TITLE: A Pilot Study of Rimegepant in Moderate Plaque-type Psoriasis

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Participating Sites: Weill Cornell Medicine, Sadick Dermatology

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Statement of Compliance

(1) [The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM, unless disclosure on ClinicalTrials.gov is federally required.

Richard D. Granstein, M.D. – PI Date

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CGRP	Calcitonin Gene-related Peptide
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ODT	Orally Disintegrating Tablet
PASI	Psoriasis Area and Severity Index
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	A Pilot Study of Rimegepant in Moderate Plaque-type Psoriasis
Short Title:	Rimegepant for psoriasis
Clinical Phase:	2
Principal Investigator:	Richard D. Granstein, MD
Study Description:	This proposal is for a double-blind, placebo-controlled pilot study examining the use of an orally administered small molecule competitive inhibitor of the calcitonin gene-related peptide (CGRP) receptor for the treatment of moderately severe plaque-type psoriasis. We hypothesize that interruption of CGRP signaling will prove beneficial in psoriasis.
Sample Size:	N=15 for each of 2 cohorts.
Enrollment:	The study will enroll 30 subjects and we anticipate screening up to 110 subjects.
Study Population:	Thirty adults with mild to moderate plaque-type psoriasis who are otherwise generally healthy. Subjects for the study will be 18 to 75 years of age.
Enrollment Period:	The enrollment period will be approximately 3 years 1 month.
Study Design:	This is a randomized, double-blind, placebo-controlled study of rimegepant 75 mg dosed every other day for the treatment of mild to moderate psoriasis. Subjects must have at 3% body surface area involvement before entry into the study. Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment (IGA) scores will be calculated and subjects will each complete the Dermatology Life Quality Index (DLQI) instrument as well an itch assessments. These assessments will be performed at baseline and every 2 weeks in follow-up. Areas of psoriasis in each subject will be photographed at baseline. At the subject's option, two very similar appearing lesions identified for biopsy of one on day 1 and the other at the end of week 16. Patients will also repeat the DLQI at each visit. Subjects will also be photographed at each visit. Subjects willdiscontinue medications after the end of week 16. Subjects will be evaluated again at weeks 18 and 20. Subjects who complete the 20-week protocol will have the option of entering a 3-month, open-label extension of the study in which they will take 75 mg of rimegepant every other day for an additional 12 weeks. Eligible subjects have 2 weeks past visit 11 to enroll in the extension. For those rolling over before visit 11, visits 11 and 12 can be combined. They will have the same assessments as in the previous portion of the study every 4

weeks including an EKG. The inclusion and exclusion criteria remain the same.

Description of Sites: This will be a multi-site study taking place at Weill Cornell Medicine/New York-Presbyterian Hospital and Sadick Dermatology

Study Duration: The projected end-date for completion of this study is approximately 47 months from initiation.

Participant Duration: Each individual participant will be in the study for approximately 20 weeks. If participating in optional extension, they will be in the study for an additional 12 weeks for a total of up to 32 weeks.

Study Agent/Device Name

Intervention Description: Rimegepant 75 mg (or placebo) taken orally every other day for 16 weeks. If a subject enters the extension phase, that subject will take rimegepant 75 mg every other day for an additional 12 weeks.

Primary Objective:

- To determine whether rimegepant, an orally available competitive inhibitor of the CGRP receptor, results in improvement in psoriasis compared to placebo as assessed by the PASI instrument.

Secondary Objectives:

- To determine if the degree of improvement in subjects given rimegepant is at least 50% compared to the placebo group as assessed by the PASI instrument.
- To determine whether rimegepant significantly improves psoriasis compared to placebo as assessed by the Investigator's Global Assessment (IGA) instrument.
- To determine whether rimegepant significantly improves quality of life as assessed by the Dermatology Quality of Life Index (DQLI) as compared to placebo for subjects with psoriasis.
- To determine whether rimegepant significantly improves the degree of itching (itch score) for patients with psoriasis as compared to placebo.

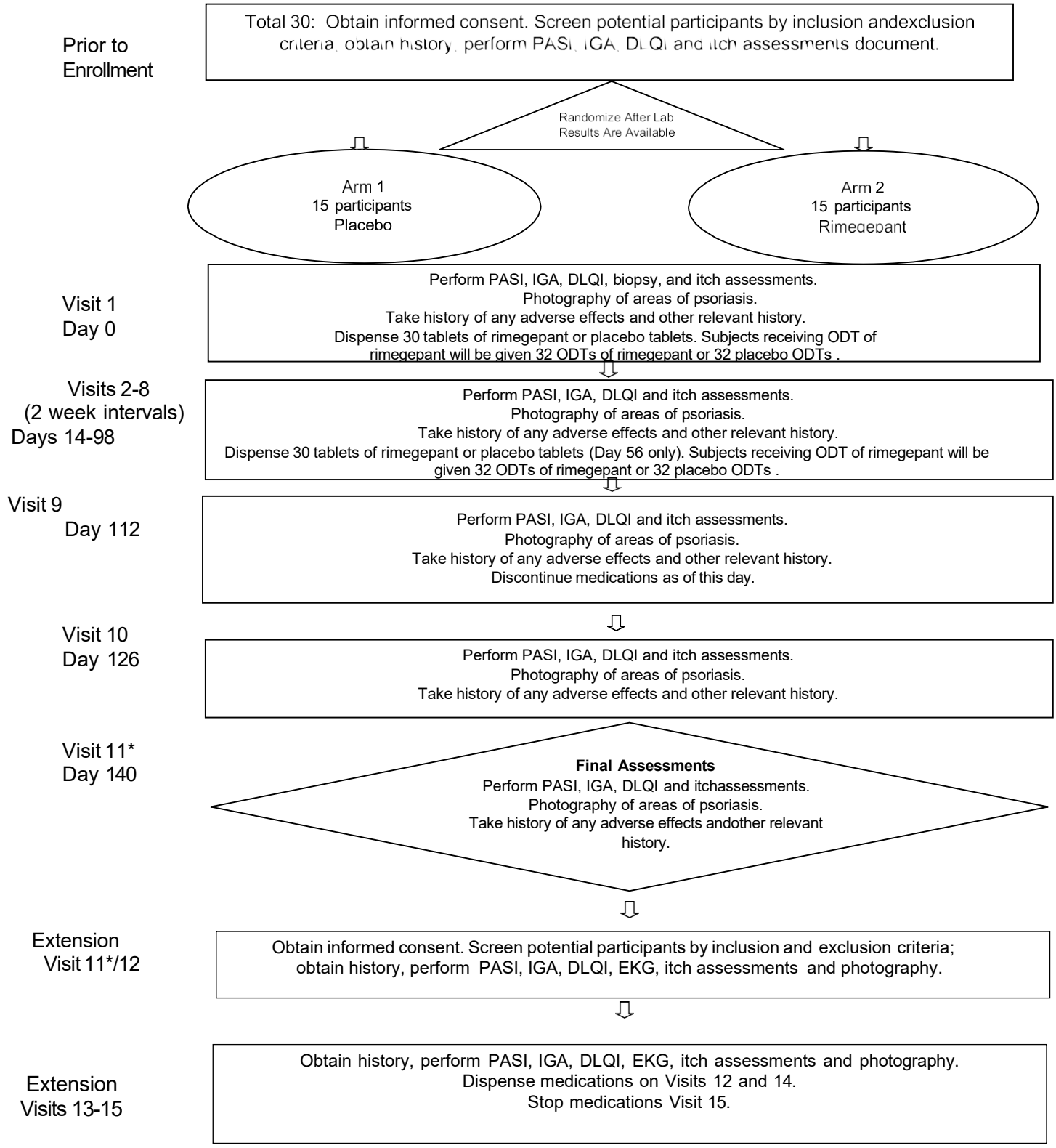
Primary Endpoints:

1. PASI instrument score
   Assessments will be made at baseline and every 2 weeks for 20 weeks.

Secondary Endpoints:

1. Fifty percent improvement in PASI instrument.
2. IGA instrument score.
3. DLQI instrument score.
4. Itch Score.

1.1 Schema


Prior to Enrollment
Total 30: Obtain informed consent. Screen potential participants by inclusion andexclusion criteria, obtain history, perform PASI, IGA, DLQI and itch assessments document.
Randomize After Lab Results Are Available
Arm 1
15 participants
Placebo
Arm 2
15 participants
Rimegepant
Visit 1
Day 0
Perform PASI, IGA, DLQI, biopsy, and itch assessments.
Photography of areas of psoriasis.
Take history of any adverse effects and other relevant history.
Dispense 30 tablets of rimegepant or placebo tablets. Subjects receiving ODT of rimegepant will be given 32 ODTs of rimegepant or 32 placebo ODTs .
Visits 2-8
(2 week intervals)
Days 14-98
Perform PASI, IGA, DLQI and itch assessments.
Photography of areas of psoriasis.
Take history of any adverse effects and other relevant history.
Dispense 30 tablets of rimegepant or placebo tablets (Day 56 only). Subjects receiving ODT of rimegepant will be given 32 ODTs of rimegepant or 32 placebo ODTs .
Visit 9
Day 112
Perform PASI, IGA, DLQI and itch assessments.
Photography of areas of psoriasis.
Take history of any adverse effects and other relevant history.
Discontinue medications as of this day.
Visit 10
Day 126
Perform PASI, IGA, DLQI and itch assessments.
Photography of areas of psoriasis.
Take history of any adverse effects and other relevant history.
Visit 11*
Day 140
Final Assessments
Perform PASI, IGA, DLQI and itchassessments.
Photography of areas of psoriasis.
Take history of any adverse effects andother relevant history.
Extension
Visit 11*/12
Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, perform PASI, IGA, DLQI, EKG, itch assessments and photography.
Extension
Visits 13-15
Obtain history, perform PASI, IGA, DLQI, EKG, itch assessments and photography.
Dispense medications on Visits 12 and 14.
Stop medications Visit 15.

1.2 Study Objectives and End Points

1.2.1 Primary Objectives

To determine whether rimegepant, an orally available competitive inhibitor of the CGRP receptor, results in improvement in psoriasis compared to placebo as assessed by the PASI instrument.

1.2.2 Secondary Objectives

To determine whether treatment of psoriasis with rimegepant significantly improves patient's quality of life as assessed by the Dermatology Quality of Life Index (DQLI), itch score, and IGA instrument, as well as by a 50% improvement according to the PASI instrument.

1.2.3 Exploratory Objectives

Explore the pattern of PASI score over time during treatment.

Describe changes in circulating $CD4^+$ $IL\text{-}17^+$ T cells during treatment with rimegepant or placebo.

Describe histologic changes in psoriasis lesions during treatment with rimegepant or placebo.

1.2.4 Primary Endpoints

1. PASI instrument score.

Assessments will be made at baseline and every 2 weeks for 20 weeks.

1.2.5 Secondary Endpoints

1. To determine if the degree of improvement in subjects given rimegepant is at least 50% compared to the placebo group as assessed by the PASI instrument.

2. To determine whether rimegepant significantly improves psoriasis compared to placebo as assessed by the Investigator's Global Assessment (IGA) instrument.

3. To determine whether treatment of psoriasis with rimegepant significantly improves patient's quality of life as assessed by the Dermatology Quality of Life Index (DQLI). The DQLI instrument will be administered at baseline and every 2 weeks for 20 weeks.

4. To determine whether rimegepant significantly improves the degree of itching (itch score) for patients with psoriasis as compared to placebo.

2. Background

2.1 Disease

Psoriasis is a common inflammatory skin disorder characterized by erythematous, scaly lesions that may occur anywhere but have a predilection for the scalp, extensor surfaces of the extremities, especially the elbows and knees, and the anogenital area (1). Psoriasis can be considered a systemic inflammatory disorder and part of the metabolic syndrome. It is frequently associated with a form of arthritis, known as psoriatic arthritis (2). It is associated, especially when severe, with cardiovascular disease, non-alcoholic fatty liver disease, inflammatory bowel disease, depression and lymphomas (2). Psoriasis affects approximately 2-3% of the population. Mild and limited psoriasis can be treated with a variety of topical agents including corticosteroids, calcipotriene, topical retinoids, crisaborole, amongst others (3-5). When severe, treatment is primarily with immunosuppressive agents including methotrexate, cyclosporine, 6-thioguanine and, more recently, a number of biological agents that block tumor necrosis alpha, interleukin-23, interleukin-17, the JAK-STAT signaling system, and phosphodiesterase inhibitors, or phototherapy (broad-band or narrow-band UVB radiation; psoralen plus UVA radiation), amongst others (3-5). All of these systemic medications and phototherapy have undesirable side effects caused by immunosuppression, gastrointestinal effects or other unwanted side effects. Thus, a need exists for safer effective systemic therapies.

2.2 Investigational Agent/Device, or Surgical Treatment/Method

PK/Clin Pharm

This study is testing the impact of rimegepant in the setting of psoriasis. Rimegepant is a small molecule antagonist of the CGRP receptors, thus limiting CGRP signaling. Rimegepant is approved for acute migraine. After administration of the 75 mg tablet, time to maximum plasma concentration (T_{max}) occurs at a median of 1.9 h. The two clinical formulations of rimegepant, the tablet and oral disintegrating tablet (ODT), are bioequivalent. The absolute oral bioavailability of rimegepant in the fasted state is approximately 64%. The effects of a high-fat meal on the tablet formulation showed that overall, a high-fat meal decreased the mean AUC and C_{max} of rimegepant by 30% and 33% , respectively, and delayed the T_{max} by approximately one hour. Based on the weight of evidence from three positive Phase 3 studies in migraine conducted without food restrictions, rimegepant 75 mg, administered as a tablet or ODT, may be administered without regard to food.

The clinical dose of rimegepant is 75 mg. Rimegepant exposures increased over the single dose range of 25 mg to 900 mg. Steady state is achieved by Day 2 following once daily dosing with no meaningful accumulation. Rimegepant 75 mg has low to moderate PK variability, with coefficient of variation (CV%) characterized as C_{max} = 40% and $AUC_{0\text{-}inf}$ = 30% for the tablet. Based on population PK analysis, the elimination half-life in normal healthy subjects is 11 hours.

The steady state volume of distribution averages approximately 120.4 L. Rimegepant is approximately 96% bound to human plasma proteins.

The primary route of elimination is through the feces. Rimegepant is the primary circulating component in plasma, with 88% to 92% unchanged parent present throughout the first 4 hours. Over longer periods of time, unchanged rimegepant represents approximately 77% of the total administered dose with only low quantifiable levels of circulating metabolites of rimegepant. CYP3A4 is the primary metabolizing enzyme.

2.3 Rationale

Considerable evidence in both humans with psoriasis and animal models of psoriatic dermatitis indicate that CGRP may play a key role in the pathophysiology of this disease. In human psoriasis, denervation, administration of local anesthetics or administration of botulinus toxin to the site of skin bearing psoriasis causes improvement or resolution of the disease at those sites demonstrating the importance of innervation for expression of the disease (6-9). In two mouse models of psoriatic dermatitis, innervation is also necessary for expression of the rash (10,11); in one mice are engineered to express the angiopoietin receptor Tie-2 (10) and in the other imiquimod is applied to the skin of mice of certain strains (11). In each, a psoriasiform dermatitis results. In humans, plasma CGRP is elevated in psoriasis patients compared to controls (12), an increased CGRP content of skin is noted in psoriatic lesions (13) and CGRP can be detected on the surface of endothelial cells in lesional skin (13). In the Tie-2 model of psoriasiform dermatitis, systemic administration of CGRP can retard the loss of the rash by denervation of the skin (6). In the imiquimod model of psoriasiform dermatitis, nerves release a factor, likely CGRP, that is key for development of the rash (14,15). Recent work from our laboratory has shown that CGRP treatment of endothelial cells endows them with the capacity, acting as bystanders, to bias the outcome of antigen presentation away from the Th1 pole towards Th17-type immunity (16). This may be relevant to psoriasis as psoriasis is an IL-17/Th17 cell mediated disorder. For all of these reasons, a trial of an agent that interrupts CGRP-signaling in psoriasis is warranted. In this regard, rimegepant is approved for use in humans for the treatment of migraine and is safe and well-tolerated (17). For all of these reasons, a trial of an agent that interrupts CGRP signaling in psoriasis is warranted.

2.4 Risk/Benefit Assessment

2.4.1 Known Potential Risks

From the package insert of Nurtec (rimegepant):

The most common adverse reaction in Study 1 was nausea (2% in patients who received NURTEC ODT compared to 0.4% of patients who received placebo).

Hypersensitivity, including dyspnea and severe rash, occurred in less than 1% of patients treated with NURTEC ODT

Hypersensitivity reactions, including dyspnea and rash, have occurred with NURTEC ODT in clinical studies. Hypersensitivity reactions can occur days after administration, and delayed serious hypersensitivity has occurred.

Concomitant administration of rimegepant with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure.

Concomitant administration of rimegepant with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant.

Concomitant administration of rimegepant with strong or moderate inducers of CYP3A can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy.

Rimegepant is a substrate of permeability glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) efflux transporters. Concomitant administration of rimegepant with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant exposure.

Potential subjects on any medication that is a strong or moderate inhibitor of CYP3A, a strong or moderate inducer of CYP3A or an inhibitor of p-gp or BCRP will be excluded from participation in the study.

2.4.2 Known Potential Benefits

Rimegepant is effective as treatment for migraine.

2.4.3 Assessment of Potential Risks and Benefits

There is a medical need for effective systemic treatments for psoriasis with better safety profiles than currently available agents. Rimegepant has been shown to be safe and effective for treatment of migraine events. It has the potential to be a safe and, based on preclinical studies, an effective systemic treatment for psoriasis.

2.5 Correlative Studies Background

Not applicable.

3. Study Design

3.1 Overall Design

This is a phase 2, randomized double-blind controlled pilot study to assess whether there is clinical improvement in psoriasis after administration of a small molecule CGRP receptor inhibitor, rimegepant, compared to placebo. Rimegepant and placebo will be identical appearing 75 mg tablets/ODTs administered orally every other day. The study will be conducted solely at Weill Cornell Medicine and last 20 total weeks with 16 weeks of medication or placebo administration and 4 additional weeks of follow-up. Subjects will present to clinic every 2 weeks for clinical assessment using the PASI, IGA, DLQI, and Itch Score instruments, along with skin biopsies on Week 1 and Week 16. Subjects will be asked to bring their medications to these visits for pill counts to determine if any doses of medication were forgotten.

Study medications will be dispensed on Day 0 and Day 56. Thirty will be dispensed eachtime so that enough medication is provided in case of a minor delay in a scheduled appointment.

Areas of psoriasis in each subject will be photographed at baseline and two very similar appearing lesions will be identified for possible biopsy of one on Day 1 and the other at the end of Week 16. Prior to starting treatment and at the end of week 16 they will have blood taken for quantification of the proportion of circulating $CD4^+$ T cells that are IL-17^+ .

At the option of each subject,biopsies of the psoriatic lesions previously identified (one before treatment and one on week 16) will be performed for light microscopy analysis. Biopsies are performed by cleaning the skin carefully with an antiseptic, then injecting a small amount of local anesthetic into the skin. A 3 or 4 mm diameter trephine punch is then used to remove a very small piece of skin. The surgicaldefect is then closed with 1 or 2 sutures that are removed 2 weeks later.

Subjects will return on weeks 18 and 20 for final assessments. Subjects must also agree to avoid the sun including but not limited to activities such as sunbathing, swimming or performing other activities in sunlight for long periods of time (e.g., > 20 minutes) for the duration of the study. Brief exposure during normal activities is permitted.

Subjects who complete the 20-week protocol will have the option of entering a 12 weeks, open label extension of the study in which they will take 75 mg of Rimegepant every other day for 12 weeks. If rolling into the extension prior to visit 11, they can combine visit 11 and 12. Otherwise, subjects have the option to enroll into the extension up to 2 weeks after visit 11. They will have the same assessments as in the previous portion of the study every 4 weeks including an EKG. The inclusion and exclusion criteria remain the same.

3.2 Justification for Dose

The dose to be employed (rimegepant 75 mg every other day) has been shown to be safe and effective for the treatment of acute migraine. Rimegepant 75 mg every other day (up to one year) has been studied in the treatment of migraine prevention.

3.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Assessments (SoA), Section 6.1. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of psoriasis who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Male or female patients with at least 3% body surface are involved with psoriasis and a PASI score ≥5.
2. Between 18 and 75 years of age.
3. Documentation of a definite diagnosis of psoriasis by a dermatologist or biopsy.
4. For women of childbearing potential, a negative urine pregnancy test within 48 hours of randomization. Female subjects should not have attempted to become pregnant in the month prior to exposure to rimegepant and agree not to attempt to become pregnant for 8 weeks after exposure to rimegepant.

5. A valid form of contraception must be documented for men and women of child-bearing potential.
    a. The two methods for women of childbearing potential should include:
        i. One barrier method (for example, Diaphragm with spermicidal gel, condom with spermicidal gel, cervical caps or intrauterine devices placed for at least four weeks before sexual intercourse); AND
        ii. One additional method. The other method could include hormonal contraceptives, or second barrier method as listed above.
    b. The two options for men of childbearing potential should include:
        i. Simultaneous use of male condom, and for the female partner, hormonal contraceptives (for example, birth control pills, implants, patch, depot injection, used since at least 4 weeks) or intra-uterine contraceptive device (placed since at least 4 weeks) before sexual intercourse; OR Simultaneous use of male condom, and for the female partner, diaphragm with intravaginally applied spermicide.

4.3 Exclusion Criteria

1. Any ongoing medical illness or condition that places the participant at higher risk for adverse outcomes or inability to complete study procedures in the opinion of the study investigator.
2. Pregnancy or breastfeeding.
3. Known autoimmune disorders other than psoriasis.
4. Current use of corticosteroids or immunosuppressive medications (for any reason).
5. Immunodeficiency diseases.
6. Use of any biologic agent/monoclonal antibody within 5 half-lifes prior to baseline.
7. Ultraviolet light treatment, cyclosporine, oral corticosteroids, methotrexate, oral retinoids, mycophenolate mofetil, thioguanine, hydroxyurea, sirolimus or azathioprine within the 4 weeks prior to baseline or had topical psoriasis treatment within the previous 2 weeks prior to baseline.
8. Participation in another clinical trial involving an investigational drug within the last 30 days prior to baseline.
9. Inability for woman of child-bearing potential to use an effective form of contraception if sexually active.
10. Use of any medication that is a strong or moderate inhibitor of CYP3A, a strong or moderate inducer of CYP3A, or an inhibitor of glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP). Please see Section 7.8 for more information.
11. Subject history with current evidence of uncontrolled, unstable or recently diagnosed cardiovascular disease, such as ischemic heart disease, coronary artery vasospasm, and cerebral ischemia. Subjects with myocardial infarction (MI), acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), cardiac surgery, stroke or transient ischemic attack (TIA) during 6 months (24 weeks) prior to screening.

12. Uncontrolled hypertension or uncontrolled diabetes (however, subjects can be included who have stable hypertension and/or diabetes for 3 months (12 weeks) prior to screening). Blood pressure greater than 150 mm Hg systolic or 100 mm Hg diastolic after 10 minutes of rest is exclusionary
13. Subjects with an active episode of major depressive episode within the last 6 months are ineligible. Subjects with major depressive disorder or any anxiety disorder are eligible only if they are on stable medication for each disorder for at least 3 months prior to theScreening visit.
14. Subject has a history or diagnosis of Gilbert's Syndrome or any other active hepatic or biliary disorder
15. Hematologic or solid malignancy diagnosis within 5 years prior to screening. Subjects with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the screening visit in this study.
16. Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder.
17. History of gallstones without cholecystectomy.
18. Subject has current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics, schizophrenia, bipolar disorder, or borderline personality disorder.
19. Subject has end-stage kidney disease.
20. The use of CGRP antagonists (biologic [e.g. Aimovig™, Emgality® and Ajovy™, Vyepti™] or small molecule [e.g. Ubrelvy™ {ubrogepant]]) other than rimegepant is prohibited during the study.
21. Concomitant use of atypical antipsychotics such as Abilify (aripiprazole), Zyprexa (olanzapine), Seroquel (quetiapine), Geodon (ziprasidone), or Risperdal (risperidone).
22. Depakote/Depakene (divalproex/valproic acid/valproate) is prohibited during the study.
23. Concomitant use of LAMICTAL (lamotrigine) is prohibited during the study.
24. Concomitant use of Modafinil (PROVIGIL®) is prohibited during the study.
25. Exclusionary screening lab test findings:

- Serum bilirubin (Total, Direct or Indirect) > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for assessment of eligibility prior to randomization)
- AST or ALT > 1 x ULN (Only abnormal values of between 1-1.5x ULN may be repeated once for assessment of eligibility prior to randomization)
- Neutrophil count ≤ 1000/µL (or equivalent)
- HbA1c > 6.5%

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a use of a disqualifying medication may be rescreened after the required period of not using that medication. Rescreened participants will be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5.2 Subject Registration (Sub-sites)

Not applicable.

6. Study Procedures

6.1 Schedule of Assessments

Visit Number:	1	2	3	4	5	6	7	8	9	10	11	
	Pre-Study	Day 0	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	
Informed consent	X												
Evaluation for Entry	X												
Demographics	X												
Medication History	X	X	X	X	X	X	X	X	X	X	X	X	
Medical History*	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X												
Weight	X												
Vital Signs	X												
Skin Exam + Photos*	X	X	X	X	X	X	X	X	X	X	X	X	
PASI Score	X	X	X	X	X	X	X	X	X	X	X	X	
IGA Score	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI Score	X	X	X	X	X	X	X	X	X	X	X	X	
Itch Score	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	
CMP, CBC w/Diff,	X									X			
T Cell FACS, Biopsy of Skin Lesion		X											
HIV Serology, HbA1c	X												

Assess Adverse Event		X	X	X	X	X	X	X	X	X	X	X	
ECG	X			X		X		X		X			
Randomization	X												
Medication Dispensation		X				X							
Pill Counts			X	X	X	X	X	X	X	X			

All visits have a +/- 2-day window. Each visit is first day of the week indicated.

Schedule of Visits in Extension Phase

Visit Number	**11/12***	**13**	**14**	**15**
	Day 1	Wk 4	Wk 8	Wk 12
Informed consent	X			
Evaluation for Entry	X			
Medication History	X	X	X	X
Medical History**	X	X	X	X
Skin Exam + Photos**	X	X	X	X
PASI Score	X	X	X	X
IGA Score	X	X	X	X
DLQI Score	X	X	X	X
Itch Score	X	X	X	X
Urine pregnancy test	X	X	X	X
Assess Adverse Event	X	X	X	X
ECG	X	X	X	X
Medication Dispensation	X		X	
Pill Counts		X	X	X

All visits have a +/- 2-day window. Each visit is first day of the week indicated.

*Subjects enrolling in extension prior to visit 11 can combine visit 11 and 12.
**Skin Exam: The entire glabrous skin surface will be examined.
**Photography: Photographs will be taken to demonstrate the extent and morphology of lesions of psoriasis.
**Medical History: Characteristics of the patient's psoriasis will be obtained (duration, areas of involvement, past therapies and degree of itch). History of active medical problems, any immunosuppressive disorders will be queried. Family history of psoriasis or other inflammatory skin diseases will also be obtained.

6.1.1 Screening Visit (*2-10 days before start of treatment*)

- Informed consent
- Demographics
- Medication history
- Medical history
- Skin exam + photos
- PASI Score
- IGA Score
- DLQI Score
- Itch Score
- Beta-HCG
- HIV Serology
- CBC w/Diff, CMP, Hemoglobin A1c
- ECG

6.1.2 Treatment Phase

Eligible subjects will be randomly assigned to rimegepant or placebo treatment groups in a 1:1 ratio using a stratified permuted block randomization scheme developed by the data manager/study statistician.

6.1.2.1 Visit 1 (baseline; Day 0)

- Medication history (changes)
- Medical history (changes)
- Skin exam + photos
- PASI score
- IGA Score
- DLQI Score
- Itch Score
- Adverse Events Assessment
- Concomitant medication

6.1.2.2 Visits 2-12 (± 2 day(s))

- Medication history (changes)
- Medical history (changes)
- Skin exam + photos
- PASI score
- IGA Score
- DLQI Score

- Itch Score
- Adverse Events Assessment
- Concomitant medication
- ECGs will be obtained on Visits 3,5,7 and 9.

6.1.3 Follow-up Phase

Visits 11 and 12 are follow-ups after completion of the treatment phase

Extension Phase

Visits 13-15 have the same assessments as visits 2-12 except they will have a frequency of every 4 weeks.

7. Study Intervention

7.1 Study Intervention/Device Description

In this protocol, the investigational product will come in 2 forms either tablet or ODTs. Both active forms of tablets and ODTs will have 75mg of rimegepant and both formulations provide bioequivalent exposures, thus support equivalent PK performance. The tablets will be provided in 30 count HDPE bottles and labeled in a double-blind fashion that is identical to placebo tablets. The ODTs are packaged into multi-laminated blisters sealed with a foil backing and labeled in a double-blind fashion that is identical to placebo ODTs. Because the blister packs are in units of 8, 32 ODTs of rimegepant or placebo will be distributed. Any leftover investigational product will be returned to the study team during visits 5, 9 and if applicable, extension visit 14.

The investigational product will be shipped to the pharmacy by Pfizer Inc. and should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

7.2 Availability

The full amount of Rimegepant and placebo will be supplied by Pfizer, Inc. and shipped to the site pharmacy prior to the initiation of the trial. If additional product is required, contact the sponsor directly.

7.3 Acquisition and Accountability

Agent Inventory Records/Device Logs – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents/device received from *Sponsor* on a Drug Accountability Record Form (DARF) or Device Log.

7.4 Formulation, Appearance, Packaging, and Labeling

The rimegepant active and placebo tablets are packaged in 30 count HDPE bottles and will have a blinded label which will include a unique bottle number, the product name, labeling lot number, storage conditions and dosing directions. The unique bottle number is linked to the treatment arm in a blinded fashion. The rimegepant active and placebo ODTs are packaged in 8-count multi-laminated blisters backed with foil and will be labeled similarly to the tablet bottles.

7.5 Product Storage and Stability

The investigational product should be stored at room temperature according to conditions on the clinical label in a secure area according to local regulations.

It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately.

7.6 Preparation

The investigational product will be assigned by the unblinded pharmacist after patient randomization through use of the unique bottle numbers. The pharmacist will add the appropriate subject number on the bottle label and provide it to the site staff for dispensation to the subject.

7.7 Dosing and Administration

Each subject will take a 75-mg tablet/ODT of rimegepant orally or a matching placebo tablet/ODT orally every other day for 16 weeks. Subjects will receive 30 tablets or 32 ODTs of rimegepant or matching placebo in each bottle or four 8-count blister packs at the initial visit after the subject is randomized. The subject will be instructed to dose around the same time every other day. The subject must bring the bottle/blister packs back for each visit for drug accountability. A second 30 tablet or 32 ODT supply will be dispensed at week 8. Pill counts will be performed at each visit to assess compliance.

7.7.1 Dosing Delays/Dose Modifications

For any serious adverse effects, dosing will be immediately discontinued and appropriate care provided. Some nausea is expected.

7.8 General Concomitant Medication and Supportive Care Guidelines

Concomitant administration of rimegepant with strong inhibitors of CYP3A4 results in a significant increase in rimegepant exposure.

CYP3A4 Inhibitors (Strong) Interacting Members: Atazanavir, Ceritinib, Clarithromycin, Cobicistat, Darunavir, Idelalisib, Indinavir, Itraconazole, Ketoconazole (Systemic), Lopinavir, MiFEPRIStone, Nefazodone, Nelfinavir, Ombitasvir, Paritaprevir,

and Ritonavir, Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir, Posaconazole, Ritonavir, Saquinavir, Telithromycin, Tucatinib, Voriconazole

Concomitant administration of rimegepant with moderate inhibitors of CYP3A4 may result in increased exposure of rimegepant.

- **CYP3A4 Inhibitors (Moderate) Interacting Members**: Aprepitant, Conivaptan, Crizotinib, DilTIAZem, Dronedarone, Duvelisib, Erythromycin (Systemic), Fedratinib, Fluconazole, Fosamprenavir, Fosnetupitant, Grapefruit Juice, Imatinib, Isavuconazonium Sulfate, Lefamulin, Letermovir, Netupitant, Nilotinib, Ribociclib, Schisandra, Verapamil

Concomitant administration of rimegepant with strong or moderate inducers of CYP3A can result in a significant reduction in rimegepant exposure, which may lead to loss of efficacy.

- **CYP3A4 Inducers (Strong) Interacting Members:** Apalutamide, CarBAMazepine, Enzalutamide, Fosphenytoin, Lumacaftor and Ivacaftor, Mitotane, PHENobarbital, Phenytoin, Primidone, RifAMPin
- **CYP3A4 Inducers (Moderate) Interacting Members:** Bexarotene (Systemic), Bosentan, Cenobamate, Dabrafenib, Efavirenz, Eslicarbazepine, Etravirine, Lorlatinib, Modafinil, Nafcillin, Pexidartinib, Rifabutin, Rifapentine, St John's Wort

Rimegepant is a substrate of permeability glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) efflux transporters. Concomitant administration of rimegepant with inhibitors of P-gp or BCRP may result in a significant increase in rimegepant exposure.

- **BCRP/ABCG2 Inhibitors Interacting Members:** Atazanavir, Capmatinib, Clopidogrel, Cobicistat, CycloSPORINE (Systemic), Daclatasvir, Darolutamide, Dasabuvir, Elbasvir, Eltrombopag, Eluxadoline, Fostamatinib, Fostemsavir, Glecaprevir and Pibrentasvir, Grazoprevir, Lapatinib, Ledipasvir, Leflunomide, Lopinavir, Ombitasvir, Paritaprevir, and Ritonavir, Ombitasvir, Paritaprevir, Ritonavir, and Dasabuvir, Osimertinib, Regorafenib, Rolapitant, Simeprevir, Tedizolid, Teriflunomide, Velpatasvir, Voxilaprevir
- **P-glycoprotein/ABCB1 Inhibitors Interacting Members:** Amiodarone, Azithromycin (Systemic), Capmatinib, Carvedilol, CycloSPORINE (Systemic), Daclatasvir, Dronedarone, Elagolix, Elagolix, Estradiol, and Norethindrone, Elexacaftor, Tezacaftor, and Ivacaftor, Eliglustat, Erythromycin (Systemic), Flibanserin, Fostamatinib, Glecaprevir and Pibrentasvir, Ivacaftor, Lapatinib, Ledipasvir, Neratinib, Osimertinib, Propafenone, QuiNIDine, QuiNINE, Ranolazine, Rolapitant, Simeprevir, Tezacaftor and Ivacaftor, Tucatinib, Velpatasvir, Vemurafenib, Verapamil
  Exceptions Clarithromycin, Itraconazole, Ketoconazole (Systemic), Ombitasvir, Paritaprevir, and Ritonavir, Ritonavir

Potential subjects on any medication that is a strong or moderate inhibitor of CYP3A, a strong or moderate inducer of CYP3A or an inhibitor of p-gp or BCRP will be excluded from participation in the study.

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study and saved in subject binder, if applicable.

7.9 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment will continue for 16 weeks or until one of the following criteria applies:

- Disease progression requiring intervention,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decides to withdraw from the study,
- Initiation of prohibited medication, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

7.10 Duration of Follow Up

Subjects will be followed for 4 weeks after discontinuation of the investigative pharmaceutical agent. Subjects removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.11 Measures to Minimize Bias: Randomization and Blinding

Screening and Registration into the Study Database
Once informed consent has been signed, participants will be registered into the study database. The study database will assign a participant's PID upon completion of the registration process.

Randomization:
Participants will be assigned a randomization number once the following has been accomplished: eligibility has been verified, eligibility has been confirmed by the study PI, and eligibility CRF has been entered into the study database.

Patients will be stratified based on severity of disease as measured by PASI scores<12 (mild/moderate) or >=12 (Severe) at screening. Within each stratum, patients will be randomized at 1: 1 ratio to the two treatment arms using permuted block randomization with varying block sizes. Randomization codes will be shared to the study pharmacist at the initiation of the trial. The randomization will be performed by the statistician who will alert the pharmacy in coordination with the study coordinator.

Screening/Registration/Randomization into Study Databases
Appropriate CRFs must be completed for any participant who signs an informed consent. If a consented participant is a screen failure and deemed ineligible, the following CRFs must be completed: 1) the Screening CRF; 2) the Registration CRF with the eligibility box checked "no", 3) the Inclusion and Exclusion CRFs showing why the participant is ineligible, 4) the Off-Study CRF, 5) the Adverse Event CRF, 6) the Concomitant Medication CRF and 7) the Verification CRF. If no Adverse Event and/or Concomitant Medications were assessed by the time the participant is deemed ineligible, the "NONE" box will be checked to complete both CRFs. All participants who sign an informed consent must formally go off study. All participant registration information will

be entered into study database. If a participant experiences a serious adverse event during the screening process, an SAE form must be completed.

Blinding and Unblinding Method

- Patients and all clinical evaluators will be blinded to treatment assignment.
- The Statistician and the Study Pharmacist at the participating sites will not be blinded to treatment assignment.
- Study assignments will be unblinded to the Study Investigators and Coordinators after all of the data are collected, the study database has been locked, and analyses are completed.
- Emergency unblinding will occur if the participant's physician deems that unblinding is necessary, such as in the case of unacceptable toxicity thought to be related to the study agent or progressive disease.
- The Independent Medical Monitor will also be blinded unless unblinding is warranted (if the participant's physician deems that unblinding is necessary, or after all of the data are collected and the study database has been locked).
- The date and reason for breaking the blind must be documented in the study database.

7.12 Study Intervention/Follow-up Compliance

Subject will be asked to complete a log documenting the date and time that the study medication is taken (every other day).

Pill counts will be done at each visit.

If necessary, 3 attempts will be made to get subject to return for study follow-up Appointments. If the patient does not respond to 3 attempts he/she will be considered "lost to follow-up" and no longer participating in the study.

8. Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Subjects will be withdrawn from study treatment permanently for the following reasons:

1. Development of any hypersensitivity phenomena that may be related to the study medication.
2. Excessive nausea making continuation of participation in the study impossible.
3. Development of any intercurrent illness or medical need to take a medication such that exclusion criteria apply.
4. Occurrence of pregnancy in a female subject.
5. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
6. Disease progression which requires discontinuation of the study intervention
7. If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

Subjects will be referred for appropriate medical care for any adverse effects.

Subjects will continue to be followed for assessment of disease severity until the 20-week period is over.

Discontinuation of treatment does not mean discontinuation from the study, and remaining study procedures (assessments of disease severity) will be completed as indicated by the study protocol.

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Criteria for interrupting the study: We will have a study monitoring committee (SMC) consisting of the study PI, the medical monitor and 1 investigator not directly involved in the conduct of this study. This committee will review all Grade 3 or 4 events, and all SAEs in real time. We will pause enrollment of new participants if there is 1 or more Serious Adverse Events that are at least possibly related to study drug, or 2 or more Grade 3 or 4 events at least possibly related to study drug. The enrollment of participants will not resume until the SMC reviews the adverse events and agrees unanimously to resume enrollment.

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. Pregnancy. However, subjects will be followed until the end of the pregnancy.
2. Significant study intervention non-compliance (failure to take medications, refuses to allow study procedures).
3. Participant lost to follow-up after 3 attempts to contact subject to schedule study visit.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she fails to return for a scheduled visit and is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 2 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable.

10. Measurement of Effect

10.1 Response Criteria

Not applicable.

10.2 Duration of Response

Not applicable.

10.3 Progression-Free Survival

Not Applicable.

10.4 Other Response

Parameters

Not Applicable.

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocolamendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

An IND, including relevant study documentation, will be submitted to the FDA, according to national requirements, for review and approval before the beginning of the study. On completion of the study, the FDA will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH- GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

12. Statistical Considerations

12.1 Study Design/Endpoints

This is a randomized, double-blind, placebo-controlled phase II study to examine the efficacy of rimegepant, an orally available competitive inhibitor of the CGRP receptor, in patients diagnosed with psoriasis. Patients in each strata of disease severity as defined by baseline PASI score (<12, or >=12) will be randomized at 1:1 ratio to receive 16-week treatment of either rimegepant or placebo. The primary endpoint includes the percent reduction in PASI score post-treatment measured at week 16 from baseline defined as 100% x (PASI.pre-PASI.post)/PASI.pre. Secondary endpoints include PASI50, an indicator of whether a patient had at least 50% improvement in PASI score at week 16 post-treatment compared to baseline, the reduction (i.e., the difference) in the Investigator's Global Assessment (IGA) score post treatment from baseline, change in Dermatology Quality of Life Index (DQLI) at week 16 post treatment compared to baseline, change in Itch Score post treatment from baseline, and the overall patterns of change in PASI scores, IGA scores and DQLI scores measured longitudinally.

12.2 Sample Size/Accrual Rate

The primary objective of the study is to examine if patients receive the rimegepant treatment had greater improvement in psoriasis in terms of the primary endpoints compared to patients received the placebo. The primary endpoints include both the percent reduction in PASI score post-treatment from baseline and the change IGA score post-treatment from baseline.

The sample size is determined to ensure adequate power to detect clinically meaningful differences in the co-primary endpoints between the treatment arms. With a sample size of 30 patients (15 per treatment arm), we will have 80% power to detect an effect size as small

as 1.06 using a two-sample t-test at a two-sided significance level of 0.05 for each of the primary endpoint. This level of effect size corresponds to >21% differences in the percent reduction in PASI scores post treatment from baseline between the two treatment arms assuming the standard deviation of the percent reduction in PASI score is about 20% which is likely to be a conservative estimate based on published results from trials in patients with moderate to severe disease. This level of effect size also corresponds to a difference of 0.5 in the change of IGA scores between the two study arms assuming the standard deviation of change is around 0.5. Accounting for a dropout rate of 25% a total of 45 patients will be recruited.

The study expects to accrue 5 patients per month and accrue all study patients within 6-10 months.

12.3 Stratification Factors

Patients will be stratified based on severity of disease as measured by PASI scores<12 or >=12 at screening. Within each stratum, patients will be randomized at 1: 1 ratio to the two treatment arms using permuted block randomization with varying block size.

12.4 Analysis of Endpoints

12.4.1 Analysis of Primary Endpoints

The primary endpoint is the week 16 PASI score. We will calculate the percent reduction in week 16 PASI scores post treatment from baseline. Summary statistics in terms mean, standard deviation, median and range or inter-quartile range will be generated for each study arm. Between treatment arm differences will be evaluated using a two-sample t-test or the non-parametric Wilcoxon rank sum test where appropriate. The primary analysis will be carried out on an intention-to-treat basis. Last value carried forward will be used to impute for patients missing week 16 measurements. Per-protocol analysis will also be carried out amongpatients who are deemed compliant to treatment (defined as at least 75% of doses taken asmeasure by pill counts) and had both baseline and week 16 measurements will also be carried out using similar statistical methods. P-values less than 0.05 will be considered statistical significant.

12.4.2 Analysis of Secondary Endpoints

Quantification of subjects in each arm achieving PASI50 at week 16, defined as achieving >=50% reduction in PASI scores measured at week 16 post treatment from baseline, will be summarized. Summary statistics including count and proportion in each treatment arm will be provided for patients enrolled in each arm. Differences in proportions between treatment arms will be summarized along with 95% confidence interval. Exploratory comparison will be carried out using Fisher's exact test.

For change in IGA scores at week 16 post treatment from baseline, summary statistics in terms mean, standard deviation, median and range or inter-quartile range will be generated for each study arm. Between treatment arm differences will be evaluated using a two-sample t-test or the non-parametric Wilcoxon rank sum test where appropriate.

For change in DQLI scores at week 16 post treatment from baseline, summary statistics in terms mean, standard deviation, median and range or inter-quartile range will be generated

for each study arm. Between treatment arm differences will be evaluated using a two-sample t-test or the non-parametric Wilcoxon rank sum test where appropriate.

For change in Itch Scores at week 16 post treatment from baseline, summary statistics in terms mean, standard deviation, median and range or inter-quartile range will be generated for each study arm. Between treatment arm differences will be evaluated using a two-sample t-test or the non-parametric Wilcoxon rank sum test where appropriate.

For longitudinal measurements of the study endpoints obtained overtime, patterns of differences between treatment arms will be evaluated using linear mixed-effects or generalized linear-mixed effects models.

For all these study endpoints, the primary analysis will be carried out on an intention-to-treat basis. For endpoints concerning change at week 16 from baseline, a conservative method for imputation such as last-value carried forward will be used for those missing measurements at week 16. For analysis concerning longitudinal data, no missing imputation will be applied. Secondary per protocol analyses will also be carried out among patients who complied to study treatments.

12.5 Interim Analysis

Not applicable.

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

All subjects will be evaluable for toxicity from the time of their first treatment with the *Investigational Agent.* Consultation with the Biostatistics Office will allow for completion of this section.

12.6.2 Evaluation of Response

All subjects included in the study will be assessed for response to treatment if they have received at least 4 weeks of treatments.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in

combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

1. Nausea.

2. Rare chance of hypersensitivity reaction.

Any adverse events will be treated appropriately in consultation with the subject's physician or other appropriate physicians.

13.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

13.1.5 Reporting Events to Participants

Any adverse events or serious adverse events will be reported to all subjects orally and in writing promptly.

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

If any pregnancies arise during the course of the study, incidence of pregnancy should be reported to the IRB according to the IRB policy of Weill Cornell Medicine.

Pregnancy testing will be conducted at each study visit. If, following the baseline visit, it is subsequently discovered that a study subject is pregnant, the subject will be discontinued from the study and study medication will be stopped.

The Investigator and/or Co-Investigator will immediately inform the Independent Medical Monitor of the event and report the event in accordance with the SAE reporting procedures as described in Section 13.2.1 – 13.2.3

13.2 Definition of SAE

SAEs include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

13.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
https://research.weill.cornell.edu/sites/default/files/immediate_reporting_policy.pdf

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.

i. death,
ii. a life-threatening adverse event,
iii. in-patient hospitalization or prolongation of existing hospitalization,
iv. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
v. a congenital anomaly or 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 patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious

Select appropriate reporting branch below

CDER INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dentistry
5901-B Ammendale Road
Beltsville, MD 20705-1266

CDER-only Biologic INDs:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologic Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

CBER INDs:

Office of *xxxx*
Center for Biologics Evaluation and Research
Food and Drug Administration
Suite 200N 1401 Rockville Pike
Rockville, MD 20852-1448

13.2.3 Reporting of SAE to Pfizer, Inc

Institution will send Pfizer, Inc copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association or relatedness with the Study Drug(s) in the course of the Clinical Trial, , at minimum once per year. The Pfizer US drug safety department may request data more frequently from the Investigator to support safety reporting. Serious adverse event reports are faxed to 1-866-997-8322. Contact information for the Pfizer US drug safety team is subject to change. For safety reporting questions, please contact Pfizer US safety mailbox contact at SAEFaxmailbox@Pfizer.com.

All SAEs that occur will be promptly reported to the IRB and medical monitor for the study. SAEs will be reported in accordance with FDA form **MedWatch 3500A** associated with the study investigator's IND. These IND submissions are Expedited Safety Reports (7-day or 15-day reports) as defined by the Code of Federal Regulations 21 CFR 312.32(c). An Expedited Safety Report is required

for **serious** adverse events that are deemed both **unexpected** and **related** to the investigative drug. The protocol may define that this attribution can include events considered "possibly related", and the IND Sponsor-investigator should align with their study protocol in this regard. Serious adverse events that do not fit these criteria should still be described in the IND's Annual Report. All MedWatch 3500A forms should be submitted to Biohaven as defined above. These documents are critical to updating the comprehensive safety information in our Investigator Brochure, which is reviewed and updated at least annually.

13.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Dr. Granstein or other study key persons will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.]

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.] ?????

15. Data and Safety Monitoring Plan (DSMP)

After discussion with representatives of the Weill Cornell Data and Safety Monitoring Board, at their recommendation we have decided to proceed with an Independent Medical Monitor. For a study of the relatively short duration of subject participation as in our proposal and the known safety of the drug being investigated, this appeared to be the best choice.

Events that will be captured and submitted to the Monitor are:

1. Accidental injuries
2. Events related to trial procedures
3. Reasons for any unfavorable and unplanned change in medication.
4. Clinically significant worsening of pre-existing conditions.
5. Reasons for admission to hospital or surgical procedures unless these admissions or procedures were planned before the subject consented to trial participation.
6. Adverse events anticipated based on the pharmacological effects of rimegepant.
7. Any laboratory abnormality felt to be clinically significant by the investigator.

Serious adverse events are defined as:

1. An event resulting in death
2. An event that is life-threatening
3. An event that requires inpatient hospitalization other than planned hospitalizations that do not fulfill the criteria for being a serious adverse event.
4. An event that results in persistent or significant disability or incapacity.
5. A medically important event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent one of the outcomes listed above.

The following adverse events will result in terminating protocol treatment:

1. Anaphylactic reaction or other systemic reaction to rimegepant.
2. Any adverse reaction that in the opinion of the investigator contraindicates further dosing.
3. Diagnosis of a malignancy during the trial excluding carcinoma in situ of the cervix or localized squamous or basal cell carcinoma of the skin.
4. Evidence of pregnancy.
5. Any infection that is opportunistic whose nature or course may suggest an immunocompromised status.
6. Significant abnormalities including an ALT or AST value more than 3 times the upper limit of normal, total bilirubin more than 2 times the upper limit of normal unless related to Gilbert Syndrome.

Adverse events that are not accurately reflected in the Informed Consent Form or the package insert of the medication that is related or possibly related to the pharmacological intervention and that has greater risk of harm to the subject is present than was previously known or recognized will be reported to the Independent Medical Monitor within 7 days. Severe adverse events will be reported to the Medical Monitor as soon as possible and definitely within 3 days. Additionally, quarterly reports on all subjects experiencing adverse events will be submitted to the monitor throughout the study.

There are no defined rules for stopping the study prior to completion by all of the enrolled subjects. Given the known safety data of the investigational agent. This seems quite reasonable.

The Independent Medical Monitor's comments will be provided to the IRB at the time of each continuing review.

16. References

1. Rajguru JP, Maya D, Kumar D, Suri P, Bhardwaj S, Patel ND. Update on psoriasis: A review. J Family Med Prim Care. 2020, 9:20-24.

2. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, Gelfand JM. Psoriasis and comorbid diseases: Implications for management. J Am Acad Dermatol. 2017, 76:393-403.

3. Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, Mehta NN, Finlay AY, Gottlieb AB. Psoriasis. Nat Rev Dis Primers. 2016, 24;2:16082.

4. Kaushik SB, Lebwohl MG. Review of safety and efficacy of approved systemic psoriasis therapies. Int J Dermatol. 2019, 58:649-658.

5. Rácz E, Prens EP. Phototherapy of Psoriasis, a Chronic Inflammatory Skin Disease. Adv Exp Med Biol. 2017, 996:287-294.

6. Farber EM, Lanigan SW, Boer J. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol. 1990, 29:418-20.

7. Zhu TH, Nakamura M, Farahnik B, Abrouk M, Lee K, Singh R, Gevorgyan A, Koo J, Bhutani T. The role of the nervous system in the pathophysiology of psoriasis: A review of cases of psoriasis remission or improvement following denervation injury. Am J Clin Dermatol. 2016, 17:257-63.

8. HH Perlman. Remission of psoriasis vulgaris from the use of nerve-blocking agents. Arch Dermatol. 1972,105:128-9.

9. Aschenbeck KA, Hordinsky MK, Kennedy WR, Wendelschafer-Crabb G, Ericson ME, Kavand S, Bertin A, Dykstra DD, Panoutsopoulou IG. Neuromodulatory treatment of recalcitrant plaque psoriasis with onabotulinumtoxin A. J Am Acad Dermatol. 2018, 79:1156-1159.

10. Ostrowski SM, Belkadi A, Loyd CM, Diaconu D, Ward NL. Cutaneous denervation of psoriasiform mouse skin improves acanthosis and inflammation in a sensory neuropeptide-dependent manner. J Invest Dermatol. 2011, 131:1530-8.

11. EM Baerveldt, AJ Onderdijk, C Wohn, M Kant, EF Florencia, IJ Hekking-Weijma, ET Walbeehm, WR Swindell, JE Gudjonsson, EP Prens. Denervation impairs clinical development of imiquimodinduced psoriasiform skin inflammation in mice. J Invest Dermatol. 2012,132(Suppl 2s), S17 (abstract).

12. Reich A, Orda A, Wiśnicka B, Szepietowski JC. Plasma concentration of selected neuropeptides in patients suffering from psoriasis. Exp Dermatol. 2007, 16:421-8.

13. He Y, Ding G, Wang X, Zhu T, Fan S. Calcitonin gene-related peptide in Langerhans cells in psoriatic plaque lesions. Chin Med J (Engl). 2000, 113:747-51.

14. Riol-Blanco L, Ordovas-Montanes J, Perro M, Naval E, Thiriot A, Alvarez D, Paust S, Wood JN, von Andrian UH. Nociceptive sensory neurons drive interleukin-23-mediated psoriasiform skin inflammation. Nature. 2014, 510:157-61.

15. Kashem SW, Riedl MS, Yao C, Honda CN, Vulchanova L, Kaplan DH. Nociceptive Sensory Fibers Drive Interleukin-23 Production from CD301b+ Dermal Dendritic Cells and Drive Protective Cutaneous Immunity. Immunity. 2015, 43:515-26.

16. Ding W, Stohl LL, Xu L, Zhou XK, Manni M, Wagner JA, Granstein RD. Calcitonin Gene-Related Peptide-Exposed Endothelial Cells Bias Antigen Presentation to CD4+ T Cells toward a Th17 Response. J Immunol. 2016,196:2181-94.