Protocol ARQ-252-205

A Phase 1/2b, Multiple Dose and 12-Week, Parallel Group, Double Blind, Dose Ranging, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.1% and ARQ-252 Cream 0.3% in Subjects with Chronic Hand Eczema

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IND Number: 140409

Protocol Version: Amendment 2

Protocol Date: 30 June 2020

GCP Statement

This study is to be performed in full compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

SITE INVESTIGATOR SIGNATURE PAGE

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Westlake Village, CA 91361

ISSUE DATE: 30 June 2020

I have read this protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the current International Conference on Harmonisation Good Clinical Practices (ICH GCPs) and applicable local and regional regulations.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Arcutis Biotherapeutics, Inc. I will discuss the material with them to ensure that they are fully informed about ARQ-252 and the study.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements. I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigational Site Name: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed in Amendment 2 of the ARQ-252-205 protocol:

Section		Summary of Changes
1.3	Schedule of Visits and Assessments (Cohort 2)	Clarified language in the footnote for IP dispensing.
2.4.2	Risks and/or Benefits to Subjects	Added the potential risks of ARQ-252 cream.
4.2	Number of Sites and Subjects	Clarified language regarding the replacement of subjects.
4.7.2	Exclusion Criteria	Clarified exclusion criterion for positive patch test with continued exposure to allergen.
4.8	Removal of Subjects from Investigational Product	Updated the reasons for discontinuation of IP.
4.10	Treatment Stopping Rules	Added additional criteria for treatment discontinuation and clarified existing criteria.
5.1.1	Screening	Added review of allergies and/or contact dermatitis to the medical history assessment at the Screening Visit.
5.1.2	Contraception Requirements	Added statements regarding nonclinical research on fetal development and the requirement to adhere to the pregnancy testing and/or contraception requirements of the protocol.
Editorial changes made throughout to improve accuracy or readability		

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ABBREVIATIONS

Abbreviation	Definition
ACR20	American College of Rheumatology 20% improvement in rheumatoid arthritis score
ACR50	American College of Rheumatology 50% improvement in rheumatoid arthritis score
ACR70	American College of Rheumatology 70% improvement in rheumatoid arthritis score
AE	Adverse Event
AUC	Area Under the Curve
BID	Twice Daily ("bis in die")
BSA	Body Surface Area
C_{max}	Maximum Concentration
Cm	Centimeter
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
FDA	U.S. Food and Drug Administration
FOCBP	Female of Childbearing Potential
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practices
Hr	Hour
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IGA	Investigator's Global Assessment
IL	Interleukin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
IRT	Interactive Response Technology

Abbreviation	Definition
Kg	Kilogram
µg	Microgram
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mL	Milliliter
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
Ng	Nanogram
NRS	Numerical Rating Scale
P-450	Cytochrome P450
PDE-4	Phosphodiesterase 4
PI	Principal Investigator
PK	Pharmacokinetics
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCPS	Tri-Council Policy Statement
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach Maximum Concentration
US	United States
WI-NRS	Worst Itch – Numeric Rating Score

1. PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:	A Phase 1/2b, Multiple Dose and 12-Week, Parallel Group, Double Blind, Dose Ranging, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.1% and ARQ-252 Cream 0.3% in Subjects with Chronic Hand Eczema
Clinical Indication:	Chronic Hand Eczema (CHE)
Investigational Product:	ARQ-252 cream will be supplied as ARQ-252 cream 0.1% (only applicable in Cohort 2) and ARQ-252 cream 0.3%. Matching vehicle cream (only applicable in Cohort 2) will contain only excipients of ARQ-252 cream. The active ingredient in ARQ-252 cream is SHR0302, a selective JAK1 inhibitor.
Study Design:	ARQ-252-205 is a Phase 1/2b, Multiple Dose and 12-week, parallel group, double blind, vehicle-controlled study of the safety and efficacy of ARQ-252 cream 0.1% and ARQ-252 cream 0.3% in subjects with chronic hand eczema. There are 2 cohorts of subjects. • Cohort 1 is a multiple dose cohort in which subjects with chronic hand eczema will be assigned to ARQ-252 cream 0.3% QD x 2 weeks to be applied to both hands (approximately 4% of BSA). PK and tolerability will be evaluated. • Cohort 2 is a parallel group, double blind, vehicle-controlled cohort in which subjects with chronic hand eczema will be randomized to ARQ-252 cream 0.3% QD, ARQ-252 cream 0.3% BID, ARQ-252 cream 0.1% QD, vehicle cream BID or vehicle cream QD x 12 weeks to be applied to both hands (approximately 4% of BSA). Safety and efficacy will be evaluated.
Study Objectives:	The objectives of this study are as follows: <u>Phase 1 (Cohort 1)</u> • To assess the safety, tolerability and PK of QD application of ARQ-252 0.3% to both hands for 2 weeks in 6 subjects with chronic hand eczema (Cohort 1) <u>Phase 2b (Cohort 2)</u> • To assess the safety and efficacy of ARQ-252 cream 0.1% QD and ARQ-252 cream 0.3% QD and BID, vs vehicle applied QD and BID for 12 weeks to subjects with chronic hand eczema (Cohort 2)
Study Sites:	Approximately 45 sites in the United States, Canada and Australia.

Study Population:	For both Cohorts, subjects will be male and female adults (≥18 years of age), with chronic hand eczema, and an Investigator's Global Assessment (IGA) of disease severity of at least Mild ('2') at Baseline. In Cohort 2, subjects with IGA of 'Mild' will be limited to 20% of total enrollment, and subjects with IGA of 'Severe' will also be limited to 20% of total enrollment. • Cohort 1 will include approximately 6 evaluable subjects, assigned to ARQ-252 cream 0.3% QD • Cohort 2 will include approximately 215 subjects, randomized 2:2:1:1:1 to ARQ-252 cream 0.3% QD : ARQ-252 cream 0.3% BID : ARQ-252 cream 0.1% QD : vehicle cream BID: vehicle cream QD
Duration of Participation for Subjects:	Cohort 1: Screening (up to 4 weeks), Treatment phase (2 weeks), and follow-up (1 week post-treatment completion) for a total of 7 weeks Cohort 2: Screening (up to 4 weeks), Treatment phase (12 weeks), and follow-up (1 week post-treatment completion); for a total of 17 weeks
Inclusion Criteria:	1. Participants legally competent to sign and give informed consent. 2. Males and females 18 years of age and older (inclusive) at the time of consent. 3. Clinical diagnosis of chronic hand eczema, defined as hand eczema persistent for more than 3 months, or returned twice or more within the last 12 months (Diepgen 2009). Generally stable disease for 6 weeks. Both irritant and non-irritant etiologic forms are allowed. All morphologic types are allowed, e.g., vesicular/dyshidrotic, hyperkeratotic, nummular, and other types. 4. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline (Visit 2). (In Cohort 2, subjects with IGA of 'Mild' will be limited to 20% of total enrollment, and subjects with IGA of 'Severe' subjects will also be limited to 20% of total enrollment). 5. Chronic hand eczema involving at least 0.3% body surface area total (i.e., approximately a third of one handprint) lesions on both hands added together at Baseline (Visit 2). 6. Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these

	subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method according to Contraception Requirements (Figure 1). 7. Females of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization or bilateral salpingectomy) according to Contraception Requirements (Figure 1). 8. Males, if engaging in sexual intercourse with a female who is pregnant or a female of childbearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks after the last investigational product administration. 9. Males must agree not to donate sperm from the first dose of investigational product until 4 weeks after the last investigational product administration. 10. Subjects in good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis. 11. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.
Exclusion Criteria:	1. Concurrent skin diseases on the hands which, in the opinion of the Investigator, could confound the study (e.g., tinnea manuum). 2. Active skin diseases not on the hands such as atopic dermatitis or psoriasis requiring medical treatment that could significantly affect hand eczema, in the Investigator's opinion. 3. Subjects with any presence or history of psoriasis. 4. History of a positive patch test with continued exposure to allergen. If, in the opinion of the Investigator, there is any suspected allergic hand eczema with continued exposure to allergen, subject must undergo diagnostic patch testing to determine if they meet entry criteria prior to Baseline (Visit 2). 5. Subjects who cannot discontinue systemic and/or topical therapies for the treatment of chronic hand eczema prior to Baseline (Visit 2) and during the study according to Excluded Medications and Treatments (Table 2), (i.e., immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids). 6. Psoralen ultraviolet A (PUVA) or ultraviolet B (UVB) therapy on the hands within 4 weeks prior to Baseline (Visit 2).

	7. Cutaneously applied treatment with immunomodulators (e.g., phosphodiesterase-4 (PDE-4) inhibitors, pimecrolimus, tacrolimus), topical urea moisturizers, topical antibiotics, or low or mid potency topical corticosteroids on the hands or elsewhere within 1 week prior to Baseline (Visit 2). Cutaneously applied treatment with high potency topical corticosteroids on the hands or elsewhere within 2 weeks prior to Baseline (Visit 2). 8. Subjects that have significant active systemic or localized infection, including known actively infected eczema or have had any infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 2 weeks prior to Baseline (Visit 2). 9. Other cutaneously applied therapy on the hands (except for the use of subject's own non-urea and non-salicylic acid emollients) within 1 week prior to Baseline (Visit 2). 10. Subjects who are unwilling to refrain from using a tanning bed or other LEDs as well as outdoor tanning or excessive sun exposure for 4 weeks prior to Baseline (Visit 2) and during the study. 11. Subjects with a history of chronic alcohol or drug abuse within 6 months prior to Baseline (Visit 2). 12. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix. 13. Subjects that have received live vaccine therapy less than 4 weeks prior to Baseline (Visit 2), immunosuppressive drugs less than 4 weeks prior to Baseline (Visit 2), or have known infection with mycobacterium tuberculosis, hepatitis B or C, or HIV, or have a diagnosis of an immunodeficiency disorder. 14. Subject had a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study. 15. Known or suspected: • severe renal insufficiency or severe hepatic disorders • hypersensitivity to component(s) of the investigational product which include SHR0302, butylated hydroxytoluene (BHT), benzyl alcohol, dimethyl sulfoxide, cyclomethicone, dimethicone (350 cst), ST-Elastomer 10, water, propylene glycol, polyethylene glycol 200, Pemulen TR1, Carbopol 974P, ethylenediaminetetraacetic acid, trolamine and D-limonene. 16. Pregnant or lactating women or women planning to become pregnant during the study and / or within 28 days following the last dose of investigational product.

	17. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin and carbamazepine for 2 weeks prior to Baseline (Visit 2) and during the study period. 18. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, fluconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to Baseline (Visit 2) and during the study period. 19. Subjects with any serious medical condition or clinically significant laboratory, ECG, vital signs or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator.
Key Assessments:	<u>Phase 1 (Cohort 1):</u> • Safety will be monitored through application site assessments, safety labs, AEs, ECGs, physical examinations, and vital signs. • Serial PK sampling will be performed on Day 1 (1, 2, 4, 6, and 24 hours post-dose administration), and at Day 15 (pre-dose and 1, 2, 4, 6, and 24 hours post-dose administration). For 24-hour timepoints, subjects return to the clinic on the following day within 2 hours of the IP application time from the previous day for PK plasma sample collection. A pre-dose/trough PK sample will be taken at Day 8. <u>Phase 2b (Cohort 2):</u> • Safety will be monitored through application site assessments, safety labs, AEs, ECGs, physical examinations, and vital signs. • Efficacy will be evaluated through IGA, HECSI, WI-NRS Pruritus, NRS Pain, Nail Dystrophy Assessments and QOLHEQ • PK will be evaluated through trough/pre-dose sampling at Baseline, Day 29, and Day 85.
Study Endpoints:	<u>Phase 1 (Cohort 1):</u> • Safety, as measured by the incidence and severity of adverse events, changes in laboratory parameters, tolerability, and pharmacokinetics. <u>Phase 2b (Cohort 2):</u> The primary endpoint of Cohort 2 is: • The rate of an IGA score of ‘clear’ or ‘almost clear’ at Week 12

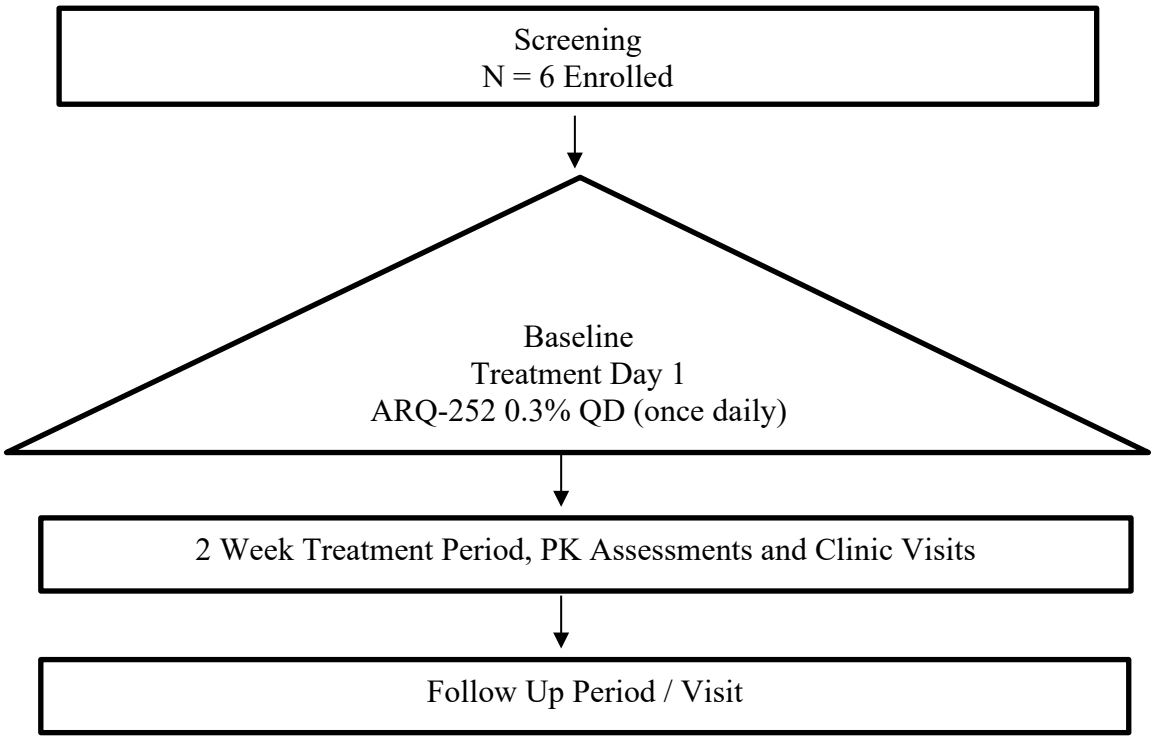
	Phase 2b (Cohort 2): The secondary endpoints of Cohort 2 are: • The rate of achievement of IGA of 'clear' or 'almost clear' PLUS at least a 2-point improvement from Baseline at Weeks 2, 4, 8 and 12 • The rate of achievement of at least a 2-point improvement from Baseline at Weeks 2, 4, 8 and 12 • Achievement of IGA of 'clear' or 'almost clear' at Weeks 2, 4, and 8 • Time to IGA of 'clear' or 'almost clear' • Change in IGA score at Weeks 2, 4, 8, and 12 as compared to Baseline • Change in WI-NRS pruritus score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks compared to Baseline • The rate of achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks in subjects with Baseline WI-NRS pruritus score of at least 4 • Time to the first achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score in subjects with Baseline WI-NRS pruritus score of at least 4 • Percent change in HECSI (Hand Eczema Severity Index) score at Weeks 2, 4, 8, and 12 compared to Baseline • Change in NRS Pain score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks compared to Baseline • The rate of achievement of ≥4-point reduction from Baseline in Pain NRS score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks in subjects with Baseline Pain NRS score of at least 4 • Time to the first achievement of ≥4-point reduction from Baseline in Pain NRS score in subjects with Baseline Pain NRS score of at least 4 • Change from Baseline in overall Quality of Life in Hand Eczema Questionnaire (QOLHEQ) score at each visit • Percent BSA affected by disease and % change from baseline in BSA affected by disease at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks. The exploratory endpoint of Cohort 2 is: • Change from Baseline in Nail Dystrophy at each visit

Power and Sample Size:	Cohort 1 will include approximately 6 evaluable subjects, which is deemed adequate for the purpose of evaluating safety and PK prior to Cohort 2. There are approximately 215 subjects planned for Cohort 2. Approximately 61 subjects will receive ARQ-252 cream 0.3% QD, approximately 61 subjects will receive ARQ-252 cream 0.3% BID, approximately 31 subjects will receive ARQ-252 cream 0.1% QD, approximately 31 subjects will receive matching vehicle cream QD, and approximately 31 subjects will receive vehicle cream BID. The randomization scheme will be 2:2:1:1:1 between these 5 treatment groups, stratified by study site and IGA at Baseline. The primary statistical comparisons will be to assess the ARQ-252 cream 0.3% BID group versus the vehicle BID group, to assess the ARQ-252 cream 0.3% QD group versus the vehicle QD group, and to assess the ARQ-252 cream 0.1% QD group versus the vehicle QD group. A sample size of 55 per active arm and 28 per vehicle arm will provide approximately 85% power at the 2-sided 5% significance level to detect a difference in the percent of subjects with IGA clear or almost clear at Week 12; for each ARQ-252-treated group versus vehicle group within the same daily dosing frequency, assuming an active treatment response rate of 45% and a vehicle response rate of 15%, with a two-sided $\alpha = 0.1$. This is based on a 2-group X^2 test of equal proportions (without continuity correction). With a 10% dropout rate, the sample size for the study is increased to 61 subjects per active arm and 31 subjects per vehicle arm (215 subjects total). The primary statistical comparisons and evaluation of the secondary endpoints will not be adjusted for multiplicity.
Statistical Analysis:	Descriptive statistics will be presented for the study endpoints. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data. The primary endpoint in Cohort 2 of 'IGA clear or almost clear at Week 12' will be analyzed using a Cochran-Mantel-Haenszel test stratified by study site and IGA at Baseline. The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation. Continuous secondary endpoints measured in Cohort 2 will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables. The ITT population will be used. Binary secondary endpoints will be analyzed similarly to the primary endpoint.

	All subjects who are randomized and receive at least one confirmed dose of investigational product will be included in the safety population. Adverse events (AEs) will be summarized within each cohort by preferred term, system organ class, and treatment group (Cohort 2 only) for all treatment-emergent AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product. Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from Baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from Baseline in weight and laboratory values will be summarized using shift tables. These summaries will be tabulated by treatment group for Cohort 2. All subjects who are enrolled and receive at least one application of investigational product and have sufficient pharmacokinetic assessments will be included in the pharmacokinetic population (Cohorts 1 and 2). When possible, the exposure to SHR0302 will be calculated based on plasma concentrations versus time profile data.

1.2 Study Schema

Phase 1 (Cohort 1)



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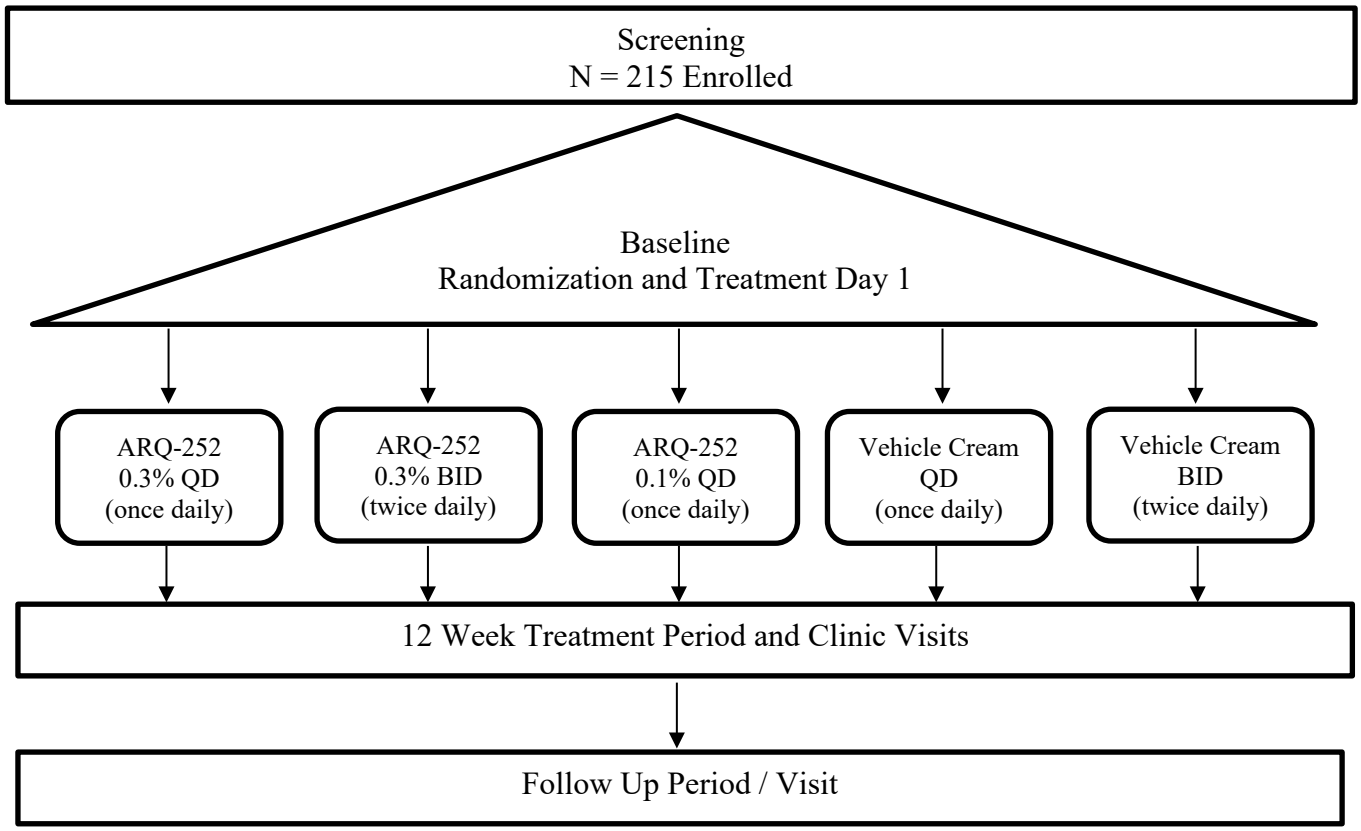
Phase 1/Cohort 1

Approximately 6 subjects with chronic hand eczema will receive ARQ-252 0.3% cream QD (once daily)

Phase 2b (Cohort 2)



A Phase 1/2b, Multiple Dose and 12-Week, Parallel Group, Double Blind, Dose Ranging, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.1% and ARQ-252 Cream 0.3% in Subjects with Chronic Hand Eczema

Phase 2b/Cohort 2

Approximately 215 subjects with chronic hand eczema will be randomized to receive either:

- ARQ-252 0.3% cream QD (once daily) N=61
- ARQ-252 0.3% cream BID (twice daily) N=61
- ARQ-252 0.1% cream QD (once daily) N=31
- Vehicle cream QD (once daily) N=31
- Vehicle cream BID (twice daily) N=31

The randomization scheme will be 2:2:1:1:1 between these 5 treatment groups, stratified by study site, and IGA at Baseline.

1.3 Schedule of Visits and Assessments

A. Cohort 1 (Phase 1)

Study Procedure	Screening	Baseline Day 1	PK Collection Day 2	Day 8	Week 2 Day 15	PK Collection Day 16	Week 3 Day 22
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	-4 Weeks		+/- 2 hrs	+/-1 day	+/- 1 day	+/- 2 hrs	+/- 3 days
Informed Consent	X						
Demographics	X						
Medical and Surgical History	X						
Physical examination[a]	X	X		X	X		X
I/E criteria	X	X					
Hematology, Serum Chemistries, Urine Analysis, TSH, T4[b]	X	X		X	X		X
Vital signs, weight, height[c]	X	X		X	X		X
Local tolerability assessment[d]		X		X	X		
BSA, IGA, HECSI[e]	X	X			X		
WI-NRS, NRS Pain[f]	X	→ Completed daily from Day 1-Day 15					
Urine pregnancy test[g]		X		X	X		X
Serum pregnancy test[g]	X						
Follicle-Stimulating Hormone (FSH)[h]	X						
Resting 12-lead ECG	X				X		
PK sampling[i]		X	X	X	X	X	
IP application in clinic[j]		X		X	X		
Dispense IP		X					
Weigh investigational product container[k]		X			X		
Dispense/review diary		X		X	X		
Adverse event assessment[l]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X

Footnotes from above table:

[a] Limited physical examination: skin, lungs, and heart only.

[b] All samples listed to be collected at Visits 1, 2, 4, 5, and 7. If Baseline visit occurs within 14 days of Screening, the Screening lab results may be utilized. Refer to Table 3.

[c] Height to be measured only at Visit 2 (Day 1). Weight will be collected at Baseline, Visits 4, 5 and 7.

[d] Local tolerability assessments to be recorded prior to IP application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post IP application for the subject's '0-3' burning/stinging assessment. **Note for investigator tolerability assessments: reactions at the site of IP application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's chronic hand eczema.**

[e] BSA will be measured as the affected BSA for each side of each hand. Affected areas of the lateral aspects of the fingers and hands should be assigned to the palmar surface. IGA will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments and by the same Evaluator at each study visit.** HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs of hand eczema and the extent of the lesions on each of 5 distinct hand anatomic areas by use of standard scales. The total HECSI score is based on a 4-point clinical sign severity scale ranging from 0 (none/absent) to 3 (severe) and a 5-point scale rating the different affected hand anatomic area(s) ranging from 0 (0% affected area) to 4 (76% to 100% affected area).

[f] Subjects will complete the WI-NRS pruritis assessment and NRS Pain assessment in the clinic during screening and then daily at home from the Baseline/Day 1 visit through the Day 15 visit.

[g] A serum pregnancy test will be administered to all females of child-bearing potential at Screening. A urine pregnancy test will be administered at Visits 2, 4, 5, and 7 to all females of childbearing potential. A negative result is required for continued participation in the study, and results must be available prior to dispensing of investigational product.

[h] FSH will be performed (if indicated) at Screening to confirm post-menopausal status.

[i] On the first day of dosing (Day 1), PK samples will be collected at 1, 2, 4, 6 (all +/- 10 mins) and 24 hours post-dose administration (Day 2, +/- 2 hours). On Day 15 (last dose application), PK samples will be collected pre-dose, 1, 2, 4, 6, (all +/- 10 mins) and 24 hours post dose administration (Day 16, +/- 2 hours). For 24-hour timepoints, subjects return to the clinic on the following day within 2 hours of the IP application time from the previous day for pre-dose PK plasma sample. A pre-dose PK sample will be taken at Day 8.

[j] Clinic personnel will apply assigned IP on Visits 2, 4 and 5 (Baseline, Day 8 and Day 15). Every tube should be weighed before and after IP application and weights recorded. For the 24-hour PK sampling timepoint the application of investigational product should occur after the PK sample has been collected.

[k] Subject should return with investigational product kit at each Visit. Every tube should be weighed before and after use and weights recorded when dispensed and returned.

[l] Any emergent AEs will be followed in the clinic for up to 1 month at the Investigator's discretion until resolved or otherwise judged as clinically stable

B. Cohort 2 (Phase 2b)

Study Procedure	Screen	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 8 Day 57	Wk 12 Day 85	Wk 13 Day 92
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	-4 weeks		+/- 3 days	+/- 5 days	+/- 5 days	+/- 7 days	+/- 3 days
Informed consent	X						
Demographics	X						
Medical and surgical history	X						
Physical examination[a]	X	X				X	
Vital signs, height, weight[b]	X	X	X	X	X	X	X
I/E criteria	X	X					
Randomization		X					
Hematology, Serum Chemistries, UA, TSH/T4[c]	X	X		X	X	X	
Resting 12-lead ECG	X			X		X	
BSA, IGA, HECSI[d]	X	X	X	X	X	X	X
NRS pain, WI-NRS[e]	X	Completed daily from Day 1 to Week 13 Visit					
QOLHEQ[e]	X	X	X	X	X	X	X
Nail dystrophy assessment[f]		X	X	X	X	X	X
Local Tolerability Assessments[g]		X	X	X	X	X	
Optional Photography[h]		X	X	X	X	X	X
Urine pregnancy test[i]		X		X	X	X	X
Serum pregnancy test[i]	X						
Follicle-Stimulating Hormone (FSH)[j]	X						
PK sampling[k]		X		X		X	
IP application/Subject training in clinic[l]		X	X	X	X	X	
Dispense IP kit[m]		X	X	X	X	X	
Dispense/review diary		X	X	X	X	X	
Weigh IP tubes[n]		X	X	X	X	X	
Compliance calculation[o]		X	X	X	X	X	
Adverse event assessment[p]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X

Footnotes from above table:

[a] Limited physical examination: skin, lungs, and heart only

[b] Height will be collected at Visit 2 (Baseline/Day 1) only. Weight will be collected at Baseline, Weeks 4, 8 and 12.

[c] If Baseline visit occurs within 14 days of Screening, the Screening lab results may be utilized.

[d] BSA will be measured as the affected BSA for each side of each hand. Affected areas of the lateral aspects of the fingers and hands should be assigned to the palmar surface. IGA will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments and by the same Evaluator at each study visit.** HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs of hand eczema and the extent of the lesions on each of 5 distinct hand anatomic areas by use of standard scales. The total HECSI score is based on a 4-point clinical sign severity scale ranging from 0 (none/absent) to 3 (severe) and a 5-point scale rating the different affected hand anatomic area(s) ranging from 0 (0% affected area) to 4 (76% to 100% affected area).

[e] Subjects will complete the WI-NRS pruritis assessment and NRS Pain assessment in the clinic during Screening and then daily at home from the Baseline/Day 1 visit until the Week 13 visit. QOLHEQ = Quality of Life in Hand Eczema Questionnaire will be completed at each visit.

[f] Assessment of nail dystrophy including Baseline identification of the nail with the worst dystrophy and measurement of the millimeters of normal appearing nail distal to the cuticle post Baseline. Sites participating in optional photography will obtain photos of nail with the worst dystrophy at Baseline/Day 1 and at subsequent visits. See Section 5.2.7 for details.

[g] Local tolerability assessments to be recorded prior to IP application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post IP application for the subject's '0-3' burning/stinging assessment. **Note for investigator tolerability assessments: reactions at the site of IP application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's chronic hand eczema.**

[h] Photography will be performed at selected investigational sites. Photography will be optional. All efforts will be made to de-identify the subjects. Sites participating in optional photography will obtain photos of nail with the worst dystrophy at Baseline/Day 1 and at subsequent visits.

[i] A serum pregnancy test will be administered to all females of childbearing potential at Screening. A urine pregnancy test will be administered at Baseline, Weeks 4, 8, 12 and 13. A negative result is required for continued participation in the study, and results must be available prior to dispensing of investigational product.

[j] FSH will be performed (if indicated) at Screening to confirm post-menopausal status.

[k] PK assessments will be collected from all subjects at Days 1, 29 and 85. The draws will be pre-dose IP application in the clinic.

[l] Subjects to apply assigned IP in clinic at these visits. The time of application will be documented.

[m] Kits will be dispensed at Baseline, Weeks 2, 4 and 8. Dispensing at Week 12 requires approval from the Medical Monitor. See IP Handling Manual for details.

[n] Each IP tube will be weighed prior to dispensing at the Baseline visit and at each follow-up clinic visit according to the Schedule of Visits and Assessments. When IP is applied in the clinic, the IP tube will be weighed before and after IP application. See IP Handling Manual for details.

[o] Compliance calculation is described in the IP Handling Manual.

[p] Any emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

2. INTRODUCTION

2.1 Background

Chronic hand eczema is a common condition which occurs in different forms. Chronic hand eczema may significantly impact quality of life and cause significant costs, e.g., through inability of patients to work. There is considerable unmet medical need for new therapies for hand eczema since few treatments are available and/or approved specifically for hand eczema (e.g., no FDA-approved therapies) and treatment is often unsatisfactory (Diepgen 2009).

Janus kinases (JAKs) are a family of intracellular nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-signal transducer and activator of transcription (STAT) pathway and have a plethora of effects on the immune system, inflammation, and hematopoiesis. In humans, the JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2). JAK1 is a human tyrosine kinase which plays a critical role in initiating responses to multiple major cytokines. It interacts with the common gamma chain of type I cytokine receptors to elicit signals from the IL-2 receptor family, the IL-4 receptor family, the gp130 receptor family and other cytokine receptor families. It is also important for transducing a signal by type I and type II interferons, and members of the IL-10 family via type II cytokine receptors. JAK2 has been implicated in signaling by the GM-CSF receptor family and controls various functions relating to hematopoiesis. JAK3 is involved in signal transduction by receptors that employ the common gamma chain of the type I cytokine receptor family (e.g., IL-2R, IL-4R, IL-7R, IL-9R, IL-15R, and IL-21R) (Villarino 2017). Finally, Tyk2 is important for Th1 and Th17 responses, transducing signals by interferons, IL-12, IL-23, IL-22, and IL-6 (O'Shea 2019).

The first demonstration of the clinical efficacy of JAK inhibitors in eczema utilized a topical formulation of the pan-JAK inhibitor, tofacitinib, which has been approved orally for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (Bissonnette 2016a). Subsequently, several topical JAK inhibitors (delgocitinib, ruxolitinib) (Kim 2019; Nakagawa 2018, Worm 2019) and oral JAK inhibitors (upadacitinib, PF-04965842, baricitinib) (Guttman-Yassky 2019a; Gooderham 2019; Guttman-Yassky 2019b) have been reported to have efficacy in the treatment of eczema. Oral JAK inhibitors can be accompanied by safety issues including the development of opportunistic infections, lymphoma and other malignancies, and hematologic and lipid abnormalities. We are pursuing development of ARQ-252 cream, a topical form of the JAK1 selective inhibitor SHR0302, as a potential treatment for particular forms of eczema aiming to maintain the efficacy of this class of agents in these diseases while minimizing systemic exposure and undesirable side effects.

SHR0302 is in Phase 2 development as an oral therapy for rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, and atopic dermatitis by development partners Jiangsu Hengrui Medicine Company (Hengrui) and Reistone Biopharma. Clinical safety data from these ongoing programs, as well as extensive nonclinical studies, provide support for Arcutis' dermal (ARQ-252) development program.

2.2 Nonclinical Safety Summary

In vitro pharmacology data supports that SHR0302 is a strong JAK inhibitor, with JAK1>JAK2>JAK3> Tyk2 inhibitory activity. Additionally, SHR0302 has demonstrated activity comparable to tofacitinib in various *in vivo* models of inflammatory conditions, including the imiquimod-induced murine model of psoriasis, the oxazolone-induced murine model of atopic dermatitis, the rat and murine models of collagen-induced arthritis, the adjuvant-induced arthritis rat model, and the murine dextran sulfate sodium-induced colitis model.

The nonclinical safety profile of orally administered SHR0302 has been well characterized through the conduct of safety pharmacology, acute and repeat dose toxicity in rats and monkeys, genetic toxicology (bacterial reverse mutation, *in vitro* micronucleus, *in vivo* micronucleus in rats), and reproductive/developmental toxicology (fertility, embryofetal development) studies.

In safety pharmacology studies, SHR0302 did not cause significant changes in cardiovascular, CNS or respiratory functions. After oral administration, SHR0302 was well absorbed and distributed into many tissues.

During the oral dosing program of SHR0302 with dose levels up to 150 mg/kg/day in rats and 15 mg/kg/day in monkeys, the major target organs identified following repeated dosing were immune system (lymph nodes, spleen, and thymus), bone marrow, reproductive organs and digestive tract. As SHR0302 is a potent inhibitor of Janus kinases which are known to affect cytokine-mediated signaling, the immunomodulatory effects observed (mainly in the rat) in the toxicity studies are consistent with the pharmacological mechanism of action of SHR0302. The genotoxicity studies on SHR0302 indicate a lack of potential to induce point mutations, chromosomal aberrations, or to interact with or damage DNA. Therefore, it is unlikely that SHR0302 poses a genotoxic risk to humans.

Results of a rat fertility study with SHR0302 showed no effects on male fertility and disrupted early embryonic development in female rats at 10 and 50 mg/kg. The no observed adverse effect level (NOAEL) was 50 mg/kg for male fertility and 1 mg/kg for female fertility and early embryonic development. Embryofetal development studies in rats demonstrated maternal and fetal toxicity and fetal teratogenicity following oral dosing of SHR0302. The NOAEL for rat dams was 10 mg/kg and 1 mg/kg for embryofetal effects. In the rabbit embryofetal study, no maternal toxicity was noted at the high dose of 25 mg/kg/day (NOAEL). Rabbit embryo-fetal developmental toxicity was noted with effects on fetal viability and development, including fetal visceral and/or skeletal malformations and resulting in a NOAEL of 1 mg/kg/day.

The nonclinical safety profile of SHR0302 was also evaluated topically in mice and minipigs in support of once-daily topical administration. Dermal toxicology studies conducted to date include 13-week mouse, 7-day tolerability in minipigs, 4-week and 16-week toxicity in minipigs, and local tolerance (ocular irritation, skin sensitization, *in vitro* phototoxicity). Planned studies include 39-week toxicity in minipigs and a 104-week carcinogenicity study in mice.

The dermal toxicity of ARQ-252 (SHR0302 cream) has been evaluated and no new risks have been identified and no target organs were identified. In the 13-week dermal toxicity study in mice and the 7-day and 16-week dermal toxicity studies in minipigs, no evidence of systemic toxicity was observed, and no dermal findings were noted. The NOAELs in each of these repeat dose dermal toxicity studies were the highest doses administered.

Local tolerance studies demonstrated ARQ-252 is not a skin sensitizer or eye irritant, and it does not have phototoxic potential.

Overall, the results suggest that topical ARQ-252 cream is safe and well tolerated in both mice an minipigs. Taken together, the results of the nonclinical toxicology studies demonstrated an acceptable topical safety profile and support the progression of ARQ-252 cream into clinical studies in patients with hand eczema.

2.3 Clinical Studies

This will be the first study of topical ARQ-252 cream in the human population.

Oral administration of SHR0302 has been studied in three Phase 1 pharmacokinetic studies, including two conducted in healthy volunteers and one conducted in subjects with rheumatoid arthritis. Oral administration of SHR0302 has also been studied in a 24-week, Phase 2 study in subjects with rheumatoid arthritis.

2.3.1 Oral Administration: Phase 1

In three Phase 1 pharmacokinetic studies, a total of 94 subjects were exposed to SHR0302 at various dosages and duration. The single maximum dose of exposure in humans was 100 mg, and the longest duration of exposure was 7 days of 10 mg SHR0302 in rheumatoid arthritis patients.

A study on human safety, pharmacokinetics, and pharmacodynamics was conducted on SHR0302 following single dose oral administration in healthy subjects (SHR0302-101). This was a randomized, double blind and placebo-controlled study with six dosage groups of 1, 5, 10, 25, 50 and 100 mg. AEs were reported mainly from the high-dose groups (50 mg and 100 mg) in this single ascending dose study. The most common AEs involved the hematologic system (neutropenia and high lymphocyte count). Adverse reactions included neutropenia in 7 subjects (10.9%), elevated lymphocytes in 6 subjects (9.4%), and leukopenia in 1 subject (1.6%). At the 25 mg dose and below, there was no obvious difference between the active and placebo arms. There were no serious adverse events.

Following single oral dose administration, SHR0302 was rapidly absorbed with median T_{max} values of 1.0 hour across all dose groups. Geometric mean C_{max} values increased 105-fold over the 100-fold increase in dose (1 to 100 mg), demonstrating dose proportional kinetics. Similarly, the geometric mean AUC_{0-24} values increased 107-fold over the same 100-fold increase in dose.

A multiple ascending dose (MAD) study of human safety, pharmacokinetics, and pharmacodynamics was conducted on orally administered SHR0302 in subjects with rheumatoid arthritis (SHR0302-102). This was a randomized, double-blind, and placebo-controlled study with four planned dosage groups of 2, 5, 10 and 25 mg. Each dosage group had 12 subjects, 10 receiving active and 2 receiving placebo. Subjects were dosed for 7 days. The 2, 5, and 10 mg dose groups were completed, for a total of 36 subjects, 30 receiving active drug. No subjects in the 25 mg dose group were enrolled.

Twenty out of 36 subjects experienced AEs during the study period, with 16 subjects experiencing AEs reported as causally related to drug. AEs reported in subjects exposed to SHR0302 included seven cases of elevated TSH, five cases of elevated alanine aminotransferase, four cases of elevated aspartate aminotransferase, three cases of anemia, three cases of urinary tract infection, two cases of lowered free thyroxine, and one case each of ear pain, conjunctivitis, hypoesthesia, constipation and hematuria. Elevated TSH in blood (five cases), urinary tract infection (three cases) and lowered free thyroxine (two cases) were concentrated in the 10 mg SHR0302 group. All AEs were Grade 1 or Grade 2, and most reversed within two weeks of drug discontinuation. No SAEs were reported. Study drug dose was not decreased or suspended in any subject due to an AE, and no subject withdrew from the trial due to an AE.

Following multiple oral dose administrations of SHR0302, the median T_{max} value was 1.0 hour across the dose groups. Geometric mean C_{max} values increased 3.5-fold over the 5-fold increase in dose (2 to 10 mg), demonstrating less than dose proportional kinetics. Similarly, the geometric mean AUC_{0-24} values increased 4.1-fold over the same 5-fold increase in dose from 1130 hr*ng/mL for the 2 mg dose to 4620 hr*ng/mL for the 10 mg dose.

A food effect study of high-fat intake on the pharmacokinetics of SHR0302 has also been conducted (SHR0302-103). In this study, SHR0302 (10 mg tablet) was safe and well tolerated in healthy subjects, and administration of SHR0302 after a high-fat meal did not significantly impact systemic exposure. Except for one AE (soft tissue contusion) unrelated to drug which was moderate, the other AEs were mild and recovered without treatment. No SAEs were reported, and no subject withdrew from the trial due to an AE.

Overall, SHR0302 was well-tolerated with no SAEs reported.

2.3.2 Oral Administration: Phase 2

Preliminary results are available from SHR0302-201, a Phase 2, double-blind, randomized study evaluating 0.5 mg, 1 mg, 2 mg, 4 mg, and 8 mg of SHR0302 as once-daily oral monotherapy for adults with active rheumatoid arthritis who were naïve to any disease modifying anti-rheumatic drug (DMARDs) or have had an inadequate response or intolerance to conventional synthetic DMARDs. The study was placebo-controlled for 12 weeks, followed by a 12-week, open label maintenance phase. The Primary Endpoint was the response rate of American College of Rheumatology 20 (ACR20) at Week 12, which is a composite measure defined as 20% improvement in the number of tender and swollen joints, and 20% improvement in 3 of 5 criteria including patient global assessment, physician global assessment, functional ability measure,

visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein. A total of 194 subjects were randomized. 174 subjects completed the placebo-controlled period.

Preliminary efficacy results include:

- SHR0302 monotherapy was demonstrated to be effective for treatment of active rheumatoid arthritis, with improvements in clinical signs and symptoms, as well as physical function versus placebo.
- A dose response relationship was observed, with the SHR0302 8 mg group having more responders than the other groups.
- The Primary Endpoint was met in the 2 mg, 4 mg, and 8 mg groups (refer to Table 1).

Table 1. Proportion of Patients Reaching ACR20/50/70 and Statistical Check (CMH-FAS-NRI) after 12-week Administration in a Multicenter, Randomized, Double-blind, Placebo-controlled Phase II Study Evaluating the Efficacy and Safety of SHR0302 Tables in Patients with Moderate to Severe Active Rheumatoid Arthritis

	Group					
	Placebo	0.5 mg	1 mg	2 mg	4 mg	8 mg
Indicator	(N=37)	(N=25)	(N=24)	(N=23)	(N=40)	(N=45)
ACR20 Percentage (%)	27.0	44.0	41.7	56.5	67.5	77.8
(95% CI)	(13.8, 44.1)	(24.4, 65.1)	(22.1, 63.4)	(34.5, 76.8)	(50.9, 81.4)	(62.9, 88.8)
% difference from placebo	-	17.0	14.6	29.5	40.5	50.8
(95% CI)		(-6.6, 39.2)	(-8.8, 37.3)	(4.1, 50.8)	(18.2, 57.5)	(29.5, 65.9)
P value	-	0.1871	0.2884	0.0223	0.0004	<0.0001
ACR50 Percentage (%)	2.7	12.0	20.8	30.4	27.5	37.8
(95% CI)	(0.1, 14.2)	(2.5, 31.2)	(7.1, 42.2)	(13.2, 52.9)	(14.6, 43.9)	(23.8, 53.5)
% difference from placebo	-	9.3	18.1	27.7	24.8	35.1
(95% CI)		(-4.3, 27.4)	(2.1, 37.9)	(9.2, 48.3)	(8.9, 40.3)	(18.2, 49.8)
P value	-	0.1661	0.0247	0.0022	0.0031	0.0002
ACR70 Percentage (%)	0.0	4.0	4.2	13.0	12.5	26.7
(95% CI)	(0.0, 9.5)	(0.1, 20.4)	(0.1, 21.1)	(2.8, 33.6)	(4.2, 26.8)	(14.6, 41.9)
% difference from placebo	-	4.0	4.2	13.0	12.5	26.7
(95% CI)		(-6.0, 19.5)	(-5.8, 20.2)	(0.4, 32.1)	(0.8, 26.1)	(12.4, 41.0)
P value	-	0.2440	0.1797	0.0267	0.0284	0.0007

Investigator's Brochure, Edition 1.0, Feb 2020.

Preliminary safety results include:

- SHR0302 was generally safe and well tolerated. A higher frequency of infections was observed in SHR0302-treated subjects, particularly in the 8mg group. The most common infections included upper respiratory tract infections and urinary tract infections.
- Mean WBC, neutrophils, lymphocyte, HGB, platelet count, serum lipid level, liver function, kidney function, and thyroid function parameters remained in the normal range in all SHR0302 treatment groups.
- Mean platelet count did not increase during the study.
- Increases in LDL, HDL, total cholesterol and triglycerides were observed. However, LDL-to-HDL remained stable.
- Increase in mean serum creatine kinase (CK) was observed in patients treated with SHR0302 versus placebo but was within normal range. CK-MB remained stable.
- Most of the reported abnormal laboratory results were classified as CTCAE grade 1 or 2. CTCAE grade 3 events included: 1 case of increased alanine aminotransferase (4 mg), 1 case of decreased neutrophils (8 mg), 1 case of decreased lymphocytes (4 mg) and 1 case of anemia (8 mg).
- From Baseline through Week 12, the most common AEs (≥5% across pooled SHR0302 groups) included upper respiratory infection, hyperlipidemia, swollen joint, urinary tract infection, hypercholesterolemia, joint pain, and cough. From Baseline to Week 12, other TEAEs occurring at rates ≥5% in individual SHR0302 groups (although <5% across pooled SHR0302 groups) included hypothyroidism, anemia, liver dysfunction (although placebo group had highest rate), elevated serum creatine phosphokinase, diarrhea, headache, hematuria, abdominal discomfort, urine protein detection, blood in urine, elevated blood lactic dehydrogenase, and upper abdominal pain. Additional common AEs (≥5% across pooled SHR0302) seen from Baseline through Week 24 included elevated serum creatine phosphokinase, anemia, and hypothyroidism.
- Overall, there were 6 severe AEs in 3 subjects including 4 severe SAEs in a subject in the 0.5 mg group during the placebo-controlled period (Craniocerebral injury, Ventricular hemorrhage, Occipital fracture and Subarachnoid hemorrhage), appendicitis in a subject in the 4 mg group during the placebo-controlled period, and elevated liver enzymes in a subject in the 4 mg group during the extension period.
- AEs leading to discontinuation were generally uncommon from Baseline through Week 12 (1 or fewer subjects per group). From Baseline through Week 24, AEs leading to discontinuation remained generally uncommon (1 or fewer subjects per group, except for 3 subjects in the 4 mg group, and 3 subjects in 8 mg group including 1 subject in placebo group then received 8 mg after Week 12).
- A total of 4 cases of herpes zoster (all in 8 mg group) and 1 case of opportunistic infection (8 mg group, cryptococcal pneumonia) were reported.
- No tuberculosis, malignancy, important cardiac events or death were reported.
- One thrombotic event was reported, a SAE of multiple lacunar infarcts in a 64 year-old woman in the 0.5mg SHR0302 group, requiring hospitalization, deemed unrelated, with dose not changed.

- From Baseline through Week 12, there were 13 SAEs in 9 subjects overall, including 3 SAEs in 2 subjects in the placebo group, 5 SAEs (Craniocerebral injury, Ventricular hemorrhage, Occipital fracture and Subarachnoid hemorrhage; Lacunar infarction) in 2 subjects in the 0.5 mg group, 3 SAEs (Hemorrhoids; Pulmonary infection; Appendicitis) in 3 subjects in the 4 mg group, and 2 SAEs (Epiglottic cyst; Tympanitis) in 2 subjects in the 8 mg group. From Week 12 through Week 24, there were 4 SAEs in 3 subjects, including Liver dysfunction in a subject in the 4 mg group, Viral gastroenteritis in a placebo-8 mg subject, and Cryptococcal pneumonia and Ureterolith in a subject in the 8 mg group.

2.3.3 Additional Studies

An open label, self-controlled study (SHR0302-105) evaluating drug interaction potential between SHR0302 and methotrexate (MTX) in subjects with rheumatoid arthritis was recently completed. Subjects were to take MTX 10 mg once daily on Day 1 and Day 8, and SHR0302 10 mg once daily on Days 3 to Day 8. Overall, 15 subjects were enrolled. A total of 18 adverse events were reported in 8 of 15 subjects (53.3%). Of the 18 adverse events, 3 subjects (20.0%) reported 5 adverse events after SHR0302 alone, 4 subjects (26.7%) reported 5 adverse events after MTX alone, and 3 subjects (20.0%) reported 8 adverse events after MTX and SHR0302 in combination. The adverse events reported in subjects given SHR0302 alone included headache, back pain, fever, constipation and tachycardia each in 1 subject (6.7%). The adverse events reported by the subjects after MTX and SHR0302 in combination included anemia, upper respiratory tract infection, urinary tract infection, elevated blood triglycerides, elevated aspartate aminotransferase, positive urine leukocytes and tachycardia each in 1 subject (6.7%). No serious adverse events were reported, and no subjects withdrew prematurely due to adverse event.

Ongoing Studies

Two studies of SHR0302 as an oral treatment of inflammatory bowel disease are ongoing. RSJ10101 is a phase 2, randomized, placebo-controlled, double-blind, 4 arm, dose-ranging study to evaluate the efficacy and safety of SHR0302 compared to placebo in adults with moderate to severe, active ulcerative colitis. Treatment groups include 3 different doses of SHR0302 (4mg QD, 8mg QD, 4mg BID) or placebo, with 1:1:1:1 randomization. The study consists of an 8-week blinded treatment phase, followed by an 8-week of blinded, active extension phase. Planned enrollment is 152 across China, Ukraine, United States, and Poland. RSJ10201 is a phase 2, randomized, placebo-controlled, double-blind, four arms dose-ranging study to evaluate the efficacy and safety of SHR0302 compared to placebo in adults with moderate to severe, active Crohn's disease. Treatment groups include 3 different doses of SHR0302 (4mg QD, 8mg QD, 4mg BID) or placebo, with 1:1:1:1 randomization. The study consists of a 12-week blinded treatment phase, followed by a 12-week of blinded, active extension phase. Planned enrollment is 144 across China, Ukraine, United States, and Poland. Analysis of blinded data from these two ongoing studies in IBD (RSJ10101 and RSJ10201) as of October 19, 2019 has been performed. Based on this analysis, 39 subjects were estimated to be exposed to SHR0302 in these two clinical trials. One SAE was reported as colitis ulcerative and the other one was synovitis. The latter SAE was unblinded and confirmed to be on SHR0302.

Overall, the reported safety data were in line with the known and expected safety profile of SHR0302.

Finally, two additional studies of SHR0302 recently started, for which no data is currently available. RSJ10303 is a phase 2 study in China of SHR0302 in atopic dermatitis. The study is a randomized, double-blind, and placebo-controlled, evaluating the efficacy and safety of SHR0302 4mg QD, SHR0302 8mg QD, or placebo in adult patients with moderate to severe atopic dermatitis. RSJ10411 is a phase 1, vehicle-controlled study in Australia and China to evaluate the safety and pharmacokinetics of SHR0302 base ointment at single dose and multiple dose in healthy adult subjects.

2.4 Rationale for Development

Since the first demonstration of the clinical efficacy of JAK inhibitors for the treatment of eczema, which utilized a topical formulation of tofacitinib for the treatment of atopic dermatitis, numerous oral JAK inhibitors and several other topical JAK inhibitors have also demonstrated efficacy in eczema. We are pursuing the development of ARQ-252 cream as a topical JAK1-selective inhibitor for the treatment of hand eczema, planning to take advantage of the efficacy of this class of agents in this disease, while minimizing systemic exposure and undesirable side effects. Nonclinical and systemic clinical data with SHR0302 to date are supportive of this plan.

The above data indicate that topical ARQ-252 could provide an important addition to the dermatologist's approach for treating hand eczema.

2.4.1 Dose Selection

ARQ-252 cream 0.3% was selected as the high clinical dose because this dose remains in solution when stored at controlled room temperature.

In Cohort 1 of this study, ARQ-252 cream 0.3% will be applied QD to approximately 4% BSA in subjects with hand eczema. It is well known that cutaneous disease states can alter drug permeability as compared to normal human skin. Since eczematous skin may have different drug permeability characteristics than normal skin (Ortiz 2009; Halling-Overgaard 2017), this study is planned in patients with hand eczema rather than healthy volunteers. Administration of ARQ-252 cream 0.3% once-daily to approximately 4% of BSA at an application rate of approximately 0.75 mg/cm^2 would result in 1.5 mg of total SHR0302 being absorbed per day, assuming 100% absorption of applied drug, an amount well covered by the oral MAD study discussed previously (Section 2.3.1). In the oral MAD, daily doses of 2 to 10 mg resulted in signals for thyroid effects (elevated TSH, decreased free T4), mild LFT abnormalities, and a few urinary tract infections. These are all easily monitored, and skin absorption is very likely to be only a small fraction of 100%. Moreover, in the Phase 2 RA study, mean WBC, neutrophils, lymphocyte, HGB, platelet count, liver function and kidney function remained in the normal range in all SHR0302 treatment groups.

Following a review of safety and PK data from Phase 1 (Cohort 1) of this study, Phase 2b (Cohort 2) can commence. Phase 2b (Cohort 2) is a parallel group, double blind, vehicle-controlled cohort in which subjects with chronic hand eczema will be randomized to ARQ-252 cream 0.3% QD, ARQ-252 cream 0.3% BID, ARQ-252 cream 0.1% QD, vehicle cream BID or vehicle cream QD.

2.4.2 Risks and/or Benefits to Subjects

The potential risks of ARQ-252 cream stem from what is known about the safety of the oral form of this drug, and risks associated with the JAK inhibitor mechanism. These risks include serious infections, other infections (e.g., upper respiratory tract infections, opportunistic infections, herpes), anemia, lymphopenia, natural killer (NK) cell reduction, neutropenia, platelet elevations or reductions, malignancy and lymphoproliferative disorders, gastrointestinal perforations, liver function abnormalities, thyroid function abnormalities, lipid elevation, serum creatinine elevations, creatine phosphokinase elevations, thrombosis, nausea, diarrhea, headache, and hypertension. In general, topical delivery is expected to carry lower risk than oral administration at therapeutic doses to the degree that systemic exposure is reduced. Previous nonclinical research showed that the active ingredient in ARQ-252 can harm fetal development. Please refer to the Investigator's Brochure for detailed information.

Phase 1 (Cohort 1)
Subjects in Cohort 1 subjects may see an improvement in their hand eczema, although the study duration of 2 weeks may limit this possibility.

Phase 2b (Cohort 2)
Subjects randomized to active treatment in Cohort 2 may see an improvement in their hand eczema with the use of ARQ-252 cream. Those receiving vehicle cream may also see improvement related to the moisturizing properties of the vehicle

The safety monitoring practices employed in this protocol (i.e., physical examinations, application site reaction assessments, hematology, serum chemistry, TSH, T4, urinalysis, ECG, and AE questioning) are adequate to protect the subjects' safety and should detect expected AEs.

3. STUDY ENDPOINTS AND OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objectives

The objectives of this study are as follows:

Phase 1 (Cohort 1):

- To assess the safety, tolerability and PK of QD application of ARQ-252 0.3% to both hands for 2 weeks in 6 subjects with chronic hand eczema

Phase 2b (Cohort 2):

- To assess the safety and efficacy of ARQ-252 cream 0.1% QD and ARQ-252 cream 0.3% QD and BID, vs vehicle applied QD and BID for 12 weeks to subjects with chronic hand eczema

3.2 Study Endpoints

3.2.1 Primary Endpoints

Phase 1 (Cohort 1):
The primary endpoint of Cohort 1 is safety, as measured by the incidence and severity of adverse events, changes in laboratory parameters, tolerability, and pharmacokinetics.

Phase 2b (Cohort 2):
The primary endpoint of Cohort 2 is:

- The rate of an IGA score of 'clear' or 'almost clear' at Week 12

3.2.2 Secondary Endpoints

Phase 2b (Cohort 2):
The secondary endpoints of Cohort 2 are:

- The rate of achievement of IGA of 'clear' or 'almost clear' PLUS at least a 2-point improvement from Baseline at Weeks 2, 4, 8 and 12
- The rate of achievement of at least a 2-point improvement from Baseline at Weeks 2, 4, 8 and 12
- Achievement of IGA of 'clear' or 'almost clear' at Weeks 2, 4, and 8
- Time to IGA of 'clear' or 'almost clear'
- Change in IGA score at Weeks 2, 4, 8, and 12 as compared to Baseline
- Change in WI-NRS pruritus score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks compared to Baseline
- The rate of achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks in subjects with Baseline WI-NRS pruritus score of at least 4
- Time to the first achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score in subjects with Baseline WI-NRS pruritus score of at least 4
- Percent change in HECSI (Hand Eczema Severity Index) score at Weeks 2, 4, 8, and 12 compared to Baseline
- Change in Pain NRS score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks compared to Baseline

- The rate of achievement of ≥4-point reduction from Baseline in Pain NRS score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks in subjects with Baseline Pain NRS score of at least 4
- Time to the first achievement of ≥4-point reduction from Baseline in Pain NRS score in subjects with Baseline Pain NRS score of at least 4
- Change from baseline in overall Quality of Life in Hand Eczema Questionnaire (QOLHEQ) score at each visit
- Percent BSA affected by disease and % change from baseline in BSA affected by disease at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks.

3.2.3 Exploratory Endpoints

Phase 2b (Cohort 2):
The exploratory endpoint of Cohort 2 is:

- Change from Baseline in Nail Dystrophy at each visit.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a phase 1/2b, multiple dose and 12-week, parallel group, double blind, dose ranging, vehicle-controlled study of the safety and efficacy of ARQ-252 cream 0.1% and ARQ-252 cream 0.3% in subjects with chronic hand eczema.

There are 2 cohorts of subjects:

- Cohort 1 is a multiple dose cohort in which subjects with chronic hand eczema will be assigned to ARQ-252 cream 0.3% QD x 2 weeks to be applied to both hands. PK and tolerability will be evaluated.
- Cohort 2 is a parallel group, double blind, vehicle-controlled cohort in which subjects with chronic hand eczema will be randomized to ARQ-252 cream 0.3% QD, ARQ-252 cream 0.3% BID, ARQ-252 cream 0.1% QD, vehicle cream BID or vehicle cream QD x 12 weeks to be applied to both hands. Safety and efficacy will be evaluated.

4.2 Number of Sites and Subjects

A total of approximately 6 evaluable subjects will be enrolled in Cohort 1 and a total of approximately 215 subjects will be enrolled in Cohort 2. Approximately 45 study sites are planned in the US, Canada and Australia. During the conduct of the study, additional countries and/or sites may be added if necessary. Subjects will be adults (≥18 years of age) males or females with chronic hand eczema.

For Cohort 1, evaluable subjects are defined as those that:

- Complete 2 weeks of treatment

- Have PK results for all timepoints required at D1, D2, D15 and D16.

Unevaluable subjects in Cohort 1 may be replaced. Subjects in Cohort 2 will not be replaced.

4.3 Subject Participation

Phase 1 (Cohort 1)
Subject participation involves a minimum of 7 clinic visits including Screening, Baseline/Day 1, Day 2, Day 8, Day 15, Day 16 and Day 22. Subjects will be treated with investigational product (ARQ-252 cream 0.3% QD) for 2 weeks. The interval between the Screening and Baseline visits could be up to 4 weeks, therefore the anticipated maximum duration of subject participation is 7 weeks.

Phase 2b (Cohort 2)
Subject participation involves a minimum of 7 clinic visits including Screening, Baseline/Day 1, Week 2, Week 4, Week 8, Week 12 and Week 13. Subjects will be randomized to a treatment group and will be treated with investigational product for 12 weeks. The interval between the Screening and Baseline visits could be up to 4 weeks, therefore the anticipated maximum duration of subject participation is 17 weeks.

4.4 Randomization

Phase 1 (Cohort 1)
Phase 1 (Cohort 1) is open label and all enrolled subjects will be assigned treatment with ARQ-252 cream 0.3% QD at the Baseline visit. Subjects will be enrolled at the Baseline visit after the Investigator confirms that the subject meets all eligibility criteria listed in Section 4.7. Enrollment will be documented by the completion of the Enrollment Notification Form.

Phase 2b (Cohort 2)
Phase 2b (Cohort 2) is randomized. Randomization will take place at the Baseline visit after the Investigator confirms that the subject meets all eligibility criteria listed in Section 4.7. Subjects will be randomly assigned to apply ARQ-252 0.3% QD, ARQ-252 0.3% BID, ARQ-252 0.1% QD, vehicle cream QD or vehicle cream BID by an interactive response technology system (IRT).

Assignment of treatment arm will be made at a 2:2:1:1:1 ratio and stratified by study site and IGA at baseline according to a computer-generated randomization list. Kits containing tubes of investigational product will be assigned to each subject by the IRT system. A subject may receive more than one kit for the treatment period. The kits and tubes will be labeled with a unique number, in a blinded manner.

4.5 Numbering of Subjects

Phase 1 (Cohort 1)
All subjects who sign informed consent will be assigned a unique six-digit subject ID number by the site. The first three digits will correspond to the site number (assigned by the Sponsor) and the next three digits correspond to the sequential order in which the subject is screened for the study.

Phase 2b (Cohort 2)
All subjects who sign informed consent will be assigned a unique six-digit subject ID number by the IRT system. The first three digits correspond to the site number (assigned by the Sponsor), the next three digits correspond to the sequential order in which the subject is screened for the study.

The clinical site is responsible for maintaining a current log of subject ID number assignments and the kit number assigned to that subject. The subject ID number is required to be entered on all clinical study documentation (e.g., case report forms, labeling of clinical materials and sample containers, investigational product accountability logs, etc.).

4.6 Blinding

Phase 1 (Cohort 1) is not blinded.

Phase 2b (Cohort 2) is double-blinded, therefore neither the subjects nor the Investigator and clinical personnel will be aware of which investigational product (ARQ-252 0.1% cream, ARQ-252 0.3% cream or vehicle cream) an individual subject receives. The subjects, Investigator and clinical personnel will be aware of whether IP is to be applied QD (once daily) or BID (twice daily).

4.6.1 Breaking Treatment Codes

Phase 2b (Cohort 2)
In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IRT system for that subject. Refer to the current version of the IRT plan for details on unblinding. Treatment assignment should, however, remain blinded unless the assignment knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the CRF, along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Sponsor promptly in the event of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have the study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

4.7 Selection of Study Population

4.7.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Participants legally competent to sign and give informed consent.
2. Males and females 18 years of age and older (inclusive) at the time of consent.
3. Clinical diagnosis of chronic hand eczema, defined as hand eczema persistent for more than 3 months, or returned twice or more within the last 12 months (Diepgen 2009). Generally stable disease for 6 weeks. Both irritant and non-irritant etiologic forms are allowed. All morphologic types are allowed, e.g., vesicular/dyshidrotic, hyperkeratotic, nummular, and other types.
4. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline (Visit 2). (In Cohort 2, subjects with IGA of 'Mild' will be limited to 20% of total enrollment, and subjects with IGA of 'Severe' subjects will also be limited to 20% of total enrollment).
5. Chronic hand eczema involving at least 0.3% body surface area total (i.e., approximately a third of one handprint) lesions on both hands added together at Baseline (Visit 2).
6. Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method according to Contraception Requirements (Figure 1).
7. Females of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, or bilateral salpingectomy) according to Contraception Requirements (Figure 1).
8. Males, if engaging in sexual intercourse with a female who is pregnant or a female of childbearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks after the last investigational product administration.
9. Males must agree not to donate sperm from the first dose of investigational product until 4 weeks after the last investigational product administration.
10. Subjects in good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.
11. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

4.7.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from participation in this study:

1. Concurrent skin diseases on the hands which, in the opinion of the Investigator, could confound the study (e.g., tinnea manuum).
2. Active skin diseases not on the hands such as atopic dermatitis or psoriasis requiring medical treatment that could significantly affect hand eczema, in the Investigator's opinion.
3. Subjects with any presence or history of psoriasis.
4. History of a positive patch test with continued exposure to allergen. If, in the opinion of the Investigator, there is any suspected allergic hand eczema with continued exposure to allergen, subject must undergo diagnostic patch testing to determine if they meet entry criteria prior to Baseline (Visit 2).
5. Subjects who cannot discontinue systemic and/or topical therapies for the treatment of chronic hand eczema prior to Baseline (Visit 2) and during the study according to Excluded Medications and Treatments (Table 2), (i.e., immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids).
6. Psoralen ultraviolet A (PUVA) or ultraviolet B (UVB) therapy on the hands within 4 weeks prior to Baseline (Visit 2).
7. Cutaneously applied treatment with immunomodulators (e.g., phosphodiesterase-4 (PDE-4) inhibitors, pimecrolimus, tacrolimus), topical urea moisturizers, topical antibiotics, or low or mid potency topical corticosteroids on the hands or elsewhere within 1 week prior to Baseline (Visit 2). Cutaneously applied treatment with high potency topical corticosteroids on the hands or elsewhere within 2 weeks prior to Baseline (Visit 2).
8. Subjects that have significant active systemic or localized infection, including known actively infected eczema or have had any infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 2 weeks prior to Baseline (Visit 2).
9. Other cutaneously applied therapy on the hands (except for the use of subject's own non-urea and non-salicylic acid emollients) within 1 week prior to Baseline (Visit 2).
10. Subjects who are unwilling to refrain from using a tanning bed or other LEDs as well as outdoor tanning or excessive sun exposure for 4 weeks prior to Baseline (Visit 2) and during the study.
11. Subjects with a history of chronic alcohol or drug abuse within 6 months prior to Baseline (Visit 2).
12. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
13. Subjects that have received live vaccine therapy less than 4 weeks prior to Baseline (Visit 2), immunosuppressive drugs less than 4 weeks prior to Baseline (Visit 2), or have known infection with mycobacterium tuberculosis, hepatitis B or C, or HIV, or have a diagnosis of an immunodeficiency disorder.

14. Subject had a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study.
15. Known or suspected:
    - severe renal insufficiency or severe hepatic disorders
    - hypersensitivity to component(s) of the investigational product which include SHR0302, butylated hydroxytoluene (BHT), benzyl alcohol, dimethyl sulfoxide, cyclomethicone, dimethicone (350 cst), ST-Elastomer 10, water, propylene glycol, polyethylene glycol 200, Pemulen TR1, Carbopol 974P, ethylenediaminetetraacetic acid, trolamine and D-limonene.
16. Pregnant or lactating women or women planning to become pregnant during the study and / or within 28 days following the last dose of investigational product.
17. Subjects who cannot discontinue the use of strong systemic Cytochome P-450 3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin and carbamazepine for 2 weeks prior to Baseline (Visit 2) and during the study period.
18. Subjects who cannot discontinue the use of strong systemic Cytochome P-450 3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, fluconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to Baseline (Visit 2) and during the study period.
19. Subjects with any serious medical condition or clinically significant laboratory, ECG, vital signs or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator.

4.8 Removal of Subjects from Investigational Product

A subject may discontinue investigational product for any of the following reasons:

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, does not allow the subject to adhere to the requirements for investigational product as per the protocol.
- Adverse Events as described in Section 4.10. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Treatment must be discontinued immediately in the event of a female subject's pregnancy.
- Subject's decision to withdraw from investigational product.
- Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
- Subject's repeated failure to comply with protocol requirements or study related procedures.

4.9 Removal of Subjects from the Study

A subject may be removed from study participation for any of the following reasons:

- Subject death.
- Subject's decision to withdraw from study.
- Subject is lost to follow-up. A subject will be considered lost to follow-up after three phone and three email attempts and documentation of a certified letter sent to the subject's address.
- Termination of the study by the Sponsor, FDA, or other regulatory authorities.

4.10 Treatment Stopping Rules

If a subject has non-cutaneous adverse events of concern, clinically significant laboratory values or any condition that the Investigator determines could possibly be related to the investigational product, the Investigator should immediately contact the Medical Monitor to discuss if the subject should be discontinued from treatment with investigational product.

Treatment for any individual subject will be discontinued if the subject experiences:

- A serious adverse event (SAE) or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being.
- A treatment-emergent severe (Grade 3 or higher) laboratory abnormality (confirmed by repeat sample).
- A severe infection (Grade 3 or higher)
- An Ischemic or thromboembolic cardiovascular event (regardless of Grade)
- Any other adverse event that represents an unacceptable risk to the subject (e.g., Grade 3 or higher)

As noted above, study treatment must be discontinued immediately in the event of a female subject's pregnancy.

Treatment should be interrupted:

- If a subject develops an application site reaction with the clinical appearance of an 'irritation reaction', and with a severity of a Dermal Response Score of 5 (erythema, edema and papules) or greater on the scale of Berger and Bowman, treatment should be interrupted for up to one week and may then be resumed if the reaction has, in the opinion of the Investigator, adequately resolved.

Treatment should be discontinued:

- If the application site reaction reoccurs, treatment should be discontinued permanently, and the subject followed until the reaction resolves.

For cases of suspected allergic contact dermatitis, the Medical Monitor and Sponsor should be notified and there should be discussion about performing patch testing to further evaluate. Patch testing is encouraged in such cases.

Phase 2b (Cohort 2)
In the event of a medical emergency where unblinding is required to provide medical care to the subject, refer to the most current IRT plan and Breaking Treatment Codes (Section 4.6.1). Contact the Medical Monitor and the Sponsor promptly.

4.11 Study Restrictions

4.11.1 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 2 (Excluded Medications and Treatments).

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and entered into the CRFs. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in Table 2.

Table 2. Excluded Medications and Treatments

Excluded Medications and Treatments	Washout Period from Baseline (Visit 2)
Topical calcineurin inhibitors, PDE-4 inhibitors (Eucrisa®), topical urea-containing emollients, topical salicylic acid-containing emollients, topical antibiotics, topical low potency corticosteroids, topical mid potency corticosteroids	7 days
Topical high potency corticosteroids	14 days
Systemic antibiotics	14 days
Systemic non-biologic treatments for eczema (e.g., cyclosporine, azathioprine, corticosteroids, methotrexate) • Oral JAK inhibitors will be allowed if stopped for reasons other than safety concerns (28 day washout required)	28 days or 5 half-lives (whichever is longer)
Biologics including Dupixent®	3 months or 5 half-lives (whichever is longer)
Oral retinoids (alitretinoin/Toctino, acitretinin, isotretinoin)	3 months
Cell-depleting biologics such as rituximab	6 months

Excluded Medications and Treatments	Washout Period from Baseline (Visit 2)
UVB or PUVA phototherapy, tanning booths	28 days
Strong Cytochrome P-450 3A4 inhibitors and strong Cytochrome P-450 3A4 inducers	14 days
All investigational drugs	3 months (biologics); 1 month (oral); 2 weeks (topical) - or 5 half-lives (whichever is longer)

Note:

- Ear drop, eye drop and nasal corticosteroid preparations are allowed.
- Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for >28 days before Baseline (Visit 2) and are continued at the same dose throughout the study.
- Non-medicated emollients, moisturizers and sunscreens will be allowed as normally used by the subjects. These should not be applied to treatment sites 2 hours before or after investigational product application.
- There is no washout for sedating or nonsedating antihistamines. During the study, systemic treatment with sedating antihistamines is prohibited. During the study, systemic treatment with nonsedating antihistamines in a nonstable regimen is prohibited, while systemic treatment with sedating or nonsedating antihistamines in a stable regimen is allowed.
- Live vaccine therapy is not allowed less than 4 weeks prior to Baseline (Visit 2).

4.12 Treatment

4.12.1 Investigational Product Supplies, Packaging and Labeling

Phase 1 (Cohort 1)
ARQ-252 cream 0.3% will be in 12-gram tubes. The tubes will be labeled in an open-label manner. The tubes dispensed to a subject will be labeled with a unique number.

Phase 2b (Cohort 2)
ARQ-252 cream 0.1%, ARQ-252 cream 0.3% or vehicle formulation will be in 12-gram tubes. The tubes will be packaged in kits, containing 2 tubes of investigational product. The number of kits dispensed to a subject will be based on the dosing frequency, either BID (twice daily) or QD (once daily). The kits and tubes will be labeled with a unique number, in a blinded manner.

Phase 1 and 2b (Cohorts 1 and 2)
The Sponsor will supply sufficient quantities of the investigational product to each site to allow for completion of this study.

Records will be made of the receipt and dispensing of the investigational product supplied. At the conclusion of the study, any unused investigational product will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

Refer to the most current version of the IP Handling Plan for details on accountability, storage, and management of IP.

4.12.2 Treatment Administration

Initial treatment with the IP will occur on Day 1. At the Baseline visit the study staff will demonstrate to the subject how to apply IP using the first tube that is assigned to the subject at enrollment/randomization. Study site staff will demonstrate how two unit doses (two pea size amounts of IP will cover approximately 4% BSA, i.e., both hands entirely) are properly squeezed from the tube and applied as a thin film to cover both hands. IP will be applied to the front and back of both hands, interlacing fingers, rubbing in thoroughly but gently, until the cream has absorbed. The subject will then practice squeezing a similar amount and applying IP. The study staff will confirm that the subject's application technique is correct.

Subjects in Cohort 1 will be instructed to apply IP once daily (QD). Subjects in Cohort 2 will be instructed to apply IP either once daily (QD) or twice daily (BID), as determined at randomization.

IP tubes must be returned by subjects at each study visit, both empty and full, and will be weighed. Re-training will be conducted at subsequent visits as needed (i.e., if the returned tube weighs substantially different than the expected weight).

Subjects will be instructed to refrain from handwashing for 4 hours after IP application, if possible. Subjects may use hand sanitizer within 4 hours of IP application, if necessary. Hand washing and use of hand sanitizer within 4 hours of IP application will be recorded in the subjects' diary and CRF.

4.12.3 Treatment Compliance

Each IP tube will be weighed prior to dispensing at the Baseline visit and at each follow-up clinic visit according to the Schedule of Visits and Assessments (Section 1.3). When IP is applied in the clinic, the IP tube will be weighed before and after IP application. If the subject's actual use is substantially different than the expected use (see IP Handling Plan), the subject will be retrained on the investigational product application technique.

Subjects will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs, handwashing or use of hand sanitizer within 4 hours. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete CRFs. If a subject misses a dose, they should be instructed to return to the protocol investigational product administration schedule (i.e., if subject forgets a dose they should wait until the next planned application and apply as usual).

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the investigational product application period and does not miss more than 3 consecutive doses.

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied will be measured for reporting purposes.

If the diary shows less than 80% of expected use, the subject is using too little investigational product and retraining must be conducted and documented.

Compliance will be documented in source and in CRF.

5. STUDY PROCEDURES

5.1 Safety Assessments

The Schedule of Visits and Assessments (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety, efficacy, and PK of ARQ-252 cream 0.1%, ARQ-252 cream 0.3% and vehicle cream. Safety will be determined by evaluating physical examinations, 12-lead ECGs, vital signs/weight, clinical laboratory parameters, local tolerability assessments, and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3). If deemed necessary, additional safety assessments will be performed at the discretion of the Investigator.

5.1.1 Screening

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and the potential risks. A subject is considered a participant of the trial once the ICF is completely signed.

The following procedures/assessments will be performed at the Screening Visit (within 4 weeks after signing the informed consent):

- Review of medical and surgical history, including any history of allergies and/or contact dermatitis
- Review of childbearing potential (subject or partner of male subject) and contraceptive use (see Section 5.1.2)
- Collection of demographic data including sex, age, race, ethnicity
- Vital signs including temperature, heart rate, and blood pressure
- Chronic Hand Eczema assessments (BSA, IGA, HECSI).
- Limited physical examination of skin, lungs, and heart
- ECG

- Laboratory tests: hematology, chemistry, urinalysis, TSH, T4, serum pregnancy test (for female subjects of childbearing potential), FSH (if indicated to confirm post-menopausal status)
- Completion of WI-NRS and NRS Pain. Subjects in Cohort 2 will also complete the QOLHEQ.
- Collection of concomitant medications and adverse events

Medical history of chronic hand eczema will include the following information, which will be recorded in the CRF:

- Morphologic subtype of HE
- Whether the subject has ever been patch tested and if so, the patch test results and any positives (e.g., nickel).
- Distribution on hands (palmar vs dorsal vs interdigital vs pulpitis)

All screened subjects will receive a screening number at the time of informed consent. Subjects in Cohort 2 will be entered into the IRT system at the time of consent.

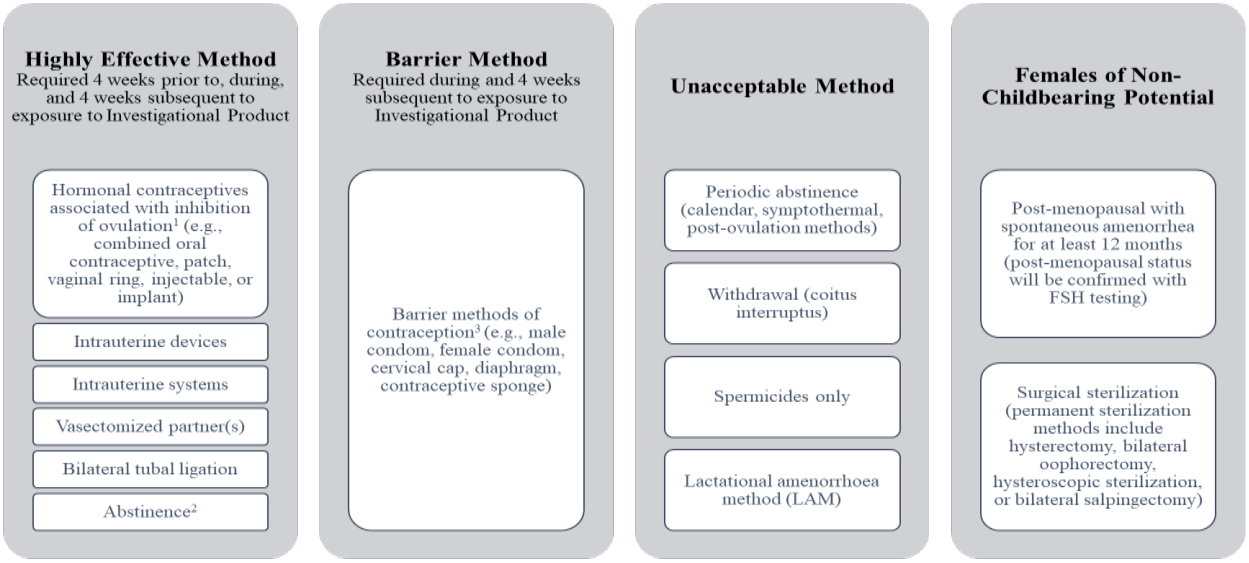
Subjects may be re-screened one time, the original assigned Subject ID screening number will be used for re-screening.

5.1.2 Contraception Requirements

Previous nonclinical research showed that the active ingredient in ARQ-252 can harm fetal development. Subjects engaging sexual intercourse that could lead to pregnancy must adhere to the following pregnancy testing and/or contraception requirements.

Female Subjects
Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method of contraception. The acceptable methods of contraception are listed below in the Figure 1.

Figure 1. Contraception Requirements for Female Subjects



[1]Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[3]Female condom and male condom should not be used together.

Male Subjects:
Males, if engaging in sexual intercourse with a female who is pregnant or a female of childbearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks after the last investigational product administration.

5.1.3 Physical Examination

Physical examinations will be performed according to the Schedule of Visits and Assessments (Section 1.3). The physical exam will be limited to skin, lungs and heart only.

5.1.4 Vital Signs, Height and Weight

Vital signs will be performed according to the Schedule of Visits and Assessments (Section 1.3). Weight, blood pressure, heart rate, and temperature will be collected in seated position after 5 mins. Subjects will be instructed to void prior to weight being taken and to remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones, wallet, key chains, etc.).

Height will be measured at Baseline (Day 1) only.

5.1.5 12-lead ECGs

12-lead ECGs will be performed according to the Schedule of Visits and Assessments (Section 1.3).

ECGs will be obtained on subjects after 5 minutes in the supine position. All ECG tracings and readouts will be reviewed by the Investigator and central reader at the ECG laboratory.

5.1.6 Laboratory Tests

All tests listed in Table 3 below will be performed according to the Schedule of Visits and Assessments (Section 1.3) unless otherwise noted. The collection of specimens will be in a non-fasting state (no food restrictions). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Table 3. Laboratory Tests

Hematology	**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count • Reticulocyte count[1]	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine • Creatine kinase
Urinalysis	**Additional Tests**
• pH • Specific gravity • Protein[2] • Glucose • Ketones • Bilirubin • Blood[2] • Nitrite[2] • Urobilinogen • Leukocyte esterase[2]	• Thyroid Stimulating Hormone T4 (TSH/T4) • Urine pregnancy test[3] (for females of childbearing potential only) • Serum pregnancy test (hCG)[4] • Follicle-stimulating Hormone (FSH) [5] • Pharmacokinetic (PK) assessments

[1] If red blood cell count, hemoglobin or hematocrit values are below the lower limit of normal, reticulocyte count will be performed

[2] If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

[3] Cohort 1: At Baseline, Day 8, Day 15 and Day 22 for FOCBP only. Cohort 2: At Baseline, Week 4, 8, 12 and 13 for FOCBP only.

[4] At screening only for FOCBP.

[5] If indicated to confirm post-menopausal status

5.1.7 Local Tolerability Assessment

The Investigator Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3). Irritation reactions are graded using the scale detailed in the following section (Berger 1982). **Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's chronic hand eczema.**

The Investigator assessments will be conducted by the Investigator prior to investigational product application in the clinic.

Dermal Response

0 = no evidence of irritation

1 = minimal erythema, barely perceptible

2 = definite erythema, readily visible; minimal edema or minimal papular response

3 = erythema and papules

4 = definite edema

5 = erythema, edema and papules

6 = vesicular eruption

7 = strong reaction spreading beyond application site

Other Effects

A = slight glazed appearance

B = marked glazing

C = glazing with peeling and cracking

D = glazing with fissures

E = film of dried serous exudates

F = small petechial erosions and/or scabs

G = no other effects

The Subject Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

This assessment will be administered by the site 10 to 15 minutes after investigational product application in the clinic.

Grade	Sensation Following Investigational Product Application
0 (none)	No sensation
1 (mild)	Slight warm, tingling sensation; not really bothersome
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort

5.1.8 Adverse Events

Adverse events (AEs) will be collected continuously during the study beginning at informed consent and assessed according to the Schedule of Visits and Assessment (Section 1.3).

Any treatment emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

For further details on Adverse Events please see Section 5.7.

5.2 Efficacy Evaluations

5.2.1 Investigator's Global Assessment (IGA)

Investigator's Global Assessment of chronic hand eczema will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The IGA is a static evaluation of qualitative overall chronic hand eczema severity. This global assessment scale is an ordinal scale with five severity grades (reported only in integers of 0 to 4). Each IGA Severity Score is defined by distinct and clinically relevant morphologic descriptions that minimizes inter-observer variability.

Every effort must be made for the same Evaluator to complete the IGA for the subject at every study visit.

IGA will be assessed at clinic visits prior to the subject applying Investigational Product and other physician assessments.

Investigator Global Assessment of Disease (IGA)

Score	Grade	Description
0	Clear	Absence of erythema and scaling, **AND** Absence of vesiculation, edema, and fissures. Note: Post-inflammatory pigmentary changes may be present.
1	Almost clear	Barely perceptible or faint erythema, **and/or** Slight flaking over limited areas, mostly fine scales, **AND** Absence of vesiculation, edema, or fissures
2	Mild	Barely perceptible or faint erythema, **and/or** Slight flaking over limited areas, mostly fine scales **AND** Scattered vesicles affecting up to 10% of hand, without erosion, **and/or** Dermal swelling over less than 10% of hands, **and/or** Cracked skin affecting a small area of the hand
3	Moderate	Either barely perceptible or faint erythema, or prominent redness, **and/or** Either slight flaking over limited areas, mostly fine scales, or flaking over widespread area(s), coarser scale **AND** Scattered or clustered vesicles affecting up to 30% of hand, without visible erosion or excoriation, **and/or** Definite dermal swelling over more than 10% of hand, **and/or** Cracked skin affecting multiple areas of the hand
4	Severe	Either prominent or deep intense red color, **and/or** Either flaking over widespread area(s), coarser scales, or desquamation covering over 30% of the hand, with coarse thick scales **AND** At least one of the following: High density of vesicles extending over large area(s), or with erosion or excoriation, **and/or** Dermal swelling with skin induration over widespread area(s), **and/or** One or more deep fissures and causing bleeding

Adapted from Ruzicka 2008.

5.2.2 Body Surface Area (BSA)

BSA Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The BSA affected by chronic hand eczema will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area (BSA). Lesions on both hands will be added together. Affected areas of the lateral aspects of the fingers and hands should be assigned to the palmar surface.

5.2.3 Worst Itch Numerical Rating Scale (WI-NRS)

Subjects will complete the WI-NRS pruritus assessment. WI-NRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Subjects will complete the WI-NRS pruritis assessment in the clinic during Screening and then daily at home from the Baseline/Day 1 visit until the last visit. Subjects will record their WI-NRS on a diary and will return the diary to the clinic at each visit. Sites will review WI-NRS entries and enter into the CRF.

The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. (Naegeli 2015). The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch").

ITCH NUMERIC RATING SCALE

Please rate your itching severity by circling the number that best describes your worst level of itching in the past 24 hours.

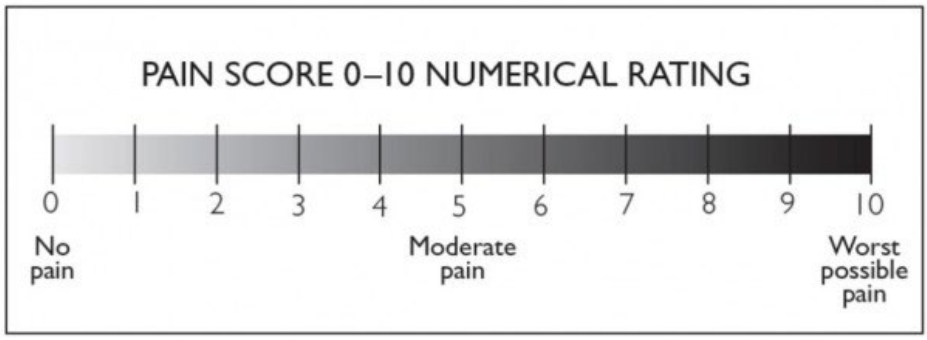
0	1	2	3	4	5	6	7	8	9	10
0 = No itch										10 = Worst itch imaginable

5.2.4 NRS-Pain Scale

The Numerical Rating Scale (NRS) for Pain will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Subjects will complete the NRS Pain assessment in the clinic during screening and then daily at home from the Baseline/Day 1 visit until the last visit. Subjects will record their NRS-Pain score on a diary and will return the diary to the clinic at each visit. Sites will review NRS-Pain entries and enter into the CRF.

The NRS-Pain Scale is the most widely used instrument for pain screening. Subjects will select the number between 0 and 10 that fits best to their worst pain intensity over the past 24 hours, where 0 represents 'no pain at all' and 10 'the worst pain possible'.



Source: https://www.physio-pedia.com/images/4/47/NRS_pain.jpg

5.2.5 HECSI

The Hand Eczema Severity Index (HECSI) will be performed according to the Schedule of Visits and Assessments (Section 1.3).

HECSI is an instrument used in clinical trials to rate the severity of 6 clinical signs of hand eczema and the extent of the lesions on each of 5 hand areas by use of standard scales. The total HECSI score is based on a 4-point severity scale ranging from 0 (none/absent) to 3 (severe) and a 5-point scale rating the affected area(s) ranging from 0 (0% affected area) to 4 (76% to 100% affected area).

Clinical Signs	**Fingertips**	**Fingers (except tips)**	**Palm of hands**	**Back of hands**	**Wrists**
Erythema (E)					
Infiltration/papulation (I)					
Vesicles (V)					
Fissures (F)					
Scaling (S)					
Oedema (O)					
SUM (E + I + V + F + S + O)					
Extent (Ex)					
Total HESCI Score =	**Sum x Ex +**	**Sum x Ex +**	**Sum x Ex +**	**Sum x Ex +**	**Sum x Ex +**

Total HECSI score (min 0; max 360). For each location (total of both hands) the affected area was given a score from 0 to 4: (0, 0%; 1, 1-25%; 2, 26-50%; 3, 51-75%; 4, 76-100%) for the extent of clinical symptoms. Finally the score given for the extent for each location was multiplied by the total sum of the intensity of each clinical feature (each contributing equally to the final score) and the total sum called the HESCI score was calculated, varying from 0 to a maximum severity score of 360 points.
Adapted from Held 2005.

5.2.6 Quality of Life in Hand Eczema Questionnaire

The Quality Of Life in Hand Eczema Questionnaire (QOLHEQ) will be performed according to the Schedule of Visits and Assessments (Section 1.3) in Phase 2b (Cohort 2). The QOLHEQ is an instrument to assess disease specific Health Related Quality of Life (HRQOL) in patients suffering from hand eczema (Appendix 1). The construct HRQOL includes all impairments or limiting conditions caused by the health state of an individual. The QOLHEQ is a disease specific instrument, thereby only assessing impairments caused by hand eczema. It consists out of 30 items which can be summarized according to four domains of HRQOL: Impairments because of (1) symptoms, (2) emotions, (3) limitations in functioning or (4) because of treatment and prevention.

5.2.7 Nail Dystrophy Assessment

Phase 2b (Cohort 2)
A Nail Dystrophy Assessment will be performed in Cohort 2 according to the Schedule of Visits and Assessments (Section 1.3) to identify any alteration of nail morphology. Assessment to include the following evaluations by the Investigator:

Baseline/Day 1:

- Does the subject have at least one nail with significant dystrophy extending to the cuticle? Yes/No
- If "Yes", record which nail has the worst dystrophy (indicating left or right)

Subsequent visits according to the Schedule of Visits and Assessments:

- For the identified fingernail with the worst dystrophy at Baseline/Day 1, is there normal appearing nail distal to the cuticle, Yes/No
- If "Yes", how many millimeters of normal appearing nail distal to the cuticle?

Sites participating in optional photography will obtain photos of nail with the worst dystrophy at Baseline/Day 1 and at subsequent visits according to the Schedule of Visits and Assessments (Section 1.3) and Section 5.3.2.

5.3 Other Evaluations

5.3.1 Pharmacokinetics Assessment

PK draws will be performed according to the Schedule of Visits and Assessments (Section 1.3) for all subjects at all sites.

Phase 1 (Cohort 1)

- Serial PK sampling will be performed on Day 1 (1, 2, 4, 6, and 24 hours post-dose administration), and at Day 15 (pre-dose and 1, 2, 4, 6, and 24 hours post-dose administration). For 24-hour timepoints, subjects return to the clinic on the following day

within 2 hours of the IP application time from the previous day for PK plasma sample collection. A pre-dose/trough PK sample will be taken at Day 8.

Phase 2b (Cohort 2):

- PK will be evaluated through trough/pre-dose sampling at Baseline, Day 29, and Day 85.

PK draws will be collected while the subject is having serum chemistries drawn at applicable visits. The draws will be pre-dose investigational product application in the clinic. Ensure investigational product is not applied in the area where PK will be drawn.

5.3.2 Medical Photography

Phase 2b (Cohort 2)
Photography will be performed at selected investigational sites using Canfield photography equipment according to the Schedule of Visits and Assessment (Section 1.3) in Phase 2b (Cohort 2). Photography will be optional. All efforts will be made to de-identify the subjects.

Sites participating in optional photography will obtain photos of nail with the worst dystrophy at Baseline/Day 1 and at subsequent visits according to the Schedule of Visits and Assessments (Section 1.3).

5.4 Final Study Visit – End of Study

Phase 1 (Cohort 1)
The approximate final study visit will occur at Week 3 (Day 22).

Phase 2b (Cohort 2):
The approximate final study visit will occur at Week 13 (Day 92).

For both Cohorts, the procedures performed during these visits are as described in the Schedule of Visits and Assessments (Section 1.3). A 3-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the subject and followed to resolution (as necessary).

5.5 Early Termination Visit

If a subject is withdrawn or wishes to exit the study prior to the final study visit, an early termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the final study visit for either Cohort 1 or Cohort 2 (Section 1.3).

5.6 Unscheduled Visit

Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted in the judgement of the Investigator.

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs
- BSA, IGA, HESCI

5.7 Adverse Events

5.7.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs will be collected following informed consent of the subject through subject study completion.

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of investigational product through study completion.

Application site reactions will be considered adverse events if they require intervention, suspension or discontinuation of investigational product.

5.7.2 Serious Adverse Event Definition

The definitions and reporting requirements of Health Canada/the Food and Drug Administration (FDA)/ Therapeutic Goods Administration (TGA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

All SAEs will be reported to the Sponsor (or delegate) via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed IP-related. All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.: The ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the IRB/ERB's policies and procedures. Refer to the Safety Reporting Instructions for SAE reporting.

An SAE is any AE that in the view of either the PI or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and

may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE that in the view of the PI or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the history documentation for the individual subject.
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

Unexpected is defined as an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current study documentation.

If a SAE occurs to a subject on this study, contact the Medical Monitor within one business day of knowledge of event.

5.7.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information. A serious event or reaction is not defined as a SUSAR when: ‘it is serious but expected’ or it does not fit the definition of an SAE, whether expected or not.

5.7.4 Safety Review with Subject

At each follow-up visit, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' Additionally, the study staff will review subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to one month after end of treatment until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

5.7.5 Adverse Event Reporting

AEs will be collected following informed consent of the subject through subject study completion.

The Investigator will review each event and assess its relationship to investigational product treatment (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE (Version 5.0) toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE to the investigational product will be assessed using the following definitions:

Unrelated	• The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. • Definitely not related to drug. • Temporal sequence of AE onset relative to administration of drug not reasonable. • Another obvious cause of an AE.
Unlikely	• Time sequence is unreasonable. • There is another more likely cause for an AE.
Possibly	• Corresponds to what is known about the drug. • Time sequence is reasonable. • Could have been due to another equally, likely cause.
Probably	• Is a known effect of the drug. • Time sequence from taking drug is reasonable. • Ceases on stopping the drug. • Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Likely	• Is a known effect of the drug (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB). • Time sequence from taking drug is reasonable. • Event stops upon stopping drug, event returns upon restarting drug.

The following CTCAE toxicity grading scale 5-point severity scale definitions for rating maximum severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.** Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Note: A semi-colon indicates 'or' within the description of the grade.
*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs will be coded using the most current MedDRA® version available at the start of the study (e.g., 21.0 or higher).

5.8 Reporting Pregnancy

During the study, all subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, Investigational Product must be discontinued immediately, the subject should be referred to an obstetrician experienced in reproductive toxicity for evaluation and counseling, and the subject should be followed until conclusion of the pregnancy. Subject may be required to sign a separate informed consent form to obtain pregnancy follow-up information, per local requirements.

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report and submitting to the Medical Monitor within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. Any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality. Any infant death that occurs after the 30 day reporting period that the Investigator suspects is related to Investigational Product must also be reported as an SAE.

Partner pregnancies of a male subject will be reported.

6. DATA ANALYSIS

Data will be handled and processed according to the Contract Research Organization's Standard Operating Procedures, which are written based on the principles of GCP.

6.1 Statistical Methods

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked and unblinded. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

All statistical processing will be performed using SAS® (Version 9.4) unless otherwise stated.

Descriptive statistics will be used to provide an overview of the safety, efficacy, and pharmacokinetic results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

Missing efficacy data for IGA will be imputed using multiple imputation.

The primary statistical comparisons and secondary endpoints will be made at the 0.10 significance level and will not be adjusted for multiple comparisons.

6.1.1 Determination of Sample Size

Cohort 1 will include approximately 6 evaluable subjects, which is deemed adequate for the purpose of evaluating safety and PK prior to Cohort 2.

There are approximately 215 subjects planned for Cohort 2. Approximately 61 subjects will receive ARQ-252 cream 0.3% QD, approximately 61 subjects will receive ARQ-252 cream 0.3% BID, approximately 31 subjects will receive ARQ-252 cream 0.1% QD, approximately 31 subjects will receive matching vehicle cream QD, and approximately 31 subjects will receive vehicle cream BID. The randomization scheme will be 2:2:1:1:1 between these 5 treatment groups, stratified by study site and IGA at Baseline.

The primary statistical comparisons will be to assess the ARQ-252 cream 0.3% group BID group versus the vehicle BID group, to assess the ARQ-252 cream 0.3% QC group versus the vehicle QD group, and to assess the ARQ-252 cream 0.1% QD group versus the vehicle QD group. A sample size of 55 per active arm and 28 per vehicle arm will provide approximately 85% power at the 2-sided 10% significance level to detect a difference in the rate of subjects attaining an IGA score of clear or almost clear (for each ARQ-252-treated group versus vehicle group within the same daily dosing frequency), assuming an active treatment response rate of 45% and a vehicle response rate of 15%. This is based on a 2-group X^2 test of equal proportions (without continuity correction). With a 10% dropout rate, the sample size for the study would be increased to 61 subjects per active arm and 31 subjects per vehicle arm (215 subjects total).

The primary statistical comparisons and evaluations of secondary endpoints will not be adjusted for multiplicity.

6.1.2 Subjects to Analyze

Five analysis populations will be defined:

- The Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication. This population will be used for all safety analyses and will be defined separately for each Cohort.
- The Intent-to-Treat will include all subjects randomized to Cohort 2. This population will be the primary analysis for the analysis of efficacy endpoints.
- The Per-Protocol Population will include all subjects in the safety population, who were at least 80% compliant with study medication application, and showed no important deviations from the study protocol that would affect the interpretation of efficacy. This population will be used as a sensitivity analysis of primary and secondary efficacy endpoints.
- The Pruritis population is a subset of the ITT population and include subjects with WI-NRS score ≥ 4 at Baseline. This population will be used for the analysis of WI-NRS.
- The PK population will include all subjects receiving the active drug with sufficient plasma concentrations of SHR0302 to define a profile, as determined by the pharmacokineticist.

6.1.3 Interim Analysis

No interim efficacy analyses are planned. Safety data will be reviewed on an ongoing basis.

6.1.4 Background and Demographic Characteristics

Demographics, baseline disease characteristics, baseline height, weight, and BSA will be summarized descriptively for all enrolled (Cohort 1) and randomized (Cohort 2) subjects.

6.1.5 Study Disposition

The number of subjects randomized, receiving IP, completing study, and withdrawing prematurely (with reason for withdrawal) will be summarized by cohort and treatment group.

6.1.6 Protocol Deviations and Eligibility Deviations

The number of subjects with important protocol deviations and/or eligibility deviations will be summarized by category and by treatment group.

6.1.7 Investigational Product Compliance

The number of IP applications by each subject based on diary data will be summarized using descriptive statistics. The amount of IP used by each subject based on product weight will be summarized by treatment using summary statistics (mean, SD, median, minimum, and maximum), and categorically. IP compliance will be calculated based on number of applications divided by the expected number (amount) of IP for each subject. Compliance will be summarized descriptively by cohort and treatment group.

6.2 Efficacy Evaluation

6.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the rate of subjects achieving an IGA score of 'clear' or 'almost clear' at Week 12.

The primary statistical comparisons will be to assess the ARQ-252 cream 0.3% group BID group versus the vehicle BID group, to assess the ARQ-252 cream 0.3% QD group versus the vehicle QD group, and to assess the ARQ-252 cream 0.1% QD group versus the vehicle QD group.

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel test stratified by IGA at Baseline and study site. Statistical significance will be concluded at the 2-sided 10% significance level for each of the primary comparisons. Missing scores will be imputed using multiple imputation.

6.2.2 Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- The rate of achievement of IGA of 'clear' or 'almost clear' PLUS at least a 2-point improvement from Baseline at Weeks 2, 4, 8 and 12
- The rate of achievement of at least a 2-point improvement from baseline at Weeks 2, 4, 8 and 12
- The rate of achievement of IGA of 'clear' or 'almost clear' at Weeks 2, 4, and 8
- Time to IGA of 'clear' or 'almost clear'
- Change in IGA score at Weeks 2, 4, 8, and 12 as compared to Baseline
- Change in WI-NRS pruritus score at Weeks 2, 4, 8, and 12 as compared to Baseline
- The rate of achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score at Weeks 2, 4, 8, and 12, in subjects with Baseline WI-NRS pruritus score of at least 4
- Time to the first achievement of ≥4-point reduction from Baseline in WI-NRS pruritus score in subjects with Baseline WI-NRS pruritus score of at least 4
- Percent change in HECSI (Hand Eczema Severity Index) score at Weeks 2, 4, 8, and 12 compared to Baseline

- Change in Pain NRS score from Baseline to Weeks, 2, 4, 8, and 12
- The rate of achievement of ≥4-point reduction from Baseline in Pain NRS score at 2 weeks, 4 weeks, 8 weeks, and 12 weeks in subjects with Baseline Pain NRS score of at least 4
- Time to the first achievement of ≥4-point reduction from Baseline in Pain NRS score in subjects with Baseline Pain NRS score of at least 4
- Change from Baseline in overall Quality of Life in Hand Eczema Questionnaire (QOLHEQ) score at each visit.
- Percent BSA affected by disease and % change from baseline in BSA affected by disease at baseline, 2 weeks, 4 weeks, 8 weeks, and 12 weeks.

6.2.3 Exploratory Endpoints

- Change from Baseline in Nail Dystrophy at each visit (Cohort 2 only)

The binary secondary endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by Baseline IGA and study site as with the primary endpoint. The continuous secondary endpoints will be analyzed using an analysis of covariance stratified by Baseline IGA and study site and Baseline values of the endpoint as independent variables. Statistical comparison between the active treatment arm and vehicle arm will be facilitated by using contrasts. Analyses may also include pooling the active treatment groups together for comparison against the vehicle treatment groups; specifications for these analyses will be included in the SAP.

6.3 Safety Analysis

Descriptive statistics will be calculated for safety data and presented by visit and treatment group for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Summaries of local tolerability will be presented by visit and treatment group.

6.3.1 Adverse Events

All treatment-emergent AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. Treatment-emergent AEs are those AEs with an onset on or after the date of study treatment. All treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting treatment-emergent AEs, system organ class, preferred term, severity, relationship, and seriousness. Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by treatment group, severity, and relationship to study treatment. For AEs, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding IP, corrective treatment, outcome, and IP relatedness. The event onset will also be shown relative (in number of days) to date of first application.

In addition, a listing of subjects who prematurely discontinue from the IP due to adverse events will also be provided.

6.3.2 Local Tolerance Assessment

For the Investigator's and Subject's assessment, the numeric application site reaction scores will be summarized individually by using number and percentage of subjects by visit, as well as mean/median scores.

6.3.3 Medical History and Physical Examinations

Clinically significant changes observed during physical examination will be captured as adverse events and included in AE tabulations.

6.3.4 Clinical Laboratory Results and Vital Signs

All clinical laboratory results and ECG measurements and their change from Baseline (pre-dose), will be summarized descriptively by parameter, along with time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

6.3.5 Prior and Concomitant Medications

Prior and concomitant medication information for all enrolled/randomized subjects will be presented in electronic datasets. Summary tables will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and product.

6.4 Pharmacokinetic Analysis

Plasma drug concentrations at pre-dose will be summarized using descriptive statistics.

A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

A detailed description of the PK analysis will be presented in the SAP.

7. STUDY ADMINISTRATION

7.1 Ethics

7.1.1 Ethics Review Board

Before enrollment of subjects into the study, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC, as required by FDA (21 CFR § 56), Health Canada, ICH GCP regulations and other local/regional regulatory requirements. A letter documenting the IRB or IEC approval must be received by the Sponsor (or delegate) before the initiation of the study

at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA, Health Canada, local and regional regulations and ICH GCP guidelines.

The Investigator, the Sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, SUSARs, or any other information that may affect the safe use of the investigational products during the study, per the IRB or IEC local requirements, and in compliance with FDA and Health Canada regulations and ICH GCP guidelines.

7.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, the principles of the Tri-Council Policy Statement (TCPS), the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 (R2), Nov 2016) and the applicable regulations of the country(ies) in which the trial is conducted.

7.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date a current version of the IRB/EC approved ICF summarizing the discussion prior to enrollment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a signed copy of their ICF.

7.2 Study Completion and Termination

7.2.1 Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the Sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

7.2.2 Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed. The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further IP development

7.3 Study Monitoring

Prior to the initiation of the clinical investigation, Sponsor representatives or designees will visit the clinical site where the investigation is to be conducted. Sponsor representatives shall ensure that the Investigator understands the investigational status of the investigational product, all requirements of the investigation to be undertaken, and all of his/her responsibilities as an Investigator. Sponsor representatives will also visit the clinical site at appropriate intervals as required to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the CRFs. The Study Director or designees shall be available for consultation with the Investigator and serve as liaisons between the clinical site and the Sponsor.

The Sponsor or authorized designees may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and investigational product dispensation logs for the subjects in this clinical investigation. The Investigator must permit access to such records. The Investigator must obtain, as part of informed consent, permission for an authorized representative of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying subjects.

7.4 Data Quality Assurance

In order to ensure the collection of accurate, consistent, complete, and reliable data during this clinical study, Sponsor representatives or designees may conduct audits of participating clinical study sites at appropriate intervals throughout the study. The results of these periodic clinical study site audits may be subject to review by independent auditors at completion of the clinical investigation.

The Clinical Study Report will undergo QC review by the Clinical Research Organization's Quality Assurance (QA) department.

All clinical data will undergo a quality control check prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

7.5 Data Handling and Record Keeping

During the clinical study, the Investigator will maintain adequate records, including medical records, records detailing the progress of the study for each subject, laboratory reports, signed informed consent forms, investigational product disposition records, correspondence with the

ERB/IRB and Study Monitor/Sponsor, AE reports, and information regarding subject discontinuation and completion of the clinical investigation.

All required study data will be recorded on CRFs. Any change of data will be recorded on the audit trail and a reason for the change will be entered.

The Principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

7.6 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

7.7 Confidentiality and Privacy

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as date of birth) will be recorded on any form or biological sample submitted to the Sponsor.

The Investigator agrees that all information received from Arcutis Biotherapeutics, Inc., including but not limited to the Investigator's Brochure, this protocol, CRF/eCRF, the IP, and any other study information, remain the sole and exclusive property of Arcutis Biotherapeutics, Inc. during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Arcutis Biotherapeutics, Inc. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

7.8 Conflict of Interest

All study investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics, Inc., or proprietary interests in the investigational product under study. This documentation must be provided prior to the Investigator's participation in the study. All investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

7.9 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

7.10 Publication Policy

The Sponsor is supportive of publishing clinical trial findings. Any form of publication that is derived from this study must be submitted to Arcutis Biotherapeutics, Inc. for review and approval. The process of coordinating publication efforts is detailed in the Clinical Trial Agreement.

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APPENDICES

Appendix 1. Quality of Life in Hand Eczema Questionnaire (QOLHEQ)

Health Questionnaire
for hand eczema patients

Please indicate how often you were bothered by the following situations during the last seven days:

I have been bothered by the skin condition of my hands...	never	rarely	sometimes	often	all the time
... being **painful.**	☐	☐	☐	☐	☐
... **restricting/impairing me in my job.**	☐	☐	☐	☐	☐
... **restricting/impairing me in doing everyday home duties.**	☐	☐	☐	☐	☐
... because **I have to wear gloves.**	☐	☐	☐	☐	☐
... making me feel **frustrated.**	☐	☐	☐	☐	☐
... **itching.**	☐	☐	☐	☐	☐
... because **treatment is time consuming.**	☐	☐	☐	☐	☐
... making me feel **annoyed.**	☐	☐	☐	☐	☐
... causing **loss of sleep.**	☐	☐	☐	☐	☐
... making me feel **anxious about the future.**	☐	☐	☐	☐	☐

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Health Questionnaire

for hand eczema patients

Please refer to the last 7 days and to the skin of your hands only!

I have been bothered by the skin condition of my hands...	never	rarely	sometimes	often	all the time
... **fissuring.**	☐	☐	☐	☐	☐
... **restricting/impairing me in my leisure time activities** (e.g. sports, , hobbies)	☐	☐	☐	☐	☐
... **because I have to use creams.**	☐	☐	☐	☐	☐
... causing **problems washing myself.**	☐	☐	☐	☐	☐
... causing **problems dressing myself.**	☐	☐	☐	☐	☐
... making me feel **I have to hide my hands.**	☐	☐	☐	☐	☐
... **because it leads to me avoiding contact with other people.**	☐	☐	☐	☐	☐
... **because I have to visit a physician.**	☐	☐	☐	☐	☐
... making me feel **sad / depressed.**	☐	☐	☐	☐	☐
... **because of redness**	☐	☐	☐	☐	☐

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Health Questionnaire

for hand eczema patients

Please refer to the last 7 days and to the skin of your hands only!

I have been bothered by the skin condition of my hands...	never	rarely	sometimes	often	all the time
... making me feel irritated.	☐	☐	☐	☐	☐
... because I have to avoid contact with certain things.	☐	☐	☐	☐	☐
... bleeding.	☐	☐	☐	☐	☐
... because of worrying about side effects of treatment.	☐	☐	☐	☐	☐
... affecting my family life and friendships.	☐	☐	☐	☐	☐
... because of the treatment costs I have to cover myself.	☐	☐	☐	☐	☐
... making me feel embarrassed.	☐	☐	☐	☐	☐
... because of dryness.	☐	☐	☐	☐	☐
... when touching my family or partner.	☐	☐	☐	☐	☐
... making me feel nervous.	☐	☐	☐	☐	☐

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