ClinicalTrials.gov Submission

Official Title: Decreasing Resident Memory T Cells While Increasing Clinical Durability: Higher Induction Doses of Risankizumab for Moderate-to-Severe Plaque Psoriasis (Knockout)

NCT Number: NCT05283135

Document Date: Version 6 Dated 22FEB2024

DECREASING RESIDENT MEMORY T CELLS WHILE INCREASING CLINICAL DURABILITY: HIGHER INDUCTION DOSES OF RISANKIZUMAB FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS (KNOCKOUT)

Protocol Number: B20-433

Principal Investigator: Benjamin D. Ehst, MD, PhD

IND Sponsor: Oregon Medical Research Center

Funded by: AbbVie Inc.

Version 6: 22 FEB 2024

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout Protocol	Format editing and update to both clinical site location and Principal Investigator.	Oregon Medical Research Center relocated to a new address, and Dr. Andrew Blauvelt is retiring on 05MAR2024 and Dr. Ehst is assuming the role of Principal Investigator.

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Clinical Trial Agreement between Oregon Medical Research Center and AbbVie Inc. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from Oregon Medical Research Center (the Investigational New Drug (IND) sponsor), AbbVie (the funder of the study), and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study 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 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. 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.

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title:	"Decreasing resident memory T cells while increasing clinical durability: higher induction doses of risankizumab for moderate-to-severe plaque psoriasis (KNOCKOUT)"
Study Description:	This is a pilot study that explores whether higher induction doses of risankizumab (2x and 4x standard induction doses) can more effectively target resident memory (Trm) cells within psoriatic lesions, and whether more profound knock-down of Trm is associated with higher levels of complete clearance (i.e., PASI 100) and for longer periods of time.
Objectives:	**Primary Objective**: to determine whether the reduction in the number and/or effector function of epidermal CD8+CD103+ Trm cells at Week 52 (compared to baseline numbers) in psoriasis patients treated with 4X standard induction doses of risankizumab (600 mg at Weeks 0, 4, and 16) is greater when compared to psoriasis patients treated with 2X standard induction doses of risankizumab (300 mg at Weeks 0, 4, and 16). **Secondary Objectives**: 1) to compare the percentage of patients with PASI 100 (complete clearance) at Weeks 28, 40, 52 and 100 in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab and 2) to compare safety events over 100 weeks in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab

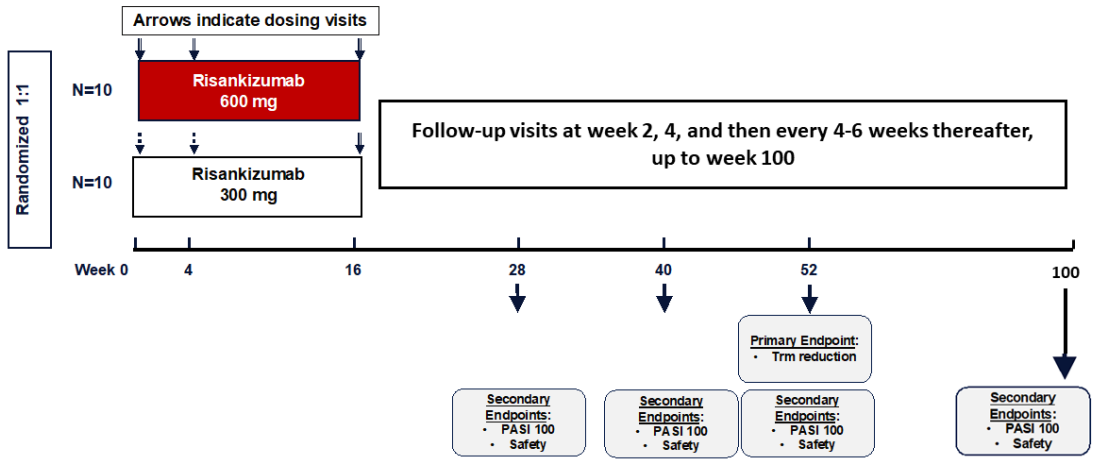
Endpoints:	**Primary Endpoint**: change from baseline in number and/or effector function of epidermal CD8+CD103+ Trm cells at Week 52 in psoriasis patients treated with 4X standard induction doses of risankizumab (600 mg at Weeks 0, 4, and 16) or 2X standard induction doses of risankizumab (300 mg at Weeks 0, 4, and 16). **Secondary Endpoints**: 1) PASI 100 (complete clearance) response at Weeks 28, 40, 52, and 100 in patients receiving 4X standard induction doses of risankizumab or those receiving 2X standard induction doses of risankizumab and 2) safety events over 100 weeks in patients receiving 4X standard induction doses of risankizumab or those receiving 2X standard induction doses of risankizumab. **Additional endpoints:** 1) Change from baseline in PASI and BSA at various timepoints, PASI 75 response, PASI 90 response, PASI 100 response, and sPGA 0/1 response at various study timepoints 2) Change from baseline in DLQI at Weeks 28 and 52 and DLQI 0/1 response at Weeks 28 and 52
Study Population:	20 patients with moderate-to-severe plaque psoriasis, males and females, 18 years of age and older, good general health, Portland metropolitan area
Phase:	2
Description of Sites/Facilities Enrolling Participants:	Single center: Oregon Medical Research Center in Portland, Oregon
Description of Study Intervention:	This is a single-center, randomized, interventional, Phase 2 study (KNOCKOUT) consisting of a 52-week double-blind period followed by a 48-week unblinded extension comparing tissue and clinical effects of 4X standard induction doses of risankizumab vs. 2X standard induction doses of risankizumab in patients with moderate-severe plaque psoriasis. Twenty patients with moderate-to-severe plaque psoriasis will be randomized in a 1:1 manner to receive either risankizumab 600 mg (4X dosing) or 300 mg (2X dosing), subcutaneous (SC), at Weeks 0, 4, and 16. All patients will receive four SC injections at Weeks 0, 4, and 16 (into right arm, left arm, right thigh, left thigh) by an unblinded pharmacist. For patients randomized into the highest induction dose arm, each shot will contain 150 mg of risankizumab; for patients randomized into the 2X induction dose arm, two shots will contain 150 mg of risankizumab each and 2 shots will contain placebo (sterile saline).

Skin biopsies of lesional and/or non-lesional skin will be obtained at Week 0, and an additional skin biopsy of lesional skin will be obtained at Week 52. Lesional is defined as current lesion or prior lesional area. These samples will beprocessed for immunohistochemical staining and RNA seq analysis. Psoriasis severity clinical assessments (PASI, sPGA, BSA) and safety assessments (vital signs, history) will be assessed at screening and Weeks 0, 2, 4, 8, 12, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, and 100 (to assess secondary endpoints). Routine labs will be performed at Screening and at Weeks 4, 8, 22, and 52.

Study Duration: 30 months

Participant Duration: Screening period (up to 4 weeks) and then 100 weeks

1.2. SCHEMA



Note: screening visit to occur 0-4 weeks prior to randomization visit at Week 0. Double blinded period is Week 0 through Week 52, and patients will be additionally followed through week 100, post the double-blind study period.

***Patients will also be seen every 6 weeks, from Week 52 to Week 100 and assessed for safety and maintenance of clinical efficacy.**

1.3. SCHEDULE OF ACTIVITIES (SOA)

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Day -28 to Day –1	Day 0/BL/Wk 0	Day 14/Wk 2	Day 28/Wk 4	Day 56/Wk 8	Day 84/Wk 12	Day 112/Wk 16	Day 154/Wk 22	Day 196/Wk 28	Day 238Wk 34	Day 280/Wk 40	Day 322/Wk 46	Day 364/Wk 52	Day 406/Wk 58	Day 448/Wk 64	Day 490/Wk 70	Day 532/Wk 76	Day 574/Wk 82	Day 616/Wk 88	Day 658/Wk 94	Day 700/Wk 100 /Early Disc
Visit window	Plus or minus 7 days																				
Interviews and Questionnaires																					
Subject information and informed consent	✓																				
Eligibility criteria	✓	✓																			
Medical history	✓																				
Psoriasis history	✓																				
Demographics	✓																				
Drug, tobacco (including e-cigarettes), and alcohol history	✓																				
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB screening	✓																				
Patient Reported Outcomes (DLQI)		✓							✓				✓								
Suicidal thoughts or actions screening (CSSRS)	✓																				
Labs and Examinations																					
Height	✓																				
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete physical examination	✓	✓		✓			✓														✓
Targeted physical examination			✓		✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test (females of childbearing potential only)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓									
TB test (QuantiFERON-TB Gold test) 4mL/0.8 teaspoon of blood	✓																				
HIV, HBV, and HCV screening 8mL/1.6 teaspoons of blood	✓																				

	Day -28 to Day –1	Day 0/BL/Wk 0	Day 14/Wk 2	Day 28/Wk 4	Day 56/Wk 8	Day 84/Wk 12	Day 112/Wk 16	Day 154/Wk 22	Day 196/Wk 28	Day 238Wk 34	Day 280/Wk 40	Day 322/Wk 46	Day 364/Wk 52	Day 406/Wk 58	Day 448/Wk 64	Day 490/Wk 70	Day 532/Wk 76	Day 574/Wk 82	Day 616/Wk 88	Day 658/Wk 94	Day 700/Wk 100 /Early Disc
Visit window	Plus or minus 7 days																				
Hematology, clinical chemistry, and urinalysis 8mL/1.6 teaspoons of blood	✓			✓	✓			✓				✓									
PASI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BSA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
sPGA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Skin biopsies (6-mm punch samples)		✓											✓								
Treatment																					
Randomization/drug assignment		✓																			
Administer study drug to subjects		✓		✓			✓														
In-clinic post-dose monitoring (30 minutes)		✓		✓			✓														

2. INTRODUCTION

2.1. STUDY RATIONALE

We postulate that risankizumab, an anti-IL-23 biologic used to treat moderate-to-severe plaque psoriasis, may lead to high levels of prolonged skin clearance due to an effect on resident memory T (Trm) cells. Here, we describe a pilot study that explores whether higher induction doses of risankizumab (4X and 2X standard induction doses) can more effectively target Trm cells within psoriatic lesions, and whether more profound knock-down of Trm cells is associated with higher levels of complete clearance (i.e., PASI 100) and for longer periods of time.

2.2. BACKGROUND

Trm cells can develop within tissues in response to certain pathogens.[1] They are long-lived and responsible for tissue protection from re-exposure to the original pathogen. When re-activated by re-exposure to that pathogen, Trm cells amplify immune responses by recruiting additional immune cells from blood. Interestingly, Trm cells are also found in skin previously affected by active psoriasis, vitiligo, and fixed drug reaction skin, and are now believed to be the cells responsible for recurrences of psoriasis.[2-6] In psoriatic skin, these cells are CD8+CD103+ epidermal T cells that produce IL-17A.[2-6] It is unknown whether psoriatic Trm cells are under the control of IL-23, but recently, guselkumab, an IL-23 blocker used to treat psoriasis, was shown to reduce Trm cells in skin after 6 months of dosing.[7] Of note, similar IL-17A-producing cells (Th17 and Tc17 effector cells) in psoriasis are dependent upon IL-23 for survival.[8]

Many excellent treatments exist for the treatment of patients with moderate-to-severe plaque psoriasis. Disease, however, recurs following withdrawal of these treatments. risankizumab, an anti-IL-23 biologic, is highly effective and safe for treating plaque psoriasis.[9-11] The standard dose for this drug is 150 mg at Weeks 0 and 4, and then 150 mg every 12 weeks after two induction doses. Approximately 80% of patients reach PASI 90 and approximately 60% reach PASI 100 at 1 year, with few-to-no side effects.[9-11] In addition, the IMMhance study revealed that some patients undergoing risankizumab withdrawal demonstrated prolonged skin clearance long after their last dose; more specifically, 10-15% of patients with completely clear skin after only 3 risankizumab doses (at Weeks 0, 4, and 16) maintained completely clear skin for up to 1 year before psoriasis recurred.[11] The combination of these prior clinical results suggests there is a need to scientifically explore the biologic basis of the duration of risankizumab's therapeutic activity; specifically, there is a need to test higher doses at weeks 0, 4, and 16 to determine whether more complete skin clearance at one year can be achieved.

2.3. RISK/BENEFIT ASSESSMENT

2.3.1. KNOWN POTENTIAL RISKS

Risankizumab (Skyrizi®) is FDA-approved for patients with moderate to severe plaque psoriasis. This information is derived largely from the product insert and is also the language placed into the patient informed consent form (ICF).

Risankizumab has been given to healthy volunteers and patients with psoriasis (PsO), erythrodermic psoriasis (EP), generalized pustular psoriasis (GPP), psoriatic arthritis (PsA), Crohn's disease (CD), ankylosing spondylitis, hidradenitis suppurativa (HS), and asthma. risankizumab has been given either by intravenous infusion (IV, slowly injected into a vein in the arm) or by subcutaneous injection (SC, injection into the deepest skin layer). It has been tested in single doses as high as 1,800 mg IV and 300 mg SC and in repeated doses as high as 1,200 mg IV and 180 mg SC. No new or different side effects were seen with higher doses of risankizumab.

Taking the study drug in this study may cause you to have one or more of the side effects as listed below.

Over 3,000 patients with psoriasis have been treated with risankizumab SC, predominantly with the 150 mg dose. The rates of overall side effects and serious side effects were similar between risankizumab treatment and placebo treatment (an inactive substance). No new safety risks have been observed with risankizumab compared to the other antibody treatments that affect the immune system and were investigated in the risankizumab clinical development. In clinical trials that compared risankizumab to placebo and either ustekinumab or adalimumab, serious side effects occurred in 2.4% for the risankizumab group compared to 4.0% for the placebo group, 5.0% for the ustekinumab group, and 3.0% for the adalimumab group.

In a Phase 2 completed psoriatic arthritis study, 185 patients received either 75 mg or 150 mg of risankizumab SC or placebo. The most frequent side effects reported in patients who received risankizumab were viral upper respiratory tract infection (common cold caused by a virus) (17.5%), upper respiratory tract infection (common cold) (5.6%), and headache (5.6%).

In a Phase 2 completed CD study, 121 patients received 200 mg or 600 mg risankizumab or placebo by IV. Overall, the number of patients who reported side effects was similar between patients treated with risankizumab and patients treated with placebo. The most frequently reported side effects (equal to 5% or more of patients) in the risankizumab treatment group were arthralgia (joint pain) (17.1%), nausea (15.9%), headache (13.4%), abdominal pain (12.2%), asthenia (lack of energy) (7.3%), pyrexia (fever) (7.3%), vomiting (7.3%), and diarrhea (6.1%).

Based on review of all the safety information to date, the following are known risks with risankizumab use:

<u>Very common (10% or more): may affect more than 1 in 10 people</u>

- upper respiratory infections with symptoms such as sore throat and stuffy nose (13%)

Common (1% or more and less than 10%): may affect up to 1 in 10 people

- feeling tired (2.5%)
- fungal skin infection (1.1%)
- injection site reactions (1.5%)
- headache (3.5%)

Uncommon (0.1% or more and less than 1%): may affect up to 1 in 100 people

- Infection of hair follicles (seen as small raised red bumps on the skin)

Skin Biopsy Risk: You may have discomfort when the local anesthetic (numbing medicine) is injected to numb the area. The biopsy procedure may cause you to have a local infection that can be treated with an antibiotic. Other risks may include an allergic reaction to the local anesthetic. Symptoms of an allergic reaction are rash, difficulty breathing, and lightheadedness. If you think you are having an allergic reaction, call the study doctor right away. You may also have some bleeding after the biopsy. After the anesthesia wears off, there may be some temporary soreness at the biopsy sites. Biopsy wounds usually heal with a small scar, but sometimes a raised scar or visible lump may result. There is also a small chance that this biopsy may result in a wound that does not heal or that heals very slowly over time. Rarely, infection, bleeding, nerve damage, and darkening and lightening of the biopsied area may occur.

Areas of Safety Interest:
Infections: Drugs that affect the body's immune system may increase the risk of infections, including tuberculosis (TB). No cases of active TB have been reported in patients treated with risankizumab. You will be screened for signs of active infection before you start on risankizumab. Talk to your study doctor before and during use of risankizumab if you:

- currently have an infection or if you have an infection that keeps coming back.
- have TB.
- have recently received or plan to receive an immunization (vaccine); you should not be given certain types of vaccines while using risankizumab.

Injection Site Reactions: Injection of study drug under the skin could result in redness, pain, swelling, or hardness at the site of the injection. Also, bleeding or bruising at the injection site may occur. Most injection site reactions are not severe and resolve without any treatment, but can be uncomfortable for a few hours to a few days.

Liver Disease: A serious adverse reaction of drug-induced liver injury in conjunction with a rash that required hospitalization was reported in a patient with Crohn's disease following two 600 mg intravenous doses of risankizumab. The liver test abnormalities resolved following administration of steroids. Risankizumab was subsequently discontinued. Patients with liver cirrhosis should not be treated with risankizumab. During risankizumab treatment, prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury. Stopping treatment is recommended, if drug-induced liver injury is suspected. Patients should seek immediate medical attention if they experience symptoms suggestive of liver disease.

Other Possible Risks:
Some drugs that affect the immune response have been associated with side effects such as serious allergic reactions, and possible increased risk of malignancy (cancer).

Allergic Reactions: All drugs have a potential risk of an allergic reaction. Allergic reactions may vary from mild (rash, hives, itching) to severe reactions such as anaphylaxis (which may include difficulty breathing, swelling of the face or throat, low blood pressure, or loss of consciousness). A severe allergic reaction requires immediate medical treatment and could result in permanent disability or death. It is important to tell your study doctor about any past allergic reactions that you may have had to other drugs including antibody drugs (which are usually given by IV or injection under the skin). If you seek medical care for a possible allergic reaction, please request the treating health care provider to contact the study physician. Serious hypersensitivity reactions, including anaphylaxis, have been reported with use of risankizumab.

Malignancy (cancer): When an immune system pathway is blocked, there is a possibility of a decreased immune defense against malignancies. In the completed studies to date, risankizumab has not been associated with an increased risk of malignancies, but the risk with long term therapy is not known.

Cardiovascular Events: Patients with inflammatory diseases such as psoriasis, psoriatic arthritis and inflammatory bowel disease have an increased risk of major cardiovascular events (such as heart attacks, strokes, or cardiovascular death). In the completed psoriasis studies to date, risankizumab has not shown an increased risk of these events. However, any new or worsening signs or symptoms such as chest, neck or arm pain, shortness of breath, sensation of rapid heart rate, new visual symptoms or muscle weakness should be immediately reported to your study site and/or primary health care provider.

There is no antidote to risankizumab. Any side effects occurring as a result of risankizumab will be treated symptomatically.

2.3.2. KNOWN POTENTIAL BENEFITS

Risankizumab, an anti-IL-23 biologic, is highly effective and safe for treating plaque psoriasis.[9-11] The standard dose for this drug is 150 mg at Weeks 0 and 4, and then 150 mg every 12 weeks after two induction doses. Approximately 80% of patients reach PASI 90 and approximately 60% reach PASI 100 at 1 year, with few-to-no side effects.[9-11] In addition, the IMMhance study revealed that some patients undergoing risankizumab withdrawal demonstrated prolonged skin clearance long after their last dose.[11]

2.3.3. ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Doses of risankizumab higher than standard dosing used for psoriasis have been used to treat other diseases, such as Crohn's disease. No new or different side effects were seen with higher doses of risankizumab in these studies. Thus, the side effect profile in the current proposed study is expected to be favorable.

When testing higher doses of risankizumab, as described here, it is possible that efficacy will be higher than reported with standard dosing. It is also possible that disease remission following drug withdrawal will be longer than remission reported following drug withdrawal after standard dosing of risankizumab.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary Objective: to determine whether the reduction in the number and/or effector function of epidermal CD8+CD103+ Trm cells at Week 52 (compared to baseline numbers) in psoriasis patients treated with 4X standard induction doses of risankizumab (600 mg at Weeks 0, 4, and 16) is greater when compared to psoriasis patients treated with 2X standard induction doses of risankizumab (300 mg at Weeks 0, 4, and 16).	**Primary Endpoint**: change from baseline in number and/or effector function of epidermal CD8+CD103+ Trm cells at Week 52 in psoriasis patients treated with 4X standard induction doses of risankizumab (600 mg at Weeks 0, 4, and 16) or 2X standard induction doses of risankizumab (300 mg at Weeks 0, 4, and 16).	Trm cells are the primary cells within psoriatic lesions (and healed skin) that are responsible for psoriasis recurrences after skin lesions have cleared. Targeting these cells, as proposed here, may lead to prolonged remission of psoriasis.
Secondary Objectives: 1) to compare the percentage of patients with PASI 100 (complete clearance) at Weeks 28, 40, 52, and 100 in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab and 2) to compare safety events over 100 weeks in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab.	**Secondary Endpoints**: 1) PASI 100 (complete clearance) response at Weeks 28, 40, 52, and 100 in patients receiving 4X standard induction doses of risankizumab or those receiving 2X standard induction doses of risankizumab and 2) safety events over 100 weeks in patients receiving 4X standard induction doses of risankizumab or those receiving 2X standard induction doses of risankizumab.	These are standard measures of efficacy and safety for psoriasis studies.
Additional Objectives: 1) to compare other standard measures of psoriasis efficacy in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab and 2) to compare quality of life in patients receiving 4X standard induction doses of risankizumab vs. those receiving 2X standard induction doses of risankizumab.	**Additional Endpoints:** 1) Change from baseline in PASI and BSA at various timepoints, PASI 75 response, PASI 90 response, PASI 100 response, and sPGA 0/1 response at various timepoints 2) Change from baseline in DLQI at Weeks 28 and 52 and DLQI 0/1 response at Weeks 28 and 52	1) These are standard measures of efficacy for psoriasis studies. 2) These are standard measures of quality of life for psoriasis studies.

4. STUDY DESIGN

4.1. OVERALL DESIGN

The overall hypothesis for this study is to determine whether high-dose risankizumab, an anti-IL-23 blocker approved for plaque psoriasis, can target Trm cells with psoriatic lesions, and whether a more marked reduction of Trm cells correlates with high levels of efficacy and longer periods of disease remission.

In summary, this is single-center, randomized, interventional, Phase 2 study (KNOCKOUT) consisting of a 52-week double-blind period followed by a 48-week unblinded extension comparing tissue and clinical effects of 4X standard induction doses of risankizumab vs. 2X standard induction doses of risankizumab in patients with moderate-severe plaque psoriasis.

Twenty patients with moderate to severe plaque psoriasis will be randomized in a 1:1 manner to receive either risankizumab 600 mg (4X dosing) or 300 mg (2X dosing), SC, at Weeks 0, 4, and 16. All patients will receive four SC injections at Weeks 0, 4, and 16 (into right arm, left arm, right thigh, left thigh) by an unblinded pharmacist. For patients randomized into the highest induction dose arm, each shot will contain 150 mg of risankizumab; for patients randomized into the 2X induction dose arm, two shots will contain 150 mg of risankizumab each and 2 shots will contain placebo (sterile saline).

Skin biopsies of lesional and/or non-lesional skin will be obtained at Week 0, and an additional skin biopsy of lesional skin will be obtained at Week 52. These samples will be processed for immunohistochemical staining and RNA seq analysis. Psoriasis severity clinical assessments (PASI, sPGA, BSA) and safety assessments (vital signs, history) will be assessed at screening and Weeks 0, 2, 4, 8, 12, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, and 100 (to assess secondary and additional endpoints). Routine labs will be performed at Screening and at Weeks 4, 8, 22, and 52.

4.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

We postulate that risankizumab, an anti-IL-23 biologic used to treat moderate to severe plaque psoriasis, may lead to high levels of prolonged skin clearance due to an effect on resident memory T (Trm) cells. Here, we describe a pilot study that explores whether higher induction doses of risankizumab (4X and 2X standard induction doses) can more effectively target Trm cells within psoriatic lesions, and whether more profound knock-down of Trm cells is associated with higher levels of complete clearance (i.e., PASI 100) and for longer periods of time.

4.3. JUSTIFICATION FOR DOSE

Risankizumab, an anti-IL-23 biologic, is highly effective and safe for treating plaque psoriasis.[9-11] The standard dose for this drug is 150 mg at Weeks 0 and 4, and then 150 mg every 12 weeks after two induction doses. Approximately 80% of patients reach PASI 90 and approximately 60% reach PASI 100 at 1 year, with few-to-no side effects.[9-11] In addition, the IMMhance study revealed that some patients undergoing risankizumab withdrawal demonstrated prolonged skin clearance long after their last dose.[11]

When testing higher doses of risankizumab (600 mg or 300 mg at Weeks 0, 4, and 16), as described here, it is possible that efficacy will be higher than reported with standard dosing. It is also possible that disease remission following drug withdrawal will be longer than remission reported following drug withdrawal after standard dosing of risankizumab.

Indeed, doses of risankizumab higher than standard dosing used for psoriasis have been used to treat other diseases, such as Crohn's disease. No new or different side effects were seen with higher doses of risankizumab in these studies. Thus, the side effect profile in the current proposed study is expected to be favorable.

4.4. END OF STUDY DEFINITION

Patients will be observed for 100 weeks after their first dose of risankizumab (84 weeks after their last dose of risankizumab).

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

1. Subject has provided written consent
2. Subject has the ability to comply with all study visits and procedures
3. Subject is at least 18 years of age
4. Subject has chronic stable plaque psoriasis:
    a. For at least 6 months
    b. Severity of BSA ≥10 and PASI ≥12
5. Female subjects of child-bearing potential must have a negative urine test at screening and baseline. Female subjects must be either postmenopausal, or permanently surgically sterile, or for women of child-bearing potential practicing at least one form of birth control (Section 5.6)

5.2. EXCLUSION CRITERIA

1. Breastfeeding or pregnant women, or women who plan to become pregnant during study period
2. Participation in any other clinical trial
3. Active infection with HIV, hepatitis B virus, or hepatitis C virus
4. Active infection with tuberculosis or untreated latent tuberculosis
5. History of known active cancer, other than non-melanoma skin cancer or cervical carcinoma *in situ*, in the past 3 years
6. History of drug or alcohol abuse in the past 6 months, as per investigator's assessment
7. History of suicidal ideation or attempts in the past 6 months
8. Presence of any concurrent illness, which in the opinion of the investigator, would place the patient at unnecessary safety risk during the trial or interfere with completion of the trial
9. Treatment with topical medications for psoriasis in the past 2 weeks
10. Treatment with oral medications for psoriasis in the past 4 weeks
11. Phototherapy for psoriasis in the past 4 weeks
12. Any prior treatment with risankizumab

13. Treatment with biologic medications for psoriasis (other than risankizumab) in the past 4 months

5.3. LIFESTYLE CONSIDERATIONS

None.

5.4. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Individuals who do not meet the criteria for participation in this trial (screen failure) may not be rescreened. Laboratory assessments used to determine subject eligibility may be repeated during the screening period before the subject is considered a screen failure.

5.5. STRATEGIES FOR RECRUITMENT AND RETENTION

OMRC, the sponsor of this trial, has a large database of psoriasis patients. We will recruit patients from this database as well as from general Google ads and referrals from community dermatologists.

5.6. CONTRACEPTION RECOMMENDATIONS

Female subjects of child-bearing potential must be ready and able to use highly effective methods of birth control, or subjects must have only vasectomized sexual partner(s) or be abstinent throughout the study. Women of child-bearing potential are defined as: having experienced menarche, and are not postmenopausal (12 months with no menses without alternative medical cause), and are not permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
The following is a list of accepted contraception methods:

- Combined (estrogen and progesterone containing) hormonal contraception (oral, intravaginal, transdermal, injectable) associated with the inhibition of ovulation, initiated at least 1 month prior to study
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with the inhibition of ovulation, initiated at least 1 month prior to study
- Bilateral tubal occlusion/ligation
- Vasectomized partner(s)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- True abstinence (refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable.

6. STUDY INTERVENTION

6.1. STUDY INTERVENTION(S) ADMINISTRATION

6.1.1. STUDY INTERVENTION DESCRIPTION

The IB for risankizumab (Skyrizi®), approved by the FDA for use in patients with moderate-to-severe psoriasis, is included with the IRB submission.

6.1.2. DOSING AND ADMINISTRATION

Twenty patients with moderate to severe plaque psoriasis will be randomized in a 1:1 manner to receive either risankizumab 600 mg (4X dosing) or 300 mg (2X dosing), SC, at Weeks 0, 4, and 16. All patients will receive four SC injections at Weeks 0, 4, and 16 (into right arm, left arm, right thigh, left thigh) by an unblinded pharmacist. For patients randomized into the highest induction dose arm, each shot will contain 150 mg of risankizumab; for patients randomized into the 2X induction dose arm, two shots will contain 150 mg of risankizumab each and 2 shots will contain placebo (sterile saline).

6.2. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1. ACQUISITION AND ACCOUNTABILITY

All investigational product will be shipped to OMRC by AbbVie. Each supplied syringe will contain either 150 mg of risankizumab or a matching placebo will be administered to patients at OMRC by an unblinded pharmacist at OMRC. All patients as well as physicians performing efficacy and safety assessments will be blinded to the treatment group (600 mg or 300 mg) during the initial 52-week period. Used syringes will be placed in sharps containers. The unblinded pharmacist will keep a record of administered drug.

6.2.2. FORMULATION, APPEARANCE, PACKAGING, AND LABELING

SKYRIZI (risankizumab-rzaa) injection 150 mg/mL prefilled syringe and prefilled pen contain a sterile, preservative-free, colorless to yellow, and clear to slightly opalescent solution. Each single-dose prefilled syringe or prefilled pen consists of a 1 mL glass syringe with a fixed 27- gauge ½ inch needle with needle guard.

A copy of the drug labels prepared for this study are provided with this protocol for reference.

6.2.3. PRODUCT STORAGE AND STABILITY

Investigational product will be stored at 4 °C (2-8 °C range), in the original carton to protect from light, and in a locked and temperature-controlled refrigerator, one that only can be accessed by the unblinded pharmacist.

6.2.4. PREPARATION

Risankizumab injections will be prepared and administered in the clinic according to dosing instructions per the IB.

- Before injecting, remove the carton with SKYRIZI from the refrigerator and without removing the prefilled pen or prefilled syringe(s) from the carton, allow SKYRIZI to reach room temperature out of direct sunlight (30 to 90 minutes for the prefilled pen and 15 to 30 minutes for the prefilled syringe(s)).
- Visually inspect SKYRIZI for particulate matter and discoloration prior to administration.
    - SKYRIZI 150 mg/mL is a colorless to yellow and clear to slightly opalescent solution. SKYRIZI 75 mg/0.83 mL is a colorless to slightly yellow and clear to slightly opalescent solution.
    - The solution may contain a few translucent to white particles. Do not use if the solution contains large particles or is cloudy or discolored.

6.3. MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To avoid unblinding of the patients and investigators as to treatment status during the double-blind period, all patients will be given 4 shots at Weeks 0, 4, and 16. An unblinded pharmacist will prepare and subcutaneously administer all drug and placebo (i.e., investigational product IP) to patients. This person will also be charged with accepting all IP shipments from AbbVie, storing IP in a locked refrigerator (maintained at 2-8 °C), and recording all IP administrations to patients. IP will be delivered in the right arm, left arm, right thigh, and left thigh by the unblinded pharmacist at Weeks 0, 4, and 16. Monitoring will occur for 30 minutes post-dose. Patients will be shielded from viewing injections performed by the unblinded pharmacist. If an investigator believes the safety of a study subject is at risk due to study drug administrations, that investigator may unblind the treatment status to help direct/coordinate medical care of that patient.

Once a subject reaches the end of the initial 52-week double blind period, the investigators, study staff and subject will be unblinded as to the treatment group.

6.4. STUDY INTERVENTION COMPLIANCE

6.5. CONCOMITANT THERAPY

6.5.1. RESCUE MEDICINE

No rescue medications or concomitant therapies for psoriasis will be allowed in this study.

7. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. DISCONTINUATION OF STUDY INTERVENTION

Subjects will be withdrawn from the study if, according to the investigator, safety of the subjects is compromised in any manner, or if subjects are no longer able to comply with study visits and procedures. Study subjects who are withdrawn will follow-up with their referring dermatologist, when possible. Study subjects who are withdrawn will not be replaced.

The reason for withdrawal will be captured in the Case Report Form (CRF).

7.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request, including post the 52-week double blind period of the study. The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. EFFICACY ASSESSMENTS

Clinical Assessments

All assessments will be performed at Oregon Medical Research Center, P.C. At screening, Week 0, Week 2, Week 4, and every visit thereafter until Week 100, the following will be done:

1. Physical examination (*complete exam at screening, baseline, Week 4, Week 16, and Week 52; targeted exam at every other visit per Investigator discretion)
2. Psoriasis Area and Severity (PASI)
3. Body Surface Area (BSA)
4. Static Physician's Global Assessment (sPGA)
5. DLQI (*at Weeks 0, 28, and 52 only)
6. Vital signs (temperature, blood pressure, heart rate, respiratory rate, and weight)
7. Past medical history, including past systemic treatments for psoriasis (*at screening visit only)
8. Columbia Suicide Severity Rating Scale (*at screening visit only)
9. Interim health history to assess for possible adverse events (*at all visits following the baseline visit)

Laboratory Assessments

At screening, Weeks 4, 8, 22, and 52, the following will be collected at Oregon Medical Research Center, P.C. and sent to a local laboratory:

1. Complete blood count (CBC) w/differential
2. Comprehensive metabolic panel
3. Urinalysis
4. Urine pregnancy test (*performed on-site only for women of child-bearing potential, at each visit up to Week 52, except Week 2)

At screening only, the following will be collected at Oregon Medical Research Center, P.C. and sent to a local laboratory:

1. HIV antibody
2. Hepatitis B panel
3. Hepatitis C antibody
4. Quantiferon Gold

At Weeks 0 and 52, the following will be collected at Oregon Medical Research Center, P.C. and shipped to the laboratory of Dr. Johann Gudjonsson at the University of Michigan:

1. One 6 mm skin biopsy of lesional skin (at Weeks 0 and 52) and one 6 mm skin biopsy of peri-lesional skin (at Week 0); both will be bisected and processed as follows:
2. **Single cell sequencing and CyTOF imaging**: A 6 mm punch biopsy will be bisected with one half cryopreserved in CryoStor CS10 media (Millipore, Sigma) in a cryogenic vial, and the other formalin fixed for CyTOF imaging and IHC. The CryoStor CS10 media is an optimized preservation media, that is formulated to address the molecular and biological aspects of cells during the cryopreservation process thereby directly reducing the level of cryopreservation-induced delayed-onset cell death and improving post-thaw cell viability and function. Tissue will be stored at -80C until shipping and processing. At processing samples will be rapidly thawed in a water bath in a continuous agitation and placed onto 25mL of cold 1xHBSS (as described Guillaumet-Adkins A, Genome Biology, 45, 2017). Samples will be incubated in 0.4% dispase (Life Technologies) in Hank's Balanced Saline Solution for 30 minutes. Epidermis and dermis are then separated. Epidermis is digested in 0.25% Trypsin-EDTA (Gibco) with 10U/mL DNase I (Thermo Scientific) for 1 hour at 37 °C, quenched with FBS (Atlanta Biologicals), and strained through a 70 µM mesh. Dermis will be minced, digested in 0.2% Collagenase II (Life Technologies) and 0.2% Collagenase V (Sigma) in plain medium for 1.5 hours at 37°C, and strained through a 70µM mesh. Epidermal and dermal cells will be recombined, and libraries will be constructed by the University of Michigan Advanced Genomics Core on the 10X Chromium system. Libraries will then be sequenced on the Illumina NovaSeq 6000 sequencer to generate 151-bp paired end reads with a goal of 10,000 cells, each with approximately 10,000 reads per cell (100 million reads per sample). Data processing including quality control, read alignment, and gene quantification will be conducted using the 10X Cell Ranger software.
3. **Data Analysis**: Initial processing of the sequencing reads will be performed using 10X Genomics Cell Ranger software, which performs sample de-multiplexing, barcode processing, and single cell 5' gene counting. As recently summarized in an excellent review (Andrews TS, Mol Aspects Med 59, 114-122,2018), the key elements of scRNA-seq analysis include feature selection, dimensionality reduction, and clustering. Low quality reads and cells will be filtered by Seurat (Butler A, Nature Biotechnology 36, 411-420, 2018), and we will apply a scalable computational approach that utilizes the differences in expression values between cells shared across experiments to facilitate robust batch correction (Haghverdi L, Nature Biotechnology 36, 421-

427, 2018) and thus cell population (type) assignment. Data will be clustered using unique molecular identifier (UMI), and then each cell subpopulation will be analyzed, and characteristic gene expression determined. Furthermore, single-cell trajectory analyses (pseudotime) will be performed to quantify the state of individual cells. Our bioinformatic team will implement computational approaches to integrate single cell and bulk RNA-seq data.

4. **Bulk RNA-seq**: For RNA seq, RNA 151 nucleotide paired-end read will be performed using the NovaSeq platform, which generates >800 million reads per sequencing run. We will use barcode oligo adapters to allow multiplexing of 15 samples per lane and expect to generate >20 million uniquely mapped reads/sample on average (assuming >75% mapping rate). We will use our in-house analysis pipeline to perform adapter trimming and quality control procedures for the RNA-seq samples. Multiple testing correction will be used to identify statistically significant results (False Discovery Rate <10%). We will also conduct in silico analysis, including pathway, transcription factor, and co-expression analysis, to provide biological inference.
5. **CyTOF Imaging**: Formalin-fixed, paraffin-embedded tissue slides will be heated for 2 hours at 60°C, deparaffinized, and rehydrated. Slides will be placed in pH 9 Tris/EDTA antigen retrieval buffer and heated at 96°C for 30 minutes. After cooling, slides will be blocked in 3% BSA, and stained with a cocktail of metal-tagged antibodies overnight at 4 °C including CD45, E-Cadherin, CD4, CD8, collagen, and pan-actin, and TRM markers CD27 (Fluidigm #3171024D), CD127 (Fluidigm # 3168026D). These have already been optimized in a panel for staining at our labs. For staining for CD69, CD103, CD49a, and circulating memory markers: CD62L, CCR7, we will optimize those using Imaging Mass Cytometry Staining Protocol for FFPE sections. The stained tissue is ablated, and raw data acquired on the Hyperion Imaging System (Fluidigm).
6. **Imaging CyTOF Data Analysis:** Multiplexed imaging CyTOF data will be pre-processed using commercial acquisition software (Fluidigm) and converted to .TIFF images. These images will be segmented into individual cells using CellProfiler v3.1.8 for single-cell analysis. The t-SNE dimensionality reduction algorithm and the Phenograph unsupervised clustering algorithm will be performed on TRM markers (CD4, CD8, CD69, CD103, CD49a, CD62L, CCR7) using HistoCAT v1.75 software. For t-SNE and PhenoGraph, the data will be normalized to the 99th percentile. The Heatmap will be generated to show z-scored mean marker expression of each cluster. P values will be computed using 2-tailed Student's t tests assuming homoscedasticity.

Remaining tissue samples will be stored at the University of Michigan laboratory until the end of trial or until arrangement for shipping to AbbVie is made. Patient ICF will include language for future use of remaining tissue samples by AbbVie in additional research.

8.2. SAFETY AND OTHER ASSESSMENTS

The Principal Investigator (PI) shall comply with applicable Laws pertaining to reporting of Adverse Events to the competent regulatory authorities. In addition, the PI shall comply with the reporting requirements that are specified for each event listed below:

Event:	**Report to AbbVie within:**
Serious Adverse Events	four (4) calendar days if reporting a death or life-threatening event, and within eight (8) calendar days for all other Serious Adverse Events

Adverse Events	fifteen (15) calendar days
Safety Signals	fifteen (15) calendar days
Negative outcomes or untoward events during the course of a Study subject's pregnancy or upon delivery	fifteen (15) calendar days
Pregnancies experienced by a Study subject or a partner of a Study subject receiving an AbbVie product	fifteen (15) calendar days
Special Situations	fifteen (15) calendar days

The PI or designee shall promptly make available to AbbVie such records as may be necessary and pertinent to investigate any Safety Information, if specifically requested by AbbVie. AbbVie's contact for reporting Serious Adverse Events, Adverse Events, pregnancies, pregnancy experiences, Safety Signals and Special Situations is PPDINDPharmacovigilance@AbbVie.com.

"Product Complaint" means any suspected quality defect in an AbbVie product or its AbbVie-provided packaging, labeling or medical device component. Product Complaints may include, but are not limited to:

1. damaged or broken product or packaging issues
2. product appearance whose color/markings do not match the labeling
3. labeling discrepancies/inadequacies in the labeling/instructions
4. missing components/product
5. any death of a patient
6. device not working properly or use errors
7. any illness, injury, or adverse event in the proximity of the device
8. an adverse event that could be a result of using the device
9. any event needing medical or surgical intervention, including hospitalization, while using the device

In order for AbbVie to comply with all FDA requirements pursuant to 21 CFR 211 and 21 CFR 820, the PI or designee shall report to AbbVie within one (1) working day any Product Complaint. The PI or designee will report Product Complaints that involve an AbbVie product, whether AbbVie has supplied the AbbVie product used in the Study or not. AbbVie's contact for reporting Product Complaints is PPDINDPharmacovigilance@AbbVie.com.

8.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

Such an event can result from use of the drug as stipulated in the labeling, as well as from "special situations" as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, lack of efficacy, or drug withdrawal, all which must be reported whether associated with an adverse event or not.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event, and suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. Examples of such 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.

The following definitions will be used to rate the severity for any adverse event being collected as an outcome/data point in the study and for all serious adverse events.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

The following definitions will be used to assess the relationship of the adverse event to the use of product:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL HYPOTHESES

The study is exploratory in nature and is not statistically powered to detect differences between the treatment arms. All analyses will be descriptive with the goal of developing hypothesis-generating data. The statistical analyses will be performed by AbbVie data and statistical sciences (DSS). Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

9.2. SAMPLE SIZE DETERMINATION

The study is exploratory in nature and is not statistically powered for hypothesis testing. The sample size of 20 subjects is determined based on study feasibility.

9.3. ANALYSIS SET

The Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy and Baseline analyses. Subjects will be grouped according to treatment as randomized.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. For the Safety Analysis Set, subjects are assigned to a treatment group based on the treatment actually received, regardless of the treatment randomized.

9.4. HANDLING OF POTENTIAL INTERCURRENT EVENTS

There will be two major types of intercurrent events (ICE) in this study: risankizumab discontinuation due to lack of efficacy or intolerability, and risankizumab discontinuation due to other reasons. Each intercurrent event will be addressed by different strategies, specifically:

Table ** Handling of Potential Intercurrent Events

Intercurrent Event	**Strategy**	**Description**
risankizumab or study discontinuation due to lack of efficacy or intolerability	Composite variable strategy	Data after risankizumab or study discontinuation due to lack of efficacy or intolerability will be set to non-responder for binary endpoints. For continuous endpoints, set to last observation before discontinuation.
risankizumab discontinuation due to other reasons	Treatment policy strategy	Data after risankizumab discontinuation due to other reasons will be used regardless of whether the intercurrent event occurs.

9.5. METHODS FOR ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline disease characteristics will be presented by descriptive statistics by treatment arm for the FAS. Medical history, prior therapy and medication, and concomitant medications will be summarized as well. Categorical variables will be summarized with frequency and percentage; percentages will be calculated with non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

9.6. METHODS FOR ANALYSIS OF PRIMARY OUTCOMES

For the primary outcomes, after handling of intercurrent events as specified in Section 9.4, the change from baseline in the number and/or effector function of epidermal CD8+CD103+ Trm cells at Week 52 will be summarized with mean, standard deviation, 95% confidence interval, and compared between the two treatment arms with t-test. Additional analysis with non-parametric test (e.g., Wilcoxon signed-rank test) will be performed, as appropriate. Details will be provided in the SAP.

9.7. METHODS FOR ANALYSIS OF SECONDARY OUTCOMES

For binary endpoints, after handling of intercurrent events in Section 9.4, the proportion will be summarized with percentage, 95% confidence interval, and compared between the two treatment arms with Fisher's exact test.

9.8. METHODS FOR ANALYSIS OF SAFETY OUTCOMES

Treatment-emergent adverse events (TEAEs) are defined as those that began or worsened in severity after the first dose of the study drug but within 140 days after the last dose of the study drug. The number and percentage of subjects experiencing TEAEs will be tabulated by symptoms, severity, and relationship to the product as assessed by the investigator. Summaries (including percentages and events per 100 patient-years) of SAEs, deaths, and AEs leading to discontinuation will be provided as well. Pre-treatment AEs will be summarized separately, based on data availability. Note that missing safety data will not be imputed. Analysis details will be specified in the SAP.

9.9. MISSING DATA HANDLING

For the primary analysis, missing data will be assumed as missing completely at random (MCAR). Data after handling intercurrent events will be used as observed.

For sensitivity analysis (as appropriate), missing data will be assumed as missing at random (MAR). Missing data after handling intercurrent events will be imputed by multiple imputation, as appropriate. Details will be documented in SAP.

9.10. SENSITIVITY ANALYSES

Analyses based on MAR, as appropriate, will be conducted as sensitivity analysis to handle missing data after handling of intercurrent events. Details of sensitivity analysis based on MAR will be provided in SAP.

9.11. MULTIPLICITY ADJUSTMENT

The study is exploratory in nature and there is no hypothesis testing for confirmatory purpose, thus no multiplicity adjustments is employed, and the results should be interpreted accordingly.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1. INFORMED CONSENT PROCESS

10.1.1.1. CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

All patients will sign and date an Informed Consent Form (ICF) prior to performing any study procedures. A copy of the completed ICF will be given to each patient.

10.1.1.2. CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2. CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the IND sponsors, investigators, and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence by the IND sponsor. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the IND sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the IND sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product 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 pharmacy records for the participants

in this study. The clinical study site will permit access to such records only in accordance with the informed consent form.

The study participant's contact information will be securely stored at the IND sponsor's site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or IND sponsor requirements.

Pseudonymized study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted by the IND sponsor to and stored at University of Michigan, AbbVie, and AbbVie's Representatives. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the IND sponsor [Oregon Medical Research Center] research staff will be secured, and password protected. At the end of the study, all study databases will be pseudonymized and archived by the IND sponsor [Oregon Medical Research Center].

10.1.3.FUTURE USE OF STORED SPECIMENS AND DATA

Permission to transmit data and biological samples to the University of Michigan, AbbVie, and AbbVie's representatives will be included in the informed consent.

These data and samples could be used by IND sponsor, University of Michigan, AbbVie, and AbbVie's representatives for future exploratory research in accordance with the informed consent form and applicable laws.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Benjamin D. Ehst, MD, PhD
Investigator, Oregon Medical Research Center
1750 S Harbor Way, Suite 330, Portland, OR 97201
[redacted]
[redacted]

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.0 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

10.1.5.1 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending

or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and record deviations. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.7 PUBLICATION AND DATA SHARING POLICY

Each party is committed to fostering the highest standard of conduct related to Scientific Publications and transparency. Accordingly, the parties agree that the following shall apply to all Scientific Publications:

1. Scientific publications should be published in a timely manner, in accordance with industry standards, and present scientific information in an accurate and balanced way that does not exclude or inappropriately downplay negative safety or health information.
2. Authorship related to scientific publications shall be determined in accordance with and governed by the criteria defined by the International Committee Of Medical Journal Editors (ICMJE) "recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals" **("ICMJE recommendations").**
3. Institution's and AbbVie's respective roles in the study and/or scientific publications shall be disclosed in all scientific publications.

10.2. ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BSA	Body Surface Area
CBC	Complete Blood Count
CD	Crohn's Disease
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DLQI	Dermatology Life Quality Index
DSMB	Data Safety Monitoring Board
DSS	Data and Statistical Sciences
DRE	Disease-Related Event
EC	Ethics Committee
EP	Erythrodermic Psoriasis
eCRF	Electronic Case Report Forms
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GPP	Generalized Pustular Psoriasis
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act

HS	Hidradenitis Suppurativa
IB	Investigator's Brochure
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IL	Interleukin
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
IV	Intravenous
LSMEANS	Least-squares Means
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
OMRC	Oregon Medical Research Center
PASI	Psoriasis Area and Severity
PI	Principal Investigator
PsA	Psoriatic Arthritis
PsO	Psoriasis

QA	Quality Assurance
QC	Quality Control
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
sPGA	Static Physician's Global Assessment
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Events
Trm	Resident Memory T Cells
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2	25Jan2022	Schedule of activities was revised, and administrative clarifications were added.	Addressed typographical and administrative changes and clarifications.
3	04Nov2022	The Title Page was updated to include the AbbVie protocol number. The endpoints were revised. The Statistical Considerations Section of the protocol was revised. The abbreviations page was updated.	Title Page did not have the assigned AbbVie protocol number listed on the original protocol or previous amendments. To clarify the endpoints for the study. Statistical Considerations Section was revised to clarify the role of AbbVie Statistics/Programming and to provide additional information for the statistical analysis. Added stats abbreviations based on the revised statistical considerations section.
4	14Feb2023	The protocol was updated to extend the study for an additional year. Study was extended from Week 52 to Week 100 throughout the protocol. Clinical assessments were also extended through Week 100.	To follow up the subjects who are remaining in the study through Week 100.
5	27Mar2023	Addition of unblinding plan and removal of non-lesional biopsy at Week 52.	Subjects will be unblinded to their treatment group once they reach Week 52.
6	22Feb2024	Update to site location and Principal Investigator.	Oregon Medical Research Center relocated to a new address, Dr. Blauvelt is retiring on 05Mar2024, and Sub-I Dr. Ehst is assuming the role of PI.

11 REFERENCES

1. Hirai T, Whitley SK, Kaplan DH. Migration and function of memory $CD8^+$ T cells in skin. J Invest Dermatol. 2020;140:748-755.
2. Cheuk S, Wikén M, Blomqvist L, Nylen, Talme T, Ståhle M. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. J Immunol. 2014;192:3111-3120.
3. Matos TR, O'Malley JT, Lowry EL, Hamm D, Kirsch IR, Robins HS, et al. Clinically resolved psoriatic lesions contain psoriasis-specific IL-17-producing αβ T cell clones. J Clin Invest. 2017;127:4031-4041.
4. Gallais Serezal I, Classon C, Cheuk S, Barrientos-Somarribas M, Wadman E, Martini E, et al. Resident T cells in resolved psoriasis steer tissue responses that stratify clinical outcome. J Invest Dermatol. 2018;138: 1754-1763.
5. Kurihara K, Fujiyama T, Phadungsaksawasdi P, Ito T, Tokura T. Significance of IL-17A-producing CD8+CD103+ skin resident memory T cells in psoriasis lesion and their possible relationship to clinical course. J Dermatol Sci. 2019;95:21–27.
6. Iversen L, Eidsmo L, Austad J, de Rie M, Osmancevic A, Skov L, et al. Secukinumab treatment in new-onset psoriasis: aiming to understand the potential for disease modification-rationale and design of the randomized, multicenter STEPIn study. J Eur Acad Dermatol Venereol. 2018;32:1930-1939.
7. Mehta H, Mashiko S, Angsana J, Rubio M, Hsieh YM, Maari C, et al. Differential changes in inflammatory mononuclear phagocyte and T cell profiles within psoriatic skin during treatment with guselkumab versus secukinumab. J Invest Dermatol. 2021;141:1707-1718.
8. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. J Immunol. 2018;201:1605-1613.
9. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392:650-661.
10. Reich K, Gooderham M, Thaçi D, Crowley JJ, Ryan C, Krueger JG, et al. risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019;394:576-586.
11. Blauvelt A, Leonardi CL, Gooderham M, Papp KA, Philipp S, Wu JJ, et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. JAMA Dermatol. 2020;156:649-658.