, and analyses population will be provided by treatment group. The data will also be presented in subject data listings.



5.6 Study Drug Exposure and Compliance

Duration of Treatment and Medication Compliance

Number of applications, days of exposure (i.e. duration of treatment), and compliance rate will be summarized by treatment group using descriptive statistics

5.7 Efficacy Variables and Analyses

5.7.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects who achieve Treatment Success, which is defined as Investigator's Global Assessment (IGA) score of None (0) or Minimal (1) with a 2-grade improvement from Baseline/Visit 1 /Day 1 at Visit 3/Week 8/Day 56.

[REDACTED]

[REDACTED] The Test product will be considered therapeutically equivalent to the Reference product if the 90% confidence interval (CI) of the difference in their proportions of subjects with treatment success, calculated by Wald's method with Yates' continuity correction, is contained within the limits -0.20 to +0.20. Rejection of the null hypothesis supports the conclusion of therapeutic equivalence between the Test and Reference products for the primary efficacy variable.

The result of the equivalence analysis in the PP population will be considered definitive and those in the mITT population will be considered supportive.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] The tests will be conducted independently for the Test product vs. Vehicle and the Reference product vs. Vehicle using two-sided, $\alpha = 0.05$, Mantel-Haenszel test. Superiority will be established if the proportion of subjects with treatment success at the Visit 3/Day 56 in the active treatment group is significantly greater ($p < 0.05$) than that in the Vehicle group. Rejection of the null hypothesis supports the conclusion of superiority of the Test and Reference products over the Vehicle for the primary efficacy variable.

Results of superiority analyses in the mITT population will be considered definitive and those in the PP population will be considered supportive.

5.8 Safety Variables and Analyses

All safety data will be listed and tabulated. The analysis will be performed on the safety/ITT population. Safety parameters include adverse events and application site reactions.

Adverse Events

Adverse events (AEs) will be coded in MedDRA, version 25.1. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurs on or after application of the first dose of study drug. Number and percent of subjects reporting TEAEs will be tabulated by treatment group. Summary of TEAEs will be presented by body system and preferred term for the ITT population, and further by severity and relationship to study medication. Most common TEAEs will include those reported by 5% or more subjects for any treatment group. Number and percent of subjects with most common events will be summarized by preferred term. In the summaries of incidence rates (frequencies and percentages), severity and relationship to study drug, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly. The difference between Test and Reference treatments with regard to severity and relationship to study drug will be statistically evaluated using Chi-Square or Fisher's exact test to compare the proportions of subjects of the two active treatment groups who report any TEAE.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TEAEs, TESAEs and TEAEs that led to study medication interruption temporarily or discontinued permanently will be presented in data listings.

Concomitant Medications and Vital Signs

Concomitant medications will be coded using the WHO Drug Dictionary, version September 2022, and will be presented in data listings. All vital signs data will be displayed in listings.

Application Site Reaction Assessments

The severity of application site reactions (dryness, scaling/peeling, burning/stinging, erosion, edema, pain, and itching) will be summarized by treatment group and visit using frequencies and percentages of subjects.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose
- the day and month are missing and the start year is the same or greater than the year of the first dose date
- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose
- the day and month are missing and the stop year is the same or greater than the year of the first dose date
- the stop date is completely missing or the medication is ongoing

6.2 Summary of Assessments

The schedule of visits and procedures to be conducted at each visit are summarized in the Schedule of Study Procedures.
