

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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[REDACTED]

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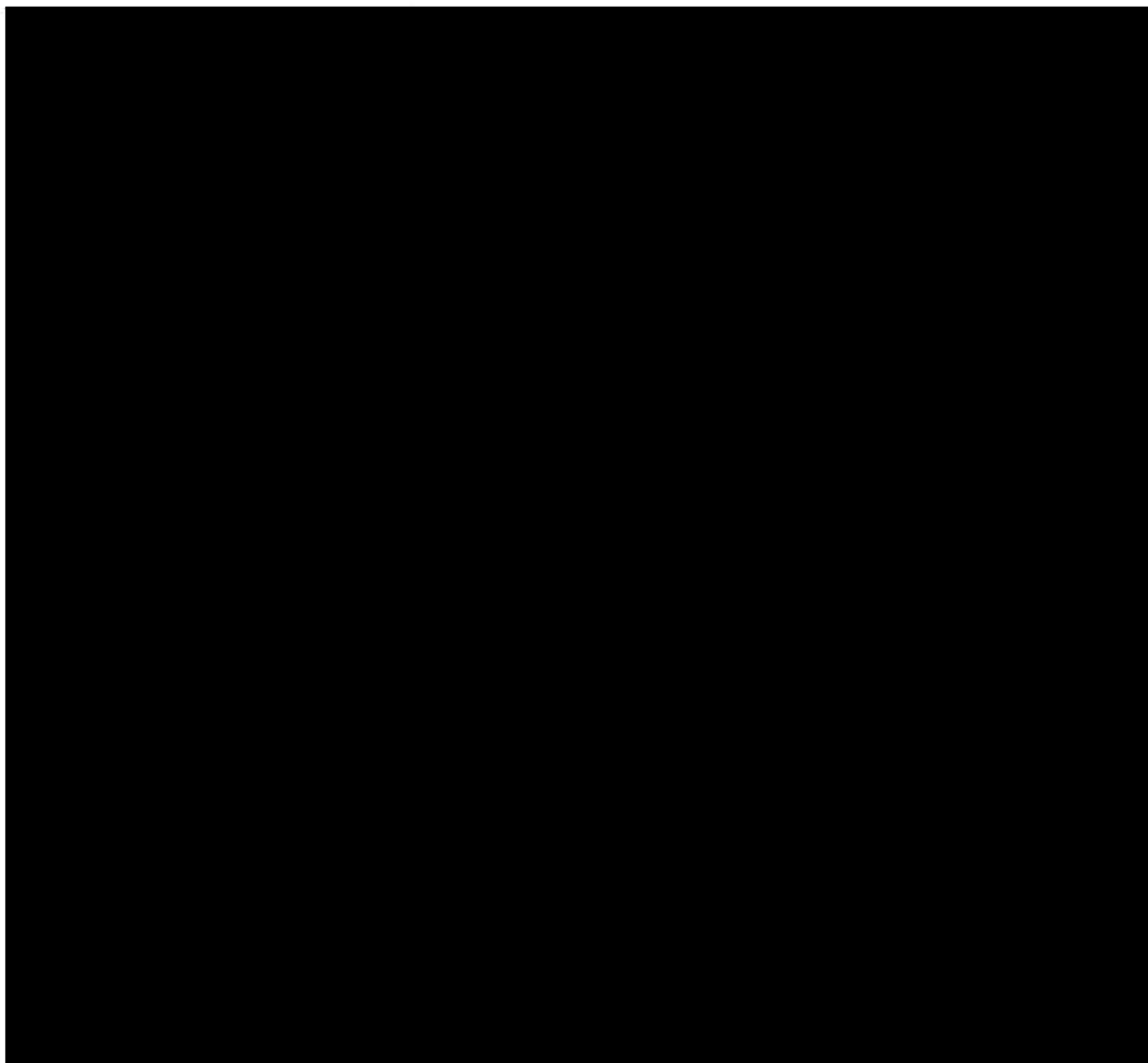
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**PROTOCOL SIGNATURE PAGE**

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[REDACTED]  
[REDACTED] [REDACTED]  
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**STUDY SYNOPSIS**

|                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title:</b>             | 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                                                                                                                            |
| <b>Treatment Period:</b>  | 8 weeks (56 days)                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Study Medications:</b> | <p><b>Test Product:</b><br/>Roflumilast Cream 0.3%<br/>[REDACTED]</p> <p><b>Reference Product:</b><br/>Zoryve™ Cream 0.3%<br/>[REDACTED]</p> <p><b>Vehicle:</b><br/>Vehicle of test product<br/>[REDACTED]</p>                                                                                                                                                                                                                                       |
| <b>Study Objectives:</b>  | To compare the safety and efficacy of Padagis's Roflumilast Cream 0.3% to Arcutis Biotherapeutics, Inc Zoryve™ (Roflumilast) 0.3% Cream and demonstrate the superior efficacy of the two active treatments to a vehicle in the treatment of plaque psoriasis.                                                                                                                                                                                        |
| <b>Study Design:</b>      | Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be admitted into the study only after written informed consent has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects, 12 to 75 years of age, inclusive, with [REDACTED] plaque psoriasis [REDACTED] on the Investigator's Global Assessment (IGA), [REDACTED] will be eligible for enrollment. |
| <b>Study Population:</b>  | Approximately [REDACTED] healthy males and females, 12 to 75 years of age, inclusive, who meet the inclusion/exclusion criteria, will be enrolled in order to obtain approximately [REDACTED] subjects in mITT population and approximately [REDACTED] subjects in the per-protocol (PP) population.                                                                                                                                                 |

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dosing:</b>       | Subjects will be randomized in a [REDACTED] ratio to either the test product, reference product or vehicle treatment group, respectively, and will apply the cream topically once daily at approximately the same time each day [REDACTED] to the designated treatment areas for 56 days. [REDACTED].                                                                                                                                        |
| <b>Study Visits:</b> | <p>Clinical Evaluations will be performed at:</p> <ol style="list-style-type: none"> <li>1. Visit 1/Day 1 (Baseline)</li> <li>2. Visit 2/Week 4/Day 28 (<math>\pm 4</math> days)(Interim)</li> <li>3. Visit 3/Week 8/Day 56 (<math>\pm 4</math> days)(End of Treatment/End Study)</li> </ol> <p>Safety will be assessed by monitoring adverse events at each visit and at the Week 2/Day 14 (<math>\pm 4</math> days) Telephone Contact.</p> |
| <b>Evaluations:</b>  | <p>The following assessments will be evaluated by the same qualified investigator at each applicable visit to the greatest extent possible.</p> <ol style="list-style-type: none"> <li>1. [REDACTED]</li> <li>2. Investigator's Global Assessment (IGA)</li> <li>3. [REDACTED]</li> </ol> <p>[REDACTED]</p>                                                                                                                                  |
| <b>Endpoints:</b>    | <p>The primary efficacy endpoint will be the Investigator's Global Assessment (IGA) and is based upon the proportion of subjects at Visit 3/Week 8/Day 56 who achieve Treatment Success, which is defined as an IGA score of None (0) or Minimal (1) with a 2-grade improvement from Baseline/Visit 1/ Day 1.</p> <p>[REDACTED]</p>                                                                                                          |
| <b>Safety</b>        | <p>The incidence of all adverse events reported during the study will be summarized by treatment group, nature, severity, and frequency. [REDACTED]</p> <p>[REDACTED]</p> <p>A pregnancy test for females of childbearing potential will be performed at Visit 1/Week 1/Day 1 and Visit 3/Week 8/Day 56 (End of Study or Early Termination).</p>                                                                                             |

## 1 BACKGROUND

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 2 STUDY OBJECTIVES

The objectives of this study are to compare the safety and efficacy of Padagis Israel Pharmaceuticals, Ltd.'s Roflumilast Cream 0.3% to Arcutis Biotherapeutics, Inc Zoryve™ (Roflumilast) 0.3% Cream and demonstrate the superior efficacy of the two active treatments to a vehicle in the treatment of plaque psoriasis.

### 2.1 Endpoints

The primary efficacy endpoint is the Investigator's Global Assessment (IGA) and is based on the proportion of subjects at Visit 3/Week 8/Day 56 who achieve Treatment Success, which is defined

[REDACTED]

as an IGA score of None (0) or Minimal (1) with a 2-grade improvement from Baseline/Visit 1 /Day 1.

## 2.2 Safety

Safety of the test and reference products will be compared by evaluating the nature, severity, and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, the relationship to study medication, and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. The Pearson's Chi-Square or Fisher's Exact test, whichever is more appropriate, will be used to compare the proportion of subjects in each treatment group who report any adverse event. Additionally, adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively and the overall summary of AEs.

## 3 STUDY DESIGN

### 3.1 Type/Design of Study

Subjects in this multi-center, double-blind, randomized, vehicle-controlled, parallel-group study will be assigned [REDACTED] to Test Product, Reference Product, or Vehicle, respectively. The assigned study medication will be applied topically to the designated treatment areas once daily for 56 days (8 weeks). Subjects will consist of males and females, 12 to 75 years of age, inclusive, with [REDACTED] plaque psoriasis [REDACTED] on the IGA [REDACTED]. Visits to the study site are scheduled at Visit 1/Day 1, Visit 2/Week 4/Day 28, and Visit 3/Week 8/Day 56.

### 3.2 Study Population

Male or female subjects, 12 to 75 years of age, inclusive, clinically diagnosed with at least [REDACTED] plaque psoriasis [REDACTED] on the IGA [REDACTED].

## 4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

#### 4.1 Inclusion Criteria

Subjects **must** meet all the following criteria:

1. Subjects must be willing and able to understand and comply with the requirements of the study, sign an informed consent/assent, apply the study medication as instructed, return for the required treatment period visits, comply with therapy prohibitions, and be able to complete the study. Subjects under the legal age of consent in certain states (e.g., Nebraska, Alabama, Mississippi and Kansas) must sign an IRB approved written informed consent/assent in addition to a parent or legally authorized representative
2. Subjects must be male or female, 12 to 75 years of age, inclusive.
3. [REDACTED]
4. Subjects must have a definite clinical diagnosis of stable [REDACTED] symptomatic plaque psoriasis, [REDACTED]
5. [REDACTED]
7. [REDACTED]
8. Subjects must be willing and able to understand and comply with the requirements of the study, apply the medication as instructed, refrain from use of all other excluded medications and treatments during the 8-week treatment period, return for the required treatment period visits, comply with therapy prohibitions, and are able to complete the study.

a. [REDACTED]

|            |            |
|------------|------------|
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] |

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|  |  |  |  |

9. Subjects must be in general good health and free from any clinically significant disease (unstable hypertension, unstable diabetes, renal failure, liver disease, any unstable neurological, pulmonary, gastrointestinal, hematological diseases, morbid obesity, etc.), other than plaque psoriasis, that might interfere with the study evaluations.

10. [REDACTED]

#### 4.2 Exclusion Criteria

Subjects may **not** be selected if any of the following criteria exist:

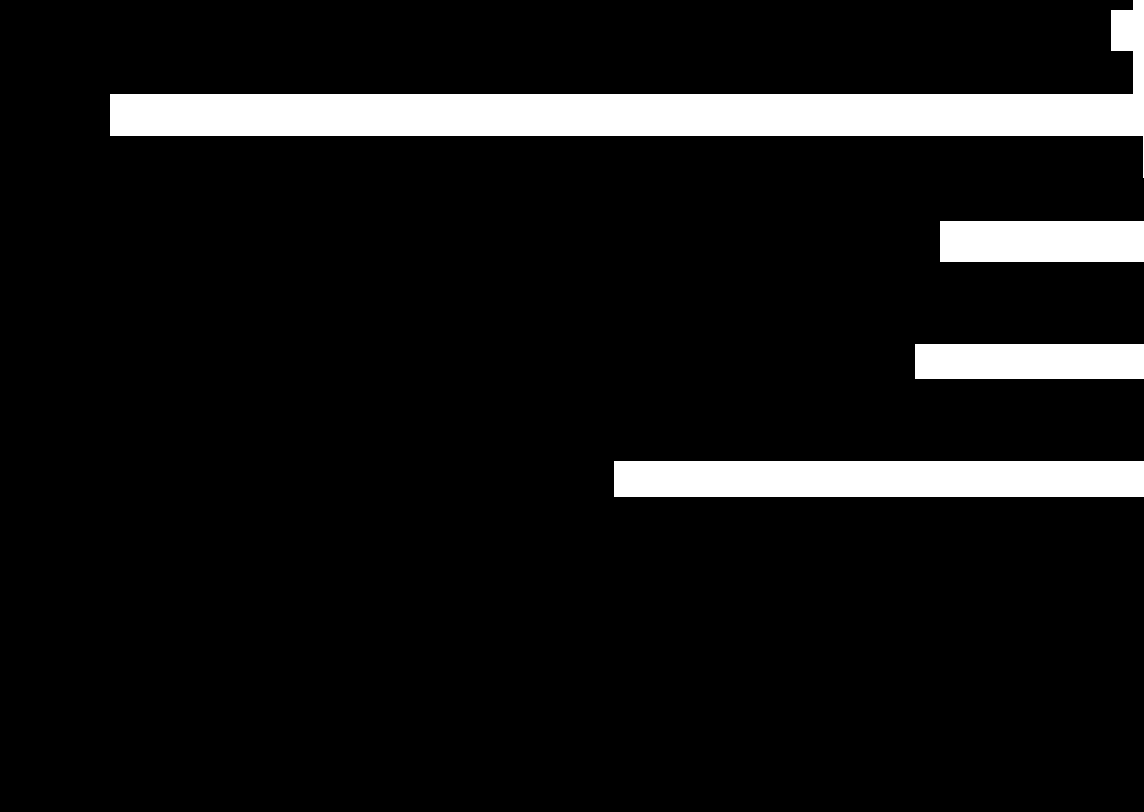
1. Subjects who are pregnant, nursing, or planning a pregnancy within the study participation period.
2. Childbearing female subjects who are not willing to use an adequate form of contraception during the study.
3. Subjects who cannot discontinue medications and treatments prior to Baseline/Visit 1/Day 1 visit and cannot refrain from using any prohibited medications during the study as described in section 4.3 Prohibited Medications.

4. [REDACTED]

6.

18. Subjects with any condition on the treatment area (e.g., other inflammatory skin disease such as atopic dermatitis, contact dermatitis, eczema, tinea corporis etc. or have presence of pigmentation, extensive scarring, pigmented lesions, or sunburn) which, in the opinion of the Investigator, could confound efficacy measurements.

19.



30. Subject consumes excessive alcohol, abuses drugs, or has a condition that could compromise the subject's ability to comply with study requirements.
31. Participation in any clinical study involving an investigational product or device in the 30 days prior to Baseline/Visit 1/Day 1 or throughout the study.
32. Previous enrollment in this study, current enrollment in this study at another participating site or current enrollment in another study (in parallel to this study) at another clinical research site.

\_\_\_\_\_

34. Subjects who in the opinion of the investigator, are unlikely to be able to follow the restrictions of the protocol and complete the study.

\_\_\_\_\_

### 4.3 Prohibited Medications

The following medications/procedures are prohibited during this study:

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\_\_\_\_\_

\_\_\_\_\_

[illegible]

[REDACTED]

#### 4.4 Precautions

The following precautions should be taken during study participation:

1. Subjects should avoid contact of the study medication with eyes, mouth, and other mucous membranes. In case of accidental exposure, the eyes should be rinsed with plenty of water.
2. Subjects should wash hands before and immediately after applying the study medication.
3. The study medication should be gently rubbed-in on the treatment areas of the body; excessive rubbing must be avoided.
4. The product should not be applied more than once daily, and subjects should not use more than the recommended amount on the treatment areas.
5. The study medication should not be applied to cuts, abrasions, eczematous or sunburned skin, or areas other than the treatment area.

[REDACTED]

[REDACTED]

[REDACTED]

## 5 PROCEDURES

### 5.1 Subject Screening, Informed Consent and Enrollment

The study personnel will review the IRB approved informed consent form and assent form (if applicable), with each subject and give the subject an opportunity to have all questions answered before proceeding. The IRB approved informed consent/assent form must be signed by each subject before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every participant (or legally authorized representative) and the original will be maintained by the study staff with the participant's records. Subjects under the legal age of consent in certain states (e.g., Nebraska, Alabama, Mississippi) must sign an IRB approved written informed assent in addition to consent provided by a parent or legally authorized representative.

Subjects that require a wash-out of more than 30 days from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

## 5.2 Assignment of Subject Number

Once the subject has consented and met inclusion/exclusion criteria, a subject number will be assigned. [REDACTED]

## 5.3 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

## 5.4 Concomitant Medications

Concomitant medications and any medications taken [REDACTED] prior to signing informed consent/assent will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. Prescription, over-the-counter (OTC) medications, and dietary supplements used by the subject will be recorded, whether taken regularly or on an as needed basis (prn) including vitamins, aspirin, and acetaminophen. A record of medication taken by the subject during the study will be obtained at each study visit including the Week 2/Day 14 ( $\pm 4$  days) telephone contact.

## 5.5 Physical Examination

The investigator, sub-investigator or appropriately delegated and qualified/medically trained designee will perform a brief physical examination, prior to distribution and use of study medication at Baseline/Visit 1/Day 1. [REDACTED]

## 5.6 Vital Signs

The investigator, sub-investigator, or appropriately delegated and qualified/medically trained designee will collect vital signs at Baseline/Visit 1/Day 1. Blood pressure, temperature (oral or infrared), heart rate, and respiratory rate should be recorded in a sitting position and after 5 minutes of rest.

## 5.7 Urine Pregnancy Test

A urine pregnancy test will be conducted at Visit 1 (before the subjects applies the first dose of the study medication at the Investigator site) and at Visit 3. An investigator may repeat the

pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant.



#### 5.8 Dermatological Assessment (Diagnosis)

The Investigator or Sub-investigator will examine the subject to establish the presence of symptomatic, stable, plaque psoriasis, as defined in this protocol, on the IGA (see section 5.9), and for plaque elevation at the Target Lesion (see section 5.10.1).

#### 5.9 Investigator's Global Assessment (IGA)

To the greatest extent possible, the same investigator who made Baseline/Visit 1/Day 1 assessments will perform a Global Assessment of the subject's overall plaque psoriasis condition at each subsequent visit.

At Baseline/Visit 1/Day 1, the investigator should perform the IGA before the subject applies the first dose of the study medication at the site.



The following scale will be used for the Investigator's Global Assessment<sup>7, 8</sup>



| Score | Grade       | Description                                                                                                                                                                                   |
|-------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0     | None        | No plaque elevation above normal skin level; may have residual non-erythematous discoloration; no psoriatic scale, no erythema                                                                |
| 1     | Minimal     | Essentially flat with possible trace elevation faint erythema; no psoriatic scales                                                                                                            |
| 2     | Mild        | Slight but definite elevation of plaque above normal skin level; may have up to moderate erythema (red coloration); fine scales with some lesions partially covered                           |
| 3     | Moderate    | Moderate elevation with rounded or sloped edges to plaque; moderate erythema (red coloration); somewhat coarser scales with most lesions partially covered                                    |
| 4     | Severe      | Marked elevation with hard, sharp edges to plaque; up to severe erythema (very red coloration); coarse, thick scales with virtually all lesions covered and a rough surface                   |
| 5     | Very Severe | Very marked elevation with very hard, sharp edges to plaque; up to very severe erythema (extreme red coloration); very coarse, thick scales with all lesions covered and a very rough surface |

#### 5.10 Selection of Target Lesion



##### 5.10.1 Evaluation of Target Lesion



##### 5.10.2 Psoriasis Area Severity Index (PASI) of the Target Lesion<sup>7, 8</sup>



|   |  |  |  |  |
|---|--|--|--|--|
| I |  |  |  |  |
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#### 5.11 Application Site Reaction Assessment

\_\_\_\_\_

\_\_\_\_\_

[illegible]

[REDACTED]

\_\_\_\_\_

### **5.13 Study Medication Masking**

#### **5.13.1 Third-Party Dispenser**

In order to mask the treatments, the study medication tubes will be labeled with identical labels and packaged in identical study medication kits. The study medication should be dispensed and collected by a designated individual of the study staff by the Investigator who is not involved in any of the baseline and post baseline IGA and PASI evaluations. The third-party dispenser will not communicate a subject's suspected treatment assignment during any communications with the investigator.

### **5.14 Study Medication Use, Subject Instructions and Subject Diary**

An independent third-party dispenser who is not performing the clinical evaluations including assessment of AEs will dispense and collect study medication. An investigator performing the clinical evaluations will not dispense or collect study medication.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **5.15 Visit Specific Procedures**

The following sections outline the procedures required at each visit.

### **5.15.1 Baseline/Visit 1/Day 1**

Prospective subjects will visit the study center and be examined by the study Investigator or Sub-Investigator. If the subject is screened and not randomized to study drug on the same

[REDACTED]

day (e.g., due to require washout of a prohibited concomitant medication), the Visit 1/Day 1 procedures should be re-confirmed on the day the subject returns prior to being randomized to study medication.

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.15.2 Telephone Contact/Week 2/Day 14 ( $\pm 4$ days)

[REDACTED]

#### 5.15.3 Visit 2/Week 4/Day 28 ( $\pm 4$ days)

[REDACTED]

[REDACTED]

[REDACTED]

#### 5.15.4 Visit 3/Week 8/Day 56 ( $\pm 4$ days)End of Treatment/Early Termination Visit

[REDACTED]

#### 5.15.5 Unscheduled/Early Termination Visit

An unscheduled visit is allowed at any time if in the investigator's opinion it is warranted. If the investigator assesses the subject's condition and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as a treatment failure, an Early Termination Visit conducted, and a standard of care treatment may be advised at the investigator's discretion.

[REDACTED]

[REDACTED]



### 5.16 Schedule of Study Procedures

[illegible]

[REDACTED]

#### **5.17 Screen Failures**

Screen failures will not be entered in the database and included in any data analyses. A screen failure is a subject who received information about the study, including signing an informed consent/assent, and possibly performing some study related procedures, but was not enrolled, dispensed nor applied the investigational product.

#### **5.18 Protocol Deviations and Violations**

This study will be conducted as described in this protocol except for an emergency situation in which the protection, safety, and wellbeing of the subject requires immediate intervention, based on the judgment of the investigator or a responsible, appropriately trained and credentialed professional(s) designated by the investigator. In the event of a significant deviation from the protocol due to an emergency, accident or mistake, the investigator or designee must contact Padagis/CRO contacts in Section 15 (Appendix A) at the earliest possible time.

[REDACTED]

[REDACTED]

#### **5.19 Subject/Treatment Compliance**

Subjects will apply the study medication once daily, at approximately the same time each day, for 56 days. At Visit 1/Day 1, third-party dispenser will be responsible for explaining to the

[REDACTED]

subject how to dose the medication and will observe the subject apply the first application. Compliance will be determined from the Subject Diary, in which the subject will be instructed to record all applications made or missed. The number of applications will be totaled by the study staff and recorded on the eCRF. [REDACTED]

[REDACTED] All used and unused tubes of study medication will be collected by the study site at appropriate visits or early termination. [REDACTED]

## 5.20 Discontinuation/Withdrawal of Study Subjects

Subjects may be removed from the study for any of the following reasons:

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

After a subject has been discontinued, he/she will not be allowed to re-enroll in the study at any facility.

The reasons for a subject being discontinued will be documented in the eCRFs and the enrollment log.

If a subject is discontinued from the study for any reason, the Visit 3 (Day 56)/End of Study Visit/Early Termination Visit procedures should be completed and any outstanding data and study medication should be collected. Data, in addition to the reason for discontinuation and the date of removal, will be recorded on the Source Document, enrollment log, and End of Study eCRF.

[REDACTED]

[REDACTED]

## 6 MATERIALS AND SUPPLIES

### 6.1 Study Medication

The study medication supplied by Padagis Israel Pharmaceuticals, Ltd. consist of:

**Test Product:**

Roflumilast Cream 0.3%

[REDACTED]

**Reference Product:**

Zoryve™ (Roflumilast Cream 0.3%)

[REDACTED]

**Vehicle:**

Vehicle of test product

[REDACTED]

### 6.2 Medication Management

#### 6.2.1 Labeling, Packaging and Distribution

The study medication assigned to each subject number is determined by a computer-generated randomization schedule. Study medication is labeled, and packaged, according to

[REDACTED]

the randomization code, so that neither the subject nor the investigator can identify the treatment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In order to nullify any differences in product packaging, an independent third-party dispenser who is not performing the clinical evaluations will dispense and collect study medication. The investigator or Sub-investigator performing the clinical evaluations will not dispense or collect study medication.

### 6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [REDACTED] study medication [REDACTED] from each shipment to be maintained as retain samples. The investigator will maintain one randomly selected block of study medication from each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel [REDACTED] [REDACTED]; [REDACTED] even after the study has concluded. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the

[REDACTED]

date of completion of the bioavailability study in which the sample from which the reserve sample was obtained or was used.” The investigator will store the retain sample study medication until such time as notification is received from Padagis that the samples are no longer required.

### 6.2.3 Storage and Test Article Accountability

Study medication used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. [REDACTED]

[REDACTED]. The medication should not be frozen and should be kept away from children and heat. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as Sub-investigators.

The clinic personnel at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each tube of study medication is dispensed and returned. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by, and used by each subject. At the conclusion of the study, all unused, partially used, and empty tubes must be inventoried by the monitor and returned to Padagis, or designee, for destruction with the exception of retention samples, which shall remain at the Investigator site.

### 6.2.4 Randomization

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. [REDACTED]

### 6.2.5 Procedure for Breaking the Blind

The investigator, staff at the study site, study monitors, and data analysis/management personnel are blinded to the subject assignment. In the event of an emergency, the specific subject treatment may be identified by removing the overlay of the blinded label, which is attached to the Study Medication Dispensation Log after dispensing; however, every effort should be made to maintain the blind. **The investigator must not scratch off the occluding layer of the label unless absolutely necessary to provide medical treatment to a subject in an emergency situation and must seek prior authorization from Padagis or designee when possible.** The reason for breaking the blind must be clearly documented in the source

documentation and eCRF and the subject discontinued from the study. Padagis must be notified immediately upon all unblinding situations.

## **7 ADVERSE REACTIONS**

The potential adverse reactions of generic roflumilast 0.3% cream are anticipated to be similar to those observed in Zoryve™ (Roflumilast) 0.3% Cream.

The following adverse reactions occurred in  $\geq 1\%$  of patients treated with Zoryve™ for 8 weeks in clinical studies include diarrhea, headache, insomnia, nausea, application site pain, upper respiratory tract infection and urinary tract infection.<sup>3</sup>

The most common adverse reaction reported in the clinical study that led to discontinuation was application site urticaria.<sup>3</sup>

If a reaction suggesting sensitivity or irritation occurs, the Investigator should assess the subject's condition as soon as possible (e.g., by scheduling an Unscheduled Visit, if required) and determine whether treatment should be discontinued. If the subject is discontinued from the study during an Unscheduled Visit, procedures from Visit 3 should be followed and the visit will be referred to as an Early Discontinuation Visit.

### **7.1 Departure from the Protocol for Individual Subjects**

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Padagis by telephone and follow up with a written description as soon as possible. The overseeing IRB should also be notified in accordance with the IRB's guidelines.

### **7.2 Definitions**

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) includes any event that results in any of the following outcomes:

- Death

- Life-threatening event (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death).
- Requires in-subject hospitalization or prolongs hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Other events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 7.3 Eliciting and Reporting of Adverse Events

[REDACTED]

[REDACTED]

[REDACTED]

### 7.4 Expedited Reporting Responsibilities of the Study Center

[REDACTED]

[REDACTED]

[REDACTED]

#### 7.5 Submitting an Expedited Safety Report to the IRB

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**7.6 Serious Adverse Events & Adverse Events Requiring Discontinuation of Study Drug, including Pregnancies**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 7.7 Pregnancy

At the time a Principal Investigator or Study Coordinator becomes aware that a study participant became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and by emailing a completed Pregnancy Report to [REDACTED] within one working day of being notified of the pregnancy.

The report will include the following elements:

- Participant coded study identifier;
- Date of participant's last menstrual period;
- Information regarding dose(s) of study treatment administered to date including dates of administration.

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or Study Coordinator must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus to [REDACTED], including:

- Participants coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;

[REDACTED]

- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by emailing a completed SAE report form to [REDACTED] within one working day of being notified of the pregnancy outcome.

If the trial is completed before the outcome of the pregnancy is known, [REDACTED] will assume the responsibility for following up on the pregnancy. [REDACTED] will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms and email to [REDACTED] within 1 day of being notified.

## **7.8 Post Study Adverse Events**

### **7.8.1 Non-serious Adverse Events (AE)**

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. These adverse events must be followed by the investigator until the events are resolved, events determined to be chronic, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event.

### **7.8.2 Serious Adverse Events (SAE)**

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF page and reported to Padagis according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Padagis up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Padagis.

## 8 Statistical Analysis

The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) will be prepared separately from this protocol. The SAP will be completed and approved before locking the database and unblinding the study and will serve as an additional document to the protocol to describe details of statistical analysis.

### Statistical Methods

#### 8.1 Analysis Populations

The following populations are defined for the purpose of analyses:

Intent-to-Treat (ITT): Any subject who was randomized, received at least one application of study medication.

Modified Intent-to-Treat (mITT):

[REDACTED]

Per Protocol (PP):

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 8.2 Planned Analysis

[REDACTED]

[REDACTED]

## 8.3 Sample Size Considerations

[REDACTED]

## 8.4 Efficacy Measures and Analysis

### 8.4.1 Endpoints

#### Primary Endpoint

The primary efficacy endpoints will be the Investigator's Global Assessment (IGA) and is based on the proportion of subjects who achieve Treatment Success, which is defined as an 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]

#### 8.4.2 Equivalent Efficacy

The Test treatment will be therapeutically equivalent to the Reference treatment if the 90% confidence interval on the difference in proportion of subjects with treatment success between the Test and Reference is contained within the interval of  $-20\%$  to  $+20\%$ . The confidence interval will be constructed using the Wald's method with Yates' continuity correction.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

#### 8.4.3 Superiority

The proportion of success for each active treatment will be compared to that of the Vehicle to determine if the active treatment has superior efficacy to that of the Vehicle Mantel-Haenszel Test

[REDACTED]

[REDACTED]

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

[REDACTED]

#### **8.4.4 Safety and Adverse Events Analysis**

The nature, severity and frequency of adverse events will be summarized for all three treatment groups. The comparable safety of the Test and Reference treatments will be evaluated by statistical comparisons of the severity and frequency of their adverse events. Safety comparisons will be performed only for the ITT population. The Pearson's Chi-Square or Fisher's Exact test, whichever is more appropriate, will be used to compare the proportion of subjects in each treatment group who report any adverse event. Additionally, adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively.

Safety analysis will be performed on the ITT population.

#### **8.5 Comparability of Subjects at Baseline**

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group will be discussed in the clinical study report.

#### **8.6 Consent Consideration and Procedures**

It will be made clear to the subject that, for the purposes of the study, they are consenting only for topical application of study medication or vehicle. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed/assent consent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Padagis, prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to Padagis.

The investigator(s) has both an ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent/assent form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent form shall include the elements required by FDA regulations in 21 CFR Part

50. The investigator agrees to obtain approval from Padagis of any written informed consent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legal authorized representative) and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from screening. In the event that the subject is re-screened for study participation, a new informed consent form must be signed.

## **8.7 Subject Confidentiality**

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Padagis, it is required that the investigator permit the study monitor, any Sponsor authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by Padagis or their authorized representative, a representative of [REDACTED] or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Padagis or their authorized representative and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the subject number. The investigator agrees to furnish Padagis with complete subject identification, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated

with strict adherence to professional standards of confidentiality and will be filed at Padagis under adequate security and restricted accessibility.

## **9 CONDUCT OF STUDY**

The investigational site is to maintain complete and accurate documentation of all events and the dates on which they occur.

### **9.1 Completion of Study**

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol, within 3 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

It is agreed that, for reasonable cause, either the investigator or Padagis may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and Padagis.

### **9.2 Protocol Amendments**

The Investigator will not make any changes to this protocol without prior written consent from Padagis and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed with [REDACTED] and Padagis. If agreement is reached regarding the need for an amendment, the amendment will be written by Padagis. The written amendment must then be submitted to the chairman of the IRB identified with this responsibility. Except for 'administrative amendments', investigators must await IRB/EB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. Padagis will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or Padagis, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent/assent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

9.3

[REDACTED]

9.4

[REDACTED]

[REDACTED]

9.5

[REDACTED]

[REDACTED]

#### 9.6 Regulatory and Study Oversight Considerations

Remote monitoring may be substituted for physical visits to the site(s) in the event that the CRA or Sites are not able to conduct an on-site visit due to site closure, local or federal guidelines, or safety guidelines in relation to COVID-19.

9.7

[REDACTED]

[REDACTED]

[REDACTED]

## 10 RECORDS MANAGEMENT

### 10.1 Data Collection

Database set-up will be performed by [REDACTED] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at [REDACTED] will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.

After all data have been verified by approved staff at [REDACTED], an Investigator or Sub-Investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will be provided with a password protected USB that will include the eCRF data from their site for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment code is broken.

During each subject's visit to the clinic, a clinician participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain:

- a) Documentation of the informed consent process;
- b) The date of the visit and the corresponding Visit or Week in the study schedule;
- c) General subject status remarks, including any *significant* medical findings. The severity, frequency, and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.
- d) Any changes in concomitant medications or dosages;
- e) A general reference to the procedures completed; and
- f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents, will be entered in **blue or black ink, initialed and dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to Padagis, information from the study progress notes and other source documents will be promptly entered into the database. The database also contains a complete audit trail to capture all regulatory components of data corrections (e.g., initial entry, new value, initials and date of the change.)

## 10.2 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent/assent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

## 10.3 File Management at the Study Site

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

## 10.4 Records Retention at the Study Site

FDA regulations 21 CFR§312.57 require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

- a) A period of at least two years following the date on which the New Drug Application is approved by the FDA;
- b) A period of two years after Padagis notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Padagis or (2) providing an opportunity for Padagis to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Padagis and Regulatory Authorities such as the FDA.

## **11 QUALITY CONTROL AND QUALITY ASSURANCE**

### **11.1 Monitoring**

Padagis has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs.

### **11.2 Auditing**

Padagis or representative may conduct audits at the study center(s). Audits will include, but are not limited to, drug supply, presence of required documents, the informed consent process, and comparison of case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Padagis immediately if notified of such an audit and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

## **12 ETHICS AND RESPONSIBILITY**

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, Health Protection Bureau (HPB) and with the ICH GCP Guidelines.

## **13 USE OF INFORMATION AND PUBLICATION**

All information supplied by Padagis in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (e.g., the clinical protocol, eCRFs ), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by Padagis in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential

information shall remain the sole property of Padagis and shall not be disclosed to any unauthorized person or use in any unauthorized manner without written consent of Padagis and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential and will be used by Padagis in connection with the development of the drug. The information may be disclosed as deemed necessary by Padagis to allow the use of the information derived from this clinical study, the investigator is obliged to provide Padagis with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Padagis. Should the investigator wish to publish or present the results of this study, the investigator agrees to provide Padagis with an abstract, manuscript, and/or presentation for review 60 days prior to submission for publication/presentation. Padagis retains the right to delete from the manuscript confidential information and to object to suggested publication and/or its timing (at Padagis's sole discretion.)



## 14 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PAD-NY-22-05

PROTOCOL TITLE: 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

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Padagis to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

---

Principal Investigator's Printed Name

---

Principal Investigator's Signature

---

Date

## 15 REFERENCES

[REDACTED]

3) Package insert Zoryve™ (Roflumilast) Cream, dated July 2022

[REDACTED]

## 16 APPENDICES

### 16.1 Appendix A: Study Personnel Contacts

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 16.2 Appendix B: Determination of BSA Affected by Plaque Psoriasis:

[REDACTED]

[REDACTED]

[REDACTED]

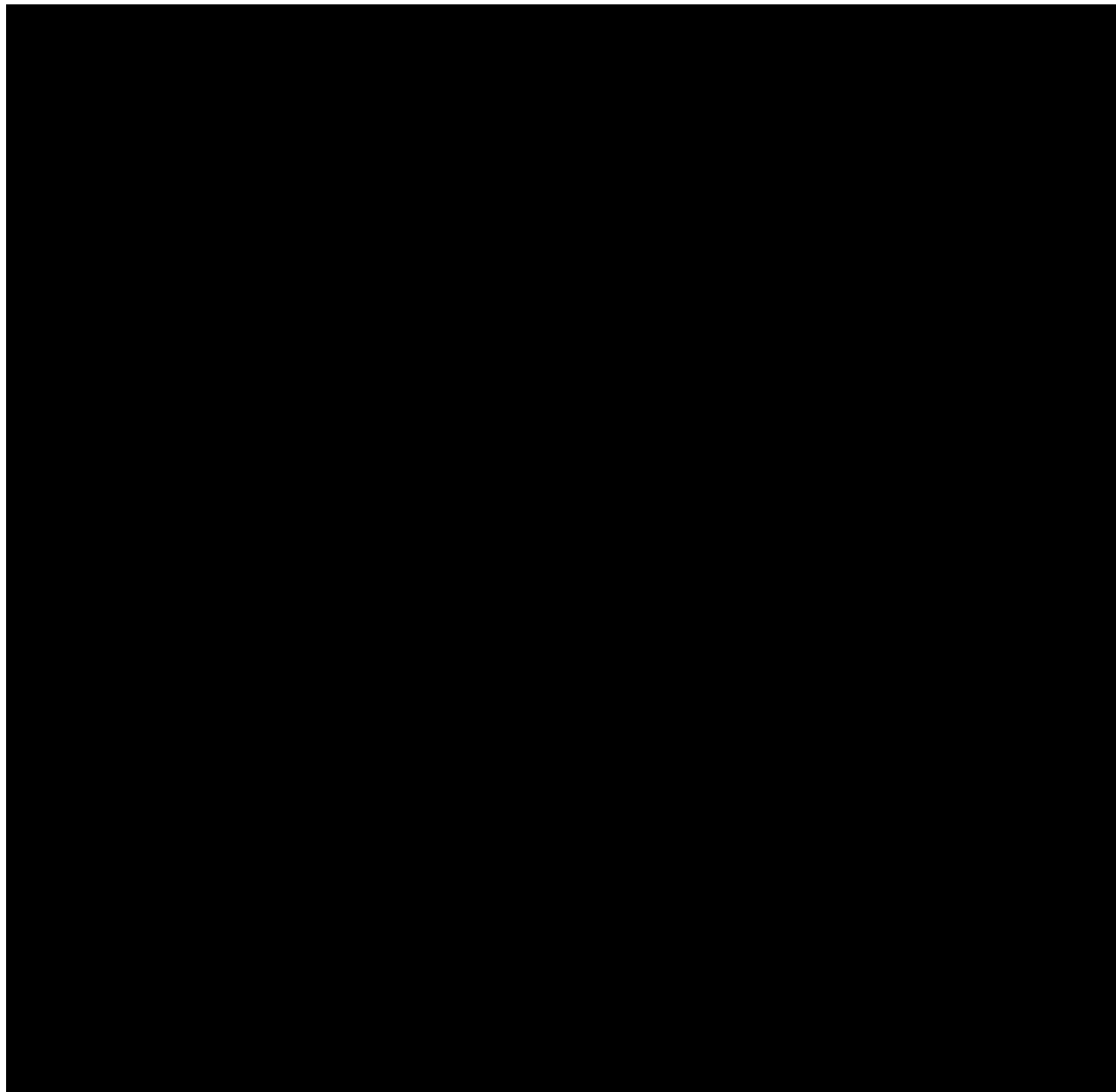
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 16.3 Appendix C: Body Diagram



#### 16.4 Appendix D: Subject Instructions

[REDACTED] ☐ [REDACTED] ☐ [REDACTED] ☐ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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