NCT 03339999

Study ID: 1957-201-001

Title: A Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of AGN-242428 in Patients With Plaque Psoriasis

Protocol Date: December 21, 2017

TITLE PAGE

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of AGN-242428 in Patients With Plaque Psoriasis

Amendment Number: Amendment 2

Brief Protocol Title: AGN-242428 in the treatment of plaque psoriasis

Product: AGN-242428

Sponsor Name and Legal Registered Address:

Vitae Pharmaceuticals Inc., a subsidiary of Allergan plc
2525 Dupont Drive
Irvine, California USA 92612

Regulatory Agency Identifying Number(s): U.S. FDA IND 124698

Emergency Telephone Number Refer to the study contacts page

SAE Reporting Fax Number/Email:

Allergan	[redacted]	[redacted]

Sponsor Signatory:

Refer to the final page of this protocol for electronic signature and date of approval.

[redacted] **Date**

Approval Date: 21-Dec-2017

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	December 2017
Amendment 1	September 2017
Original Protocol	June 2017

Amendment 2 (December 2017)

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in Protocol Amendment 2 was to modify alcohol intake and food consumption during the study, clarify prohibited medications, and describe pharmacokinetic analyses.

Section No. and Name	Description of Change	Brief Rationale
1 Synopsis (Objectives and Endpoints)	Deleted "across scheduled postbaseline visits" and "Plasma concentrations of AGN-242428 at randomly selected times relative to last dose at the Week 6 and Week 10 visits" and replaced them with "and pharmacokinetic parameters"	To modify the pharmacokinetic objective
2 Schedule of [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
3.3 Benefit/Risk Assessment	Added strong CYP3A4 inhibitors and inducers	To update based on in vitro studies
4 Objectives and Endpoints	For consistency, the change that was made in Section 1 Synopsis (as described above) was also made here	To modify the pharmacokinetic objective
[redacted]	[redacted]	[redacted]
6.2 Exclusion Criteria	Added "with any anti-TNFα biologic therapy within 3 months or 5 half-lives of study, and/or all other" to 2.03. Note: Made this change throughout the protocol, where applicable	To clarify exclusion criteria
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
6.3.1 Meals and Dietary Restrictions	Added a grapefruit and Seville orange restriction for the entire study population	To modify verbiage regarding dietary restrictions
6.3.1 Meals and Dietary Restrictions	Removed the fruit restriction in the PK subset	To modify verbiage regarding dietary restrictions
6.3.2 Caffeine, Alcohol, and Tobacco	Deleted caffeine paragraph	To eliminate caffeine restrictions
6.3.2 Caffeine, Alcohol, and Tobacco	Deleted the following phrase from the Alcohol subsection: "no alcohol for the first month and then no more than a total of 3 drinks per week."	To modify verbiage regarding alcohol intake during the study
[redacted]	[redacted]	[redacted]
6.4 Screen Failures	Deleted "Participants who rescreen for the study must be reconsented." Replaced the text with "A participant who is rescreened is not required to sign another ICF	To modify verbiage regarding consent during rescreening

Section No. and Name	Description of Change	Brief Rationale
	if the rescreening occurs within 28 days from the previous ICF signature date."	
7.7.1 Prohibited Treatments and Washout Before the Study	Added "Any previous use of systemic psoriasis medications/treatments used by the participant prior to enrollment must be recorded on the eCRF."	To clarify what medication should be captured on the eCRF
[redacted]	[redacted]	[redacted]
8.1.1 Temporary Discontinuation	Deleted this section and replaced it with "The DMC allows for temporary discontinuation of dosing pending further analysis of possible safety issues (an option open to the DMC)."	To clarify temporary discontinuation
9.1.4 Photograph of Primary Lesion	Added "The images can be captured before or after the study medication is administered."	To clarify when the images can be captured
9.1.4 Photograph of Primary Lesion	Added "Participants may decline permission for use of their study photographs for advertising, publicity, and promotional purposes."	To clarify that participation is optional
[redacted]	[redacted]	[redacted]
9.4.4 Clinical Safety Laboratory Assessments	Deleted the local laboratory paragraph and replaced it with "All laboratory tests should be sent to the central laboratory for the study."	To clarify that the central laboratory should be used
9.5 Pharmacokinetics	Added additional pharmacokinetics text	To provide additional details on the pharmacokinetics
9.6 Pharmacodynamics	Deleted "Participants will consent to these additional analyses."	To reflect additional consent is not required
9.8 Biomarkers	Updated this section	To reflect biomarkers will be evaluated
10.3.1 Disposition and Baseline Demographic Characteristics Analyses	Deleted "and the safety analysis set"	Safety analysis set is similar to the mITT analysis set
10.3.4 Pharmacokinetic Analyses	Updated text to describe the pharmacokinetic analyses	To provide more detail on the analyses
10.3.5 Pharmacodynamic Analyses	Added "and Pharmacokinetic-Pharmacodynamic Analyses" to the title and text to this section	To provide additional detail on the pharmacokinetic-pharmacodynamic analyses
12.6 Liver Safety	Deleted HPLC assay and associated reference. Note:	HPLC is not necessary

Section No. and Name	Description of Change	Brief Rationale
	The reference was also deleted from Section 11	
12.8 List of Prohibited Medications	Added “sensitive” before substrates. Updated the medication in the table and added strong CYP3A4 inhibitors and inducers	To provide more clarification on what is prohibited
12.9 Protocol Amendment History	Moved Amendment 1 text here	To allow for Amendment 2 text to be in the beginning of this protocol
Throughout	Minor editorial revisions	Minor, therefore, have not been summarized

Table of Contents

List of Tables

1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of AGN-242428 in Patients With Plaque Psoriasis

Protocol Number: 1957-201-001

Brief Title: AGN-242428 in the treatment of plaque psoriasis

Study Phase: Phase 2b

Study Rationale:

This study will evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of 3 doses of AGN-242428, [redacted] and [redacted] once-daily, relative to placebo, in participants with moderate to severe plaque-type psoriasis. A previous proof-of-concept (POC) study (VTP-43742-002 Part 2) evaluated efficacy and safety of AGN-242428 over a 28-day treatment period. The treatment duration is increased to 16 weeks in the current trial to allow evaluation of efficacy and safety over the longer term.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare the efficacy of AGN-242428 with placebo, administered orally once-daily for a period of 16 weeks, in participants with moderate to severe plaque psoriasis	• The percentage of participants achieving a reduction (improvement) in Psoriasis Area and Severity Index (PASI) score of ≥ 75% from baseline to Week 16
Secondary	
• To compare the efficacy of AGN-242428 with placebo, with respect to the Physician's Global Assessment (PGA) score	• Percentage of participants achieving ≥ 2-point improvement in PGA score at Week 16 • Percentage of participants achieving a clear (0) or almost clear (1) score in PGA at Week 16
• To compare the efficacy of AGN-242428 with placebo, with respect to PASI score	• Percentages of participants achieving reductions of 50% and 90% from baseline in PASI score at Week 16
• To assess the safety and tolerability of AGN-242428 in participants with moderate to severe plaque psoriasis	• Incidence of adverse events (AEs) including severity and causality of AEs, as well as AEs leading to discontinuation • Change from baseline in clinical laboratory tests, vital signs and electrocardiogram (ECG)

Objectives	Endpoints
• To characterize the pharmacokinetics of AGN-242428 in participants with moderate to severe plaque psoriasis	• Plasma concentrations of AGN-242428 and pharmacokinetic parameters

Overall Study Design:

This is a double-blind, randomized, placebo-controlled trial to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of AGN-242428 when administered once-daily for 16 weeks to adults with moderate to severe plaque psoriasis. The study consists of 3 periods, as described below. Details of individual assessments to be completed at each study visit are included in Section 2.

Screening Period: The purpose of the screening period is to evaluate potential study participants and to qualify them for enrollment into the study. This period begins at the point of informed consent and ends when the participant is randomized to treatment. The screening period will be up to 4 weeks (≤ 28 days) in duration.

Treatment Period: Participation in the study begins at the point the participant is randomized. The treatment starts after his/her first dose of study medication and ends after 16 weeks of treatment or at the point of permanent study medication withdrawal should the participant discontinue treatment prior to completion of Week 16.

On Day 1 of the treatment period, qualified participants will be randomly assigned to receive 16 weeks of once-daily oral treatment with [redacted] AGN-242428, [redacted] AGN-242428, [redacted] AGN-242428, or placebo. Baseline data for evaluation of participant efficacy and safety will be obtained on Day 1, prior to receiving the first dose. Participants will complete study visits on the first day of treatment and following 2, 4, 6, 8, 10, 12 and 16 weeks of treatment for evaluation of efficacy, safety and tolerability assessments.

A subset of approximately 14 to 18 participants in each treatment group (includes placebo), who have provided consent, will have sequential blood samples collected at scheduled times before and up to 24 hours after study medication administration during the Week 4 visit to establish AGN-242428 pharmacokinetic (PK) concentration versus time profiles. All participants will have blood samples collected to determine trough AGN-242428 concentrations obtained on Day

1 and at the Week 4, 8, 12 and 16/early termination visits. Random time PK sampling at Weeks 6 and 10 (in addition to other assessments eg, select laboratory tests [see Table 9-4] and AEs [Section 9.2]) will also be obtained in all participants.

Any participant who exhibits a predefined change in clinical laboratory parameters may be required to complete unscheduled visits to further monitor abnormal safety laboratory test results. See Section 2 for testing criteria. Investigators may complete unscheduled study visits at any point they feel necessary to monitor and ensure participant safety. [redacted]

Follow-up Period: Participants will return for a follow-up visit 14 ± 3 days after completion or premature discontinuation of study medication for end-of-study assessments.

A Data Monitoring Committee (DMC) will review select safety and exposure data (as needed), when approximately 10%, 30%, 60% and 80% of the total participants have completed treatment through Week 4. Ad-hoc meetings of the DMC may be scheduled to evaluate potential safety signals, as indicated. The DMC will review blinded data. If there is a significant safety signal, then unblinded data may be reviewed in a closed session by DMC members designated as unblinded reviewers. Policies, procedures and composition of the DMC are described in the DMC charter for this trial.

Key inclusion criteria: Male or female participants who have a confirmed diagnosis of plaque psoriasis, diagnosed at least 6 months before study, with a PGA score ≥ 3 at screening and baseline. Severity of disease must be at least moderate, defined as Psoriasis Area and Severity Index (PASI) ≥ 12 and % body surface area (BSA) ≥ 10. Participant is a candidate for phototherapy or systemic therapy for psoriasis.

Key exclusion criteria: Non-plaque forms of psoriasis (erythrodermic, guttate, pustular) or drug-induced psoriasis. Psoriasis which has not been stable for the 4 weeks prior to screening and which is unstable at Study Day 1. History of Gilbert's, Rotor, or Dubin-Johnson syndromes or any other disorder of bilirubin metabolism. History of active mycobacterium tuberculosis (TB) infection or untreated or inadequately treated latent TB. Positive QuantiFERON test for TB infection. Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline. Positive drug and/or alcohol test at screening (with the exception of marijuana). Retesting in the case of a positive alcohol test is allowed at the discretion of the sponsor. Current treatment or history of treatment for psoriasis with any anti-TNFα biologic therapy within 3 months or 5 half-lives of study, and/or all other biologics within 6 months of study (Day 1) is prohibited. Efficacy failure on 2 or more biologic agents for the treatment of psoriasis when the failures occurred within 1 year of the initiation of the therapy of the first biologic agent. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin (TBL) exceeding 1.5 times the upper limit of normal (ULN) at screening (may be repeated once to confirm value). Values that are above the ULN and ≤ 1.5 x ULN must be repeated to confirm that the value is stable.

Number of Participants:

Participants will be screened to achieve approximately 200 randomly assigned to study medication and an estimated total of 160 evaluable participants who will complete the study (estimated 40 evaluable participants per treatment group).

Number of Sites:

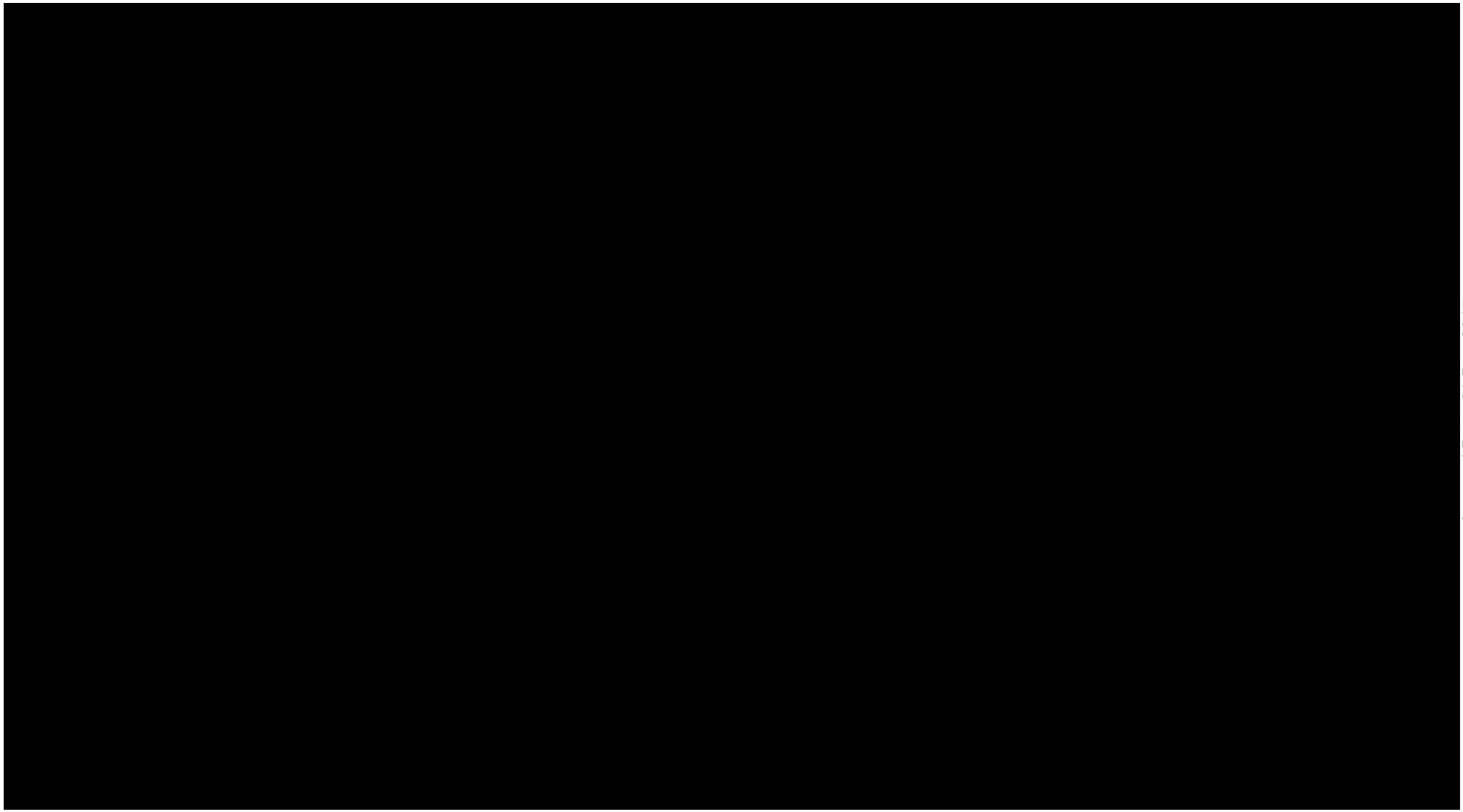
Approximately 40 study centers in the United States

Treatment Groups and Study Duration:

The trial will consist of a screening period of up to 4 weeks (≤ 28 days), a treatment period of once-daily administration for 16 weeks and a follow-up period of 14 ± 3 days after completion of study medication, or after early withdrawal. Thus, the trial duration for each participant will be up to 22 weeks ± 3 days from screening to follow-up.

Approximately 200 participants will be randomly assigned (1:1:1:1) to once-daily study medication (50 participants to AGN-242428 [redacted] 50 participants to AGN-242428[redacted], 50 participants to AGN-242428 [redacted] and 50 participants to placebo) to provide an estimated total of 160 evaluable participants who will complete the study.

[redacted]



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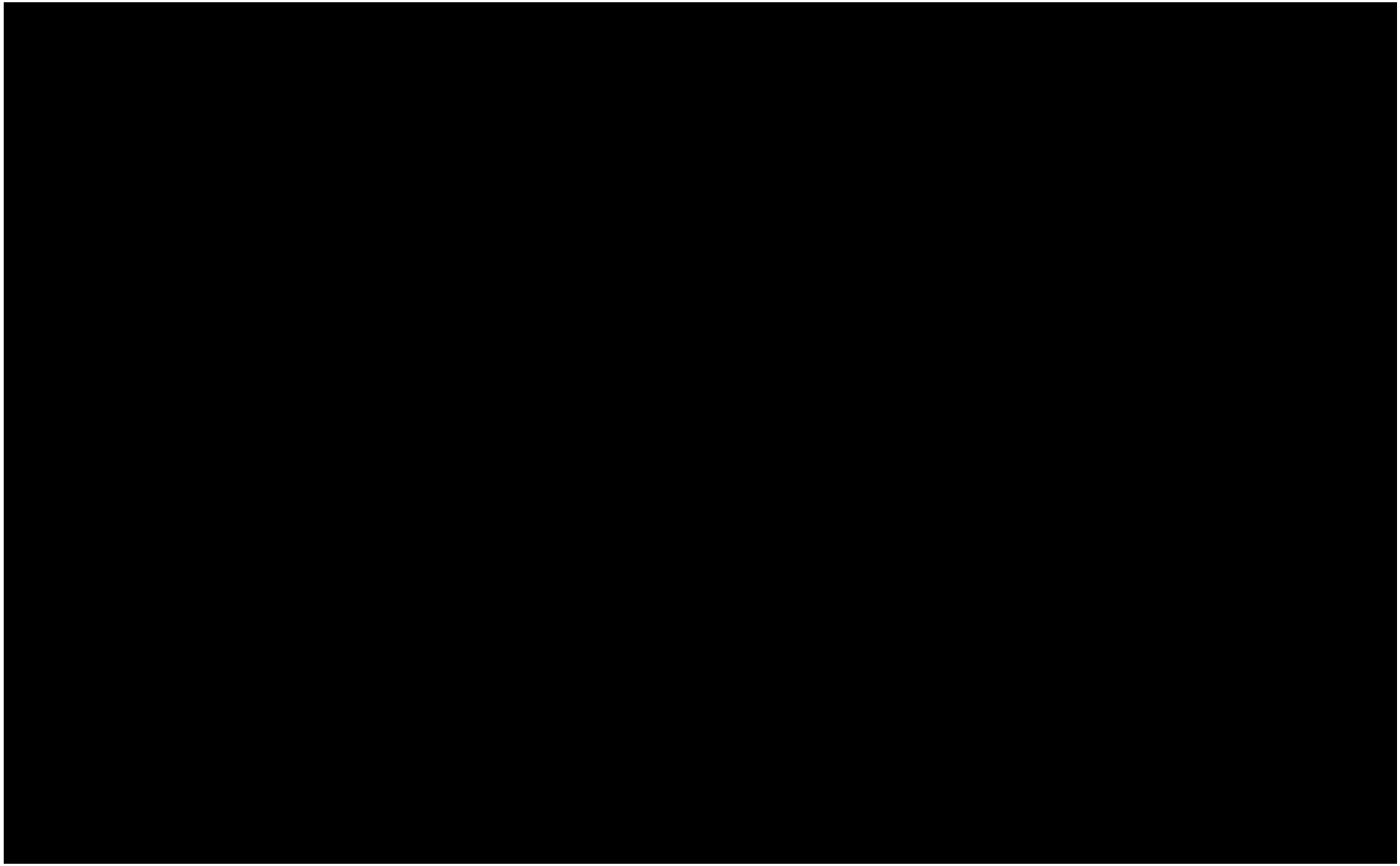

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[redacted]

3. Introduction

AGN-242428 (formerly Vitae Pharmaceuticals compound VTP-43742) is an orally active small molecule inhibitor of RORγt activity that is being pursued as a potential treatment for psoriasis and other autoimmune disorders. Increased production of the inflammatory cytokine interleukin-17A (IL-17A) appears to be a critical part of the pathophysiology in certain autoimmune disorders. RORγt is a nuclear hormone receptor that is essential for the formation of T helper 17 (Th17) cells and for the synthesis of IL-17A. It is expected that inhibition of RORγt activity in Th17 and other cells will be beneficial for the treatment of multiple autoimmune disorders.

Summaries and detailed results of individual studies and assays included in the nonclinical investigational program are included in the investigator's brochure (IB). Clinical investigators must read and use the IB in conjunction with this protocol.

3.1. Study Rationale

This study will evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of 3 doses of AGN-242428, [redacted], [redacted] and [redacted] once-daily, relative to placebo, in participants with moderate to severe plaque-type psoriasis. A previous proof-of-concept (POC) study (VTP-43742-002 Part 2) evaluated efficacy and safety of AGN-242428 over a 28-day treatment period. The treatment duration is increased to 16 weeks in the current trial to allow evaluation of efficacy and safety over the longer term.

3.2. Background

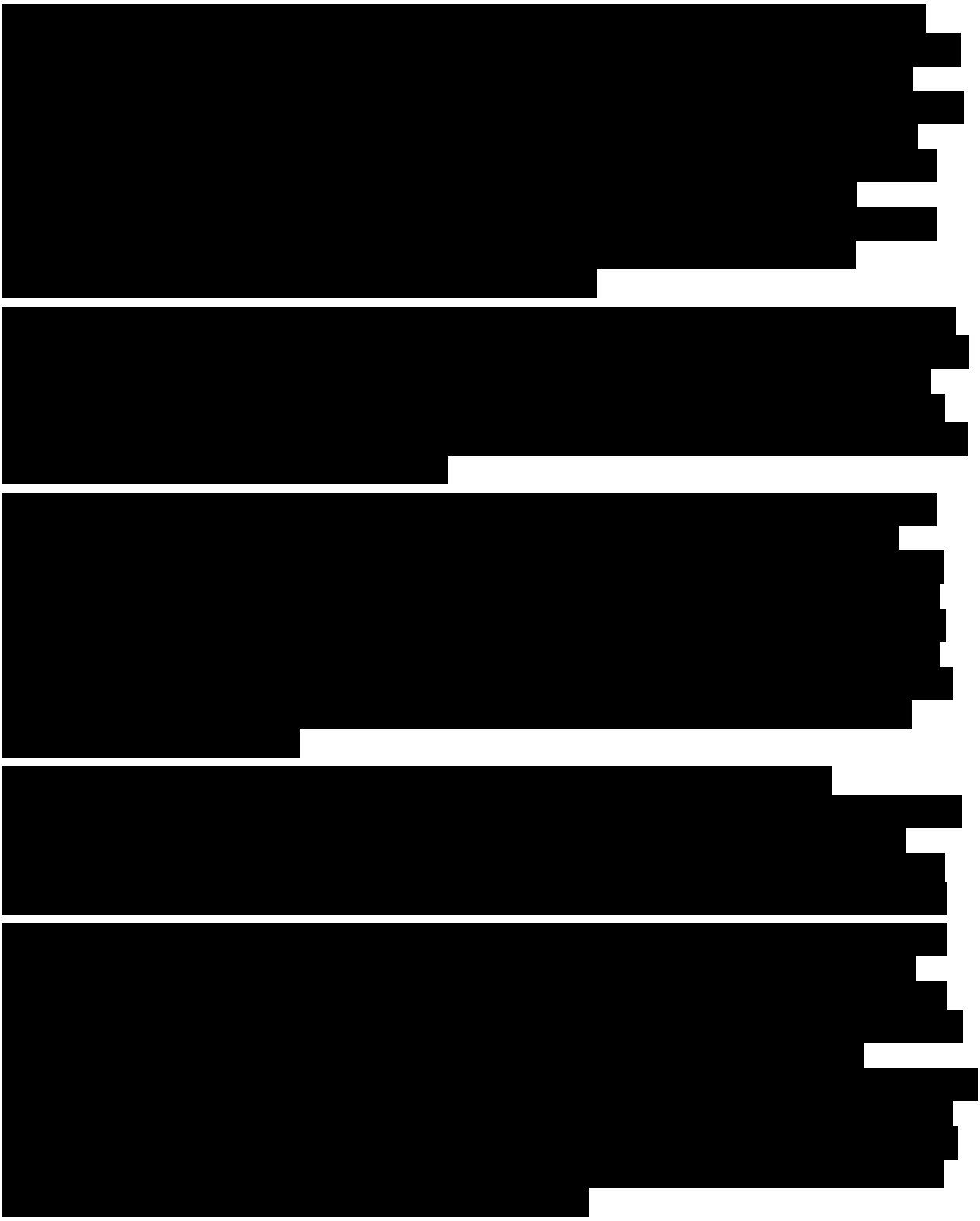
Brief summaries of topline results from a single ascending-dose study (VTP-43742-001) and a multiple-ascending dose study (VTP-43742-002) in healthy volunteers are provided in this protocol. Preliminary data from a POC study conducted in patients with moderate to severe plaque psoriasis are also summarized. Additional results of each study are provided in the IB which must be read and used in conjunction with this protocol.

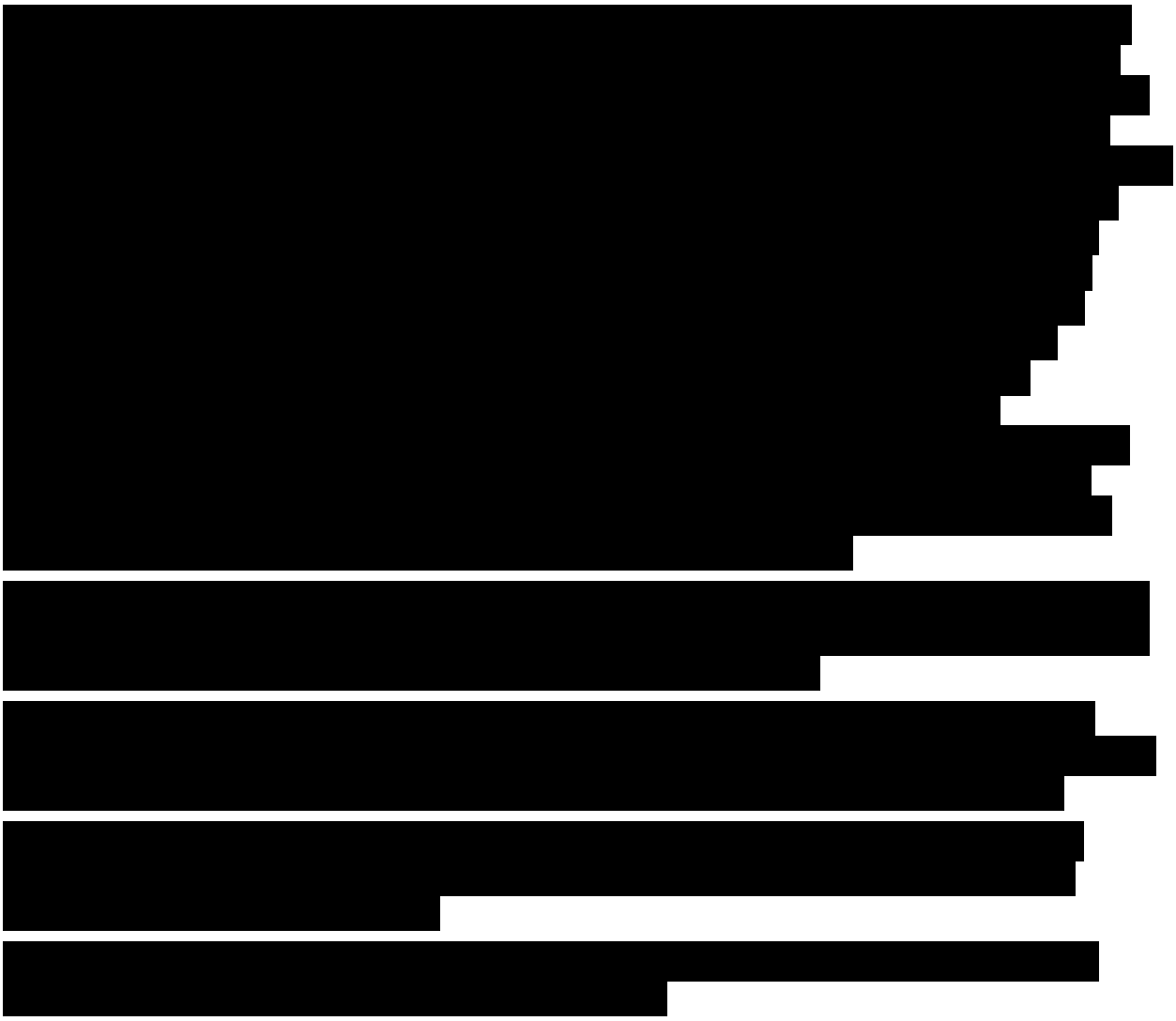
[redacted]

[redacted]

[redacted]

[redacted]





4. Objectives and Endpoints

Table 4-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the efficacy of AGN-242428 with placebo, administered orally once-daily for a period of 16 weeks, in participants with moderate to severe plaque psoriasis	• The percentage of participants achieving a reduction (improvement) in Psoriasis Area and Severity Index (PASI) score of ≥ 75% from baseline to Week 16
Secondary	
• To compare the efficacy of AGN-242428 with placebo, with respect to the Physician's Global Assessment (PGA) score	• Percentage of participants achieving ≥ 2-point improvement in PGA score at Week 16 • Percentage of participants achieving a clear (0) or almost clear (1) score in PGA at Week 16
• To compare the efficacy of AGN-242428 with placebo, with respect to PASI score	• Percentages of participants achieving reductions of 50% and 90% from baseline in PASI at Week 16
• To assess the safety and tolerability of AGN-242428 in participants with moderate to severe plaque psoriasis	• Incidence of adverse events (AEs) including severity and causality of AEs, as well as AEs leading to discontinuation • Change from baseline in clinical laboratory tests, vital signs and electrocardiogram (ECG)
• To characterize the pharmacokinetics of AGN-242428 in participants with moderate to severe plaque psoriasis	• Plasma concentrations of AGN-242428 and pharmacokinetic parameters
[redacted]	

Clinical Hypotheses

1. The percentage of participants achieving ≥ 75% reduction (improvement) in PASI score will be higher for AGN-242428-treated participants relative to placebo-treated participants.
2. AGN-242428 [redacted], [redacted] and [redacted] doses administered for 16 weeks will decrease clinical scores (eg, PASI, Physicians Global Assessment [PGA]) in participants with psoriasis to a greater extent than in participants receiving placebo.
3. AGN-242428 [redacted] dose administered for 16 weeks may decrease clinical scores in participants with psoriasis to a greater extent than treatment with [redacted] AGN-242428.
4. AGN-242428 at all 3 doses will be generally safe and well tolerated.

5. Study Design

5.1. Overall Design

This is a double-blind, randomized, placebo-controlled trial to evaluate the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of AGN-242428 when administered once-daily for 16 weeks to adults with moderate to severe plaque psoriasis. The study consists of 3 periods, as described below. Details of individual assessments to be completed at each study visit are included in Section 2.

Screening Period: The purpose of the screening period is to evaluate potential study participants and to qualify them for enrollment into the study. This period begins at the point of informed consent and ends when the participant is randomized to treatment. The screening period will be up to 4 weeks (≤ 28 days) in duration.

Treatment Period: Participation in the study begins at the point the participant is randomized. The treatment starts after his/her first dose of study medication and ends after 16 weeks of treatment or at the point of permanent study medication withdrawal should the participant discontinue treatment prior to completion of Week 16.

On Day 1 of the treatment period, qualified participants will be randomly assigned to receive 16 weeks of once-daily oral treatment with [redacted] AGN-242428, [redacted] AGN-242428, [redacted] AGN-242428, or placebo. Baseline data for evaluation of participant efficacy and safety will be obtained on Day 1, prior to receiving the first dose. Participants will complete study visits on the first day of treatment and following 2, 4, 6, 8, 10, 12 and 16 weeks of treatment for evaluation of efficacy safety and tolerability assessments.

A subset of approximately 14 to 18 participants in each treatment group (includes placebo), who have provided consent, will have sequential blood samples collected at scheduled times before and up to 24 hours after study medication administration during the Week 4 visit to establish AGN-242428 PK concentration versus time profiles. All participants will have blood samples collected to determine trough AGN-242428 concentrations obtained on Day 1 and at the Week 4, 8, 12 and 16/early termination visits. Random time PK sampling at Weeks 6 and 10 (in addition to other assessments eg, select laboratory tests [see Table 9-4] and AEs [Section 9.2]) will also be obtained in all participants.

Photography of primary lesions will be taken in a subset of participants that consent to have their photos taken. A primary lesion that is representative of the severity of the PGA and PASI scores at baseline (Day 1) will be selected and photographed at scheduled visits (see Section 2).

Any participant who exhibits a predefined change in clinical laboratory parameters may be required to complete unscheduled visits to further monitor abnormal safety laboratory test results. See Section 2 for testing criteria. Investigators may complete unscheduled study visits at any point they feel necessary to monitor and ensure participant safety. [redacted]

[redacted].

Follow-up Period: Participants will return for a follow-up visit 14 ± 3 days after completion of study medication or after early withdrawal for end-of-study assessments.

A DMC will review select safety and exposure data when approximately 10%, 30%, 60% and 80% of the total participants have completed treatment through Week 4. Ad-hoc meetings of the DMC may be scheduled to evaluate potential safety signals, as indicated. The DMC will review blinded data. If there is a significant safety signal, then unblinded data may be reviewed in a closed session by DMC members designated as unblinded reviewers. Policies, procedures and composition of the DMC are described in the DMC charter for this trial.

5.2. Participant and Study Completion

The study will be conducted at approximately 40 study centers in the United States. Approximately 200 participants will be randomly assigned (1:1:1:1) to study medication (50 participants to AGN-242428 [redacted], 50 participants to AGN-242428 [redacted] 50 participants to AGN-242428[redacted] and 50 participants to placebo) to provide an estimated total of 160 evaluable participants who will complete the study (estimated 40 evaluable participants per treatment group).

If an inadequate number of participants complete the study, and the decrease in evaluable participant data compromise the statistical validity of the primary endpoint, the sponsor may elect to enroll additional participants to ensure sufficient data. Participants who withdraw due to an AE will not be replaced.

The treatment period ends after 16 weeks of treatment or at the point of permanent study medication discontinuation should the participant discontinue treatment prior to completion of the 16th week.

5.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study globally. A participant is considered to have completed the study if he/she has completed all phases of the study including the follow-up visit. In addition, all SAEs must be reported from the date of participant's written consent until 30 days post-discontinuation of study medication or participation in the study if the last scheduled visit occurs at a later time.

5.4. Scientific Rationale for Study Design

This study is designed to address the following main questions:

1. Is AGN-242428 efficacious, relative to placebo, in treating participants with moderate to severe plaque psoriasis after 16 weeks of treatment?
2. Is AGN-242428 generally safe and well tolerated with long-term dosing?

Participant selection: Entry criteria are designed to select a population that is representative of participants with moderate to severe plaque psoriasis. Prohibited medications and diseases that may interact with AGN-242428 are excluded. Participants who have failed treatment for psoriasis with biologics targeting IL-17 and IL-23 are also excluded from the study.

Trial design: A randomized, double-blind, placebo-controlled design is used to reduce bias in the estimation of treatment effects. Participants are informed of the probability of being randomized to placebo and they may discontinue the trial at any time they choose.

Efficacy and safety assessments are standardized and performed regularly throughout the 16-week treatment period. Clearly defined processes for evaluation and follow-up of hepatic enzyme elevations and signs and symptoms of hepatic impairment are also included to enhance safety monitoring in the study.

5.5. Justification for Dose

The doses of AGN-242428 selected for this study are [redacted] once-daily for 16 weeks.

The [redacted] dose of AGN-242428 has been evaluated previously in healthy participants and patients for up to 28 days, and was shown to be generally safe and well tolerated. Administration for 28 days to patients with psoriasis resulted in an improvement in disease as measured by percent change from baseline in PASI scores. The [redacted] dose provided a plasma exposure that was $\geq IC_{90}$ for inhibition of IL-17 secretion in an ex vivo whole blood assay of IL-17 secretion, and this inhibition was sustained over a full 24 hours duration with chronic dosing. Previous studies with multiple agents have demonstrated that it takes 12 to 16 weeks to see full efficacy for improvement in psoriasis. Thus, improvement from baseline in the PASI score at 28 days most likely does not represent the full potential for clinical efficacy. The current study (1957-201-001) extends the treatment duration to 16 weeks of once-daily dosing, providing the opportunity to more completely assess clinical efficacy at the 350 mg per day dose level.

The [redacted] and [redacted] doses of AGN-242428 allow for evaluation of a dose response. The [redacted] dose is expected to demonstrate improvement in disease as measured by change from baseline in the PASI score while maintaining a larger safety margin. The [redacted] dose is expected to demonstrate a greater improvement in disease than the lowest ([redacted] dose) as measured by change from baseline in the PASI score.

During the 4-week POC trial in participants with moderate to severe psoriasis (VTP-43742-002), elevations of ALT/AST were noted at a dose level of [redacted] but not at a dose level of [redacted]

Selection of the [redacted] dose for evaluation in the current study thus provides a dose that has previously been demonstrated to be efficacious and to not have a liver function test (LFT) signal. Modeling of exposure and hepatic transaminase data from the VTP-43742-002 study suggest that a [redacted] dose is unlikely to result in elevations of hepatic transaminase levels greater than 3 x ULN for most participants. Given that the higher dose results in greater exposure, the [redacted] dose is expected to be more efficacious than the lower doses of [redacted] and [redacted].

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Table 6-1 Inclusion Criteria

1.	**Age**
1.01	Participant must be 18 to 75 years of age inclusive, at the time of signing the informed consent.
2.	**Type of Participant and Disease Characteristics**
2.01	Participants who have a confirmed diagnosis of plaque psoriasis, diagnosed at least 6 months before study, with a PGA score ≥ 3 at screening and baseline.
2.02	Severity of disease must be at least moderate, defined as Psoriasis Area and Severity Index (PASI) ≥ 12 and % body surface area (BSA) ≥ 10.
2.03	Participant is a candidate for phototherapy or systemic therapy for psoriasis.
2.04	Participants who are overtly healthy as determined by medical evaluation. Includes medical history, physical examination, laboratory tests, and cardiac monitoring.
3.	**Weight and Body Mass Index**
3.01	Body weight of at least 55 kg (121 lbs).
4.	**Sex**
4.01	Male or female.
[redacted]	[redacted]

Table 6-1 Inclusion Criteria

5.01	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Participants who do not meet the criteria for participation in this study (screen failures) may be rescreened (Section 6.4).

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Table 6-2 Exclusion Criteria

1.	**Medical Conditions**
1.01	Non-plaque forms of psoriasis (erythrodermic, guttate, pustular) or drug-induced psoriasis.
1.02	Psoriasis which has not been stable for the 4 weeks prior to screening and which is unstable at Study Day 1.

Table 6-2 Exclusion Criteria

1.03	History or presence of significant and/or not well controlled cardiovascular, pulmonary, hepatic, renal, hematologic, coagulation, gastrointestinal, endocrine, immunologic, dermatologic (other than psoriasis), neurologic or psychiatric disease. Significant is defined as any disease that, in the assessment of the investigator, would put the safety of the patient at risk through participation, or which would prevent or confound protocol specified assessments.
1.04	History of Gilbert's, Rotor, or Dubin-Johnson syndromes or any other disorder of bilirubin metabolism.
1.05	[redacted].
1.06	[redacted]
1.07	History of active mycobacterium tuberculosis (TB) infection or untreated or inadequately treated latent TB. Adequacy of treatment will be determined by the investigator based upon local standards. Individuals treated for TB must have completed treatment prior to screening.
1.08	Positive QuantiFERON test for TB infection at screening. Two successive indeterminate test results will be considered a positive result.
1.09	Had a vaccination with Bacillus Calmette-Guérin (BCG) within 12 months prior to baseline or intend to have this vaccination with BCG during the course of the study, or within 12 months of completing treatment in this study.
1.10	[redacted]
1.11	Positive drug and/or alcohol test at screening (with the exception of marijuana). Participants with a documented medical condition and a current prescription to a medication for which they have tested positive, may be allowed at the discretion of the sponsor. Retesting in the case of a positive alcohol test is allowed at the discretion of the sponsor.
1.12	[redacted]

Table 6-2 Exclusion Criteria

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
2.03	Current treatment or history of treatment with any anti-TNFα biologic therapy within 3 months or 5 half-lives of study, and/or all other biologics within 6 months of study (Day 1). Treatment with biologics is further prohibited for the duration of the study (see Section 7.7.4).
[redacted]	[redacted]
2.05	Efficacy failure on 2 or more biologic agents for the treatment of psoriasis when the failures occurred within 1 year of the initiation of the therapy of the first biologic agent (see Section 7.7.1). Efficacy failure is defined as a treatment or treatment regimen that was administered as prescribed and which did not result in a therapeutic effect or beneficial change in the disease signs and symptoms. The treatment did not produce the projected outcomes as stated in the product labeling.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 6-2 Exclusion Criteria

	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
	[redacted]
4.07	ALT, AST or TBL exceeding 1.5 times the testing laboratory's ULN at screening (may be repeated once to confirm value). Values that are above the ULN and ≤ 1.5 x ULN must be repeated to confirm that the value is stable.
	[redacted]
	[redacted]
	[redacted] .

Table 6-2 Exclusion Criteria

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Fasting: Participants should fast for at least 8 hours before study visits when clinical laboratory specimens are collected with the exception of the Screening Visit and Week 6 and Week 10 visits, when participants are not required to fast. Water is allowed during the fast for all clinical laboratory specimens, including the PK samples.

All participants in the study should refrain from consuming grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during the treatment period.

In addition, in the PK subset of approximately 14 to 18 participants per treatment arm who have provided consent, at the Week 4 visit the following restrictions apply:

- Participants in the PK subset will fast for at least 8 hours prior to dosing and continue to fast until after collection of the 0.5 hour postdose blood sample has been collected at the Week 4 visit. Water (240 mL) will be administered with the study medication at the time of dosing.
- A light meal will be served after all assessments scheduled at 0.5 hour are completed. Participants may only consume the food and beverages provided by the study staff. The meals provided must not contain prohibited or restricted foods and beverages.
- Participants will remain at the clinic until after collection of the 8-hour postdose sample and will return for collection of the 24-hour postdose sample which is collected BEFORE administration of study medication on Day 29.

6.3.2. Alcohol and Tobacco

Alcohol: Consumption of alcohol should be limited to no more than 1 drink per day. A drink is defined as 12 ounces of beer, 8 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of distilled spirits or liquor.

Tobacco: Tobacco users are to keep use stable over the course of the study.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment/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).

Participants who do not meet the criteria for participation in this study (screen failures) may be rescreened. A participant who is rescreened is not required to sign another ICF, if the rescreening occurs within 28 days from the previous ICF signature date.

7. Treatments

Study medication is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

The study medications in this study are:

- AGN-242428 capsules
- Placebo to match AGN-242428 capsules

Table 7-1 Treatments Administered

Study Treatment Name	AGN-242428/Placebo
Dosage Formulation	Capsule (White, opaque, size 00 capsule)
Unit Dose Strength	[redacted], Placebo
Route of Administration	Oral
Dosing Instructions	Two capsules taken in the morning with 240 mL of water and approximately 30 minutes before the participant consumes food (see Section 7.4)
Packaging and Labeling	Study medication will be provided in blister cards for individual participant use and will be labeled as required per country requirement.

7.1.1. Medications and Administration

Administration in the clinic: On days when study medication is administered during a clinic visit (Section 2), the study medication will be administered in the morning and under fasted conditions. The study medication will be administered from the remainder of the study medication blister cards returned by the participant (Week 4, 8, 12, and 16 visits). Participants will receive AGN-242428 and/or placebo administered as 2 capsules with 240 mL of water. The time of dosing will be recorded on the electronic case report form (eCRF).

Administration outside the clinic: On days when the study medication is self-administered by the participant, the study medication will be administered in the morning with 240 mL of water and approximately 30 minutes before the participant consumes food. Participants will be counseled to take their daily dose of study medication at approximately the same time each day in the morning.

7.1.2. Study Supplies

AGN-242428 and matching placebo will be packaged in blister cards for individual participant use, each containing a sufficient number of capsules to support once-daily dosing for 28 days with an overage appropriate to accommodate the visit window schedule at each designated visit when study medication is dispensed. Study medication will be clearly labeled with the contents, directions for use, storage condition, protocol identification, and all required regulatory caution statements including a caution to 'Keep away from children'. The labeling for the placebo and AGN-242428 will be identical.

7.2. Dose Modification

A participant's randomized dose of study medication may not be adjusted (increased or decreased) during the trial.

Retreatment Criteria

If a participant is required to discontinue their study medication (eg, protocol defined safety stopping criteria are met), re-challenge will not be permitted.

7.3. Method of Treatment Assignment

Participants will be randomized to receive either AGN-242428 or placebo according to a computer-generated randomization schedule, prepared and validated in advance of the study start. A central randomization will be used for the study with a ratio of 1:1:1:1 ([redacted] AGN-242428: [redacted] AGN-242428: [redacted] AGN-242428: placebo).

All participants will be centrally assigned to randomized study medication using an interactive response system (IxRS). Before the study is initiated, access and instructions for use of the study medication will be provided to each site.

Study medication will be dispensed at the study visits summarized in the SoA (Section 2).

Returned study medication should not be re-dispensed to the participants.

7.4. Blinding/Masking

The investigator, site staff, participant, and sponsor will be blinded to randomized treatment allocation. Only the unblinded staff of the Allergan Global Clinical Supplies Management (GCSM) Group will be aware of treatment assignment. To maintain the blind, AGN-242428 and placebo will be provided as capsules that are identical in appearance and that are packaged and labeled identically. Participants will take the same number of capsules each day, irrespective of treatment allocation.

If randomized to [redacted] AGN-242428 treatment:

- Daily dose = one (1) [redacted] AGN-242428 capsule AND one (1) placebo capsule

If randomized to [redacted] AGN-242428 treatment:

- Daily dose = two [redacted] AGN-242428 capsules

If randomized to 450 mg AGN-242428 treatment:

- Daily dose = two [redacted] AGN-242428 capsules

If randomized to placebo:

- Daily dose = two (2) placebo capsules

A unique identification number will be printed on the study medication label to maintain the blind of the treatment allocation at the participant- and site-level. This identification number will be traceable to randomized treatment allocation available only to the unblinded Allergan GCSM Group.

Blinding is critical to the integrity of the clinical trial. However, in the event of a medical emergency for an individual participant and for which the knowledge of the study medication allocation is essential to the participant's medical management, the blind for that participant may be broken by the investigator.

Before breaking the blind of an individual participant's treatment, the investigator should have determined that the information is necessary (ie, that it will alter the participant's immediate management). In many cases, particularly when the emergency is not likely to be related to investigational treatment, the problem may be properly managed by assuming that the participant is receiving active product without the need for unblinding.

The need to break the blind for an individual participant must first be discussed with the responsible Medical Safety Physician (MSP), unless not possible to do so in advance of the break. If such unblinding occurs, the investigator shall notify the MSP immediately or as soon as reasonably possible.

Procedures for breaking of the blind are provided to the investigator independent of this protocol. The date, time and reason for breaking the blind must be recorded.

7.5. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.
2. Only participants enrolled in the study may receive study medication, and only authorized site staff may supply or administer study medication. All study medications must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study medication are provided in the study reference manual.

7.5.1. Study Medication Accountability

Adequate records of all study medication receipt, storage conditions, dispensing to participants, return from participants and reconciliation of dose administration will be maintained by the study site. Participant level compliance will be recorded.

7.5.2. Study Medication Handling and Disposal

AGN-242428 and matching placebo will be stored in a secure area with restricted access and according to local regulations. It is the responsibility of the investigator to ensure that the study medication is dispensed only to study participants. The study medication must only be dispensed from official study sites by authorized personnel according to local regulations.

Any study medication remaining at the end of the study, including original containers (even if empty), should be returned to sponsor or designee at study completion.

7.6. Treatment Compliance

The first dose of study medication will be administered at the study site on Day 1 and after collection of the baseline blood samples for AGN-242428 and IL-17 concentrations. During the intervals between study visits, participants will take their study medication as instructed. On days of clinic visits (Weeks 4, 8, 12, and 16), participants will withhold taking their daily dose of study medication and will take their daily dose after collection of trough blood samples for AGN-242428 and IL-17 concentrations (see Section 2). The date and time of study medication administration during clinic visits will be recorded in the eCRF. During scheduled study visits, designated study staff will inspect the returned study medication and reconcile the amount of study medication dispensed with the amount of study medication returned.

Participants who show poor compliance with study medication administration will be counseled on the importance of medication compliance.

7.7. Concomitant Therapy

The use of any concomitant, prescription or OTC medication, is to be recorded on the participant's eCRF at each visit along with the reason the medication is taken. In addition, concurrent procedures are to be recorded on the participant's eCRF.

7.7.1. Prohibited Treatments and Washout Before the Study

Any previous use of systemic psoriasis medications/treatments used by the participant prior to enrollment must be recorded on the eCRF. Topical treatments for psoriasis used by the

participant within 2 years prior to enrollment must be recorded on the eCRF. The psoriasis medication or therapy, the dose and regimen, the duration of treatment, and the reason for discontinuation of the therapy will be recorded on the eCRF. All other medications (prescription, OTC, vitamins, or herbal) taken within 4 weeks prior to enrollment must be recorded on the eCRF. Investigational medications taken within 4 weeks or 6 half-lives (if known), whichever period is longer, will also be recorded on the eCRF.

[redacted]

[redacted]

7.7.2. Permitted Treatments

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

Please refer to Section 7.7.1,Section 7.7.4, and Appendix 8, Section 12.8 for details of prohibited treatments prior to and during the study.

7.7.3. Rescue Medicine

The study site or sponsor will not provide rescue medication.

7.7.4. Prohibited Medications During the Study

Participants are prohibited from using prescription, OTC, and herbal products for the duration of the study unless the medication has been approved by the investigator and sponsor, with the exception of prescribed hormonal contraceptives. Participants are also prohibited from using treatments/therapies for psoriasis, with the exception of study medication, for the duration of the study.

Participants may be discontinued if they take a prohibited medication that has not been previously approved by the investigator and sponsor.

Please refer to Section 7.7.1 for prohibited treatments and the washout period prior to the study.

7.8. Treatment After the End of the Study

No study medication will be provided following the end of the study.

8. Discontinuation/Withdrawal Criteria

Withdrawn participants are those who do not complete all evaluations and procedures outlined in the protocol. Participants who discontinue taking study medication for any reason must also be withdrawn from the study. All AEs that are present when the participant withdraws from the study will be followed as described in Section 9.2.

Participants may voluntarily withdraw from the study at any time.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF.

Reasons for discontinuation from the study treatment and/or the study may include the following:

- AE
- Death
- Lost to follow-up
- Non-compliance with study drug
- Meets study defined stopping criteria
- Investigator decision
- Pregnancy
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject
- Completed
- Other

8.1. Discontinuation of Study Treatment

Participants may stop study medication on the basis of intolerability, as determined by AE, vital sign or physical examination findings, clinically important laboratory or ECG findings, or investigator opinion. If a participant does not tolerate study medication, the participant will be observed until the intolerable AE has either resolved or satisfactorily stabilized in the judgment of the investigator, and the participant will be withdrawn from the study.

A participant will be permanently withdrawn from study medication if any of the criteria in Table 8-1 are met and considered related to AGN-242428. Re-challenge with AGN-242428 will not be permitted.

Table 8-1 Safety Criteria for Individual Participants Stopping Study Treatment

Parameter	Definition
Study treatment-related serious adverse event (SAE)	Study treatment-related SAE, as assessed by investigator
Increased liver transaminases[a]	Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increased to ≥ 5 × upper limit of normal (ULN)[c]
Increased liver transaminases with increased total bilirubin (TBL) or increased INR	AST and/or ALT increased to ≥ 3 x ULN AND TBL increased to ≥ 2 x ULN or INR > 1.5[c]
Increased liver transaminases with symptoms[a,b]	AST and/or ALT increased to ≥ 3 x ULN with symptoms[c]
Decreased total leukocyte count[a]	Leukopenia to < 3000/µL [< 3.0 × 10^9/L]
Decreased total neutrophil count[a]	Neutropenia to < 1000/µL [< 1.0 × 10^9/L]
Decreased lymphocyte count[a]	Lymphopenia to < 500/µL [< 0.5 × 10^9/L]
Decreased platelet count[a]	Thrombocytopenia to < 100,000/µL [< 100 × 10^9/L]
Increased serum creatinine[a]	Serum creatinine increased to ≥ 2 x ULN
Unspecified	Based on medical judgment of sponsor's Medical Safety Physician, Medical Expert and investigator

[a] To be confirmed by a repeat of the test within 2 to 5 calendar days.
[b] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia > 5%)
[c] Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined, or if the investigator believes that it is in best interest of the participant.

Liver Safety Suggested Actions and Follow-up Assessments Section can be found in Appendix 6, Section 12.6.

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

8.1.1. Temporary Discontinuation

The DMC allows for temporary discontinuation of dosing pending further analysis of possible safety issues (an option open to the DMC).

8.1.2. Criteria for Study Termination

The study may be terminated for any of the following reasons:

- Sponsor decides to terminate the trial for any reason.

- There are multiple similar AEs or SAEs that are deemed by the sponsor and its medical experts as a safety signal that poses a medically unacceptable risk to patients.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

See the schedule of activities (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants withdrawn due to AEs will not be replaced. Participants who are withdrawn for other reasons may be replaced at the discretion of the sponsor if deemed necessary to ensure sufficient data are obtained at each dose level to adequately assess safety.

8.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Study Assessments and Procedures

Study procedures and their timing are summarized in the schedule of activities (Section 2).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

To be eligible to take part in the study, all screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 440 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

Efficacy assessments and data will be collected for all participants receiving AGN-242428 or placebo. Efficacy will be assessed by medical review of PASI, total BSA and PGA scores and changes from baseline values. PD measures including IL-17A and IL-17F plasma concentrations will be determined, but the assessment of efficacy will be determined primarily by clinical signs and symptoms and improvement in clinical psoriasis scores.

9.1.1. Determination of Percent Body Surface Area

The % body surface area (BSA) will be determined using the participant's palm area to approximate 1% of BSA (handprint method). To the extent possible, the same trained and qualified dermatologist will complete estimation of % BSA for a participant at all study timepoints when % BSA is assessed including screening and baseline. The same trained and qualified dermatologist must determine the baseline and Week 16 % BSA.

The palmar surface of the participant's hand (entire palmar surface including fingers) will approximate 1% of BSA:

- Head and neck = 10% (10 palms)
- Upper extremities = 20% (20 palms)
- Trunk (axillae and groin) = 30% (30 palms)
- Lower extremities (buttocks) = 40% (40 palms)

Estimate the total BSA affected and record in the eCRF. If multiple small lesions are present, combine several to equal 1 participant palm. If there is central clearing, include only the edge and not the areas that have cleared.

9.1.2. Psoriasis Area and Severity Index

The PASI score will be determined by the same trained and qualified dermatologist, to the extent possible, at all study timepoints when PASI score is assessed including the screening and baseline visits. Assessment of PASI at Day 1 (baseline) and Week 16 will be completed by the same trained and qualified dermatologist.

The PASI score combines the severity (erythema, induration, and desquamation) and percentage of affected area. Each of 4 body regions will be assessed for surface area involvement and graded for erythema, thickness (induration) and scaling (desquamation). By combining the individual scores from each body region, the total PASI score is determined.

9.1.2.1. Surface Area Involvement by Body Regions

The 4 body regions to be assessed are:

- Head and neck – 10% of total BSA
- Upper extremities – 20% of total BSA
- Trunk including axillae and groin – 30% of total BSA
- Lower extremities including buttocks – 40% of total BSA

The surface area covered by plaques in each body region is determined using the palm method (handprint method) and assigned a score for that body region according to the scoring criteria tabulated below. Surface area involvement of each of the 4 anatomic regions is scored on a scale of 0 (no involvement of that specific body region) to 6 (90% to 100% involvement of that specific body region).

Table 9-1 **Score Assignment for Body Region based on Body Surface Area (BSA) (Surface Area Involvement Score)**

Score to Assign	Percent of Body Region Involvement
0	No involvement
1	1% to 9%
2	10% to 29%
3	30% to 49%
4	50% to 69%
5	70% to 89%
6	90% to 100%

9.1.2.2. Erythema, Thickness and Scaling Intensity Grading

Erythema: Each of the 4 body regions is given an erythema score ranging from 0 to 4:

- 0 = none
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

Thickness (induration): Each of the 4 body regions is given an induration score ranging from 0 to 4:

- 0 = none
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

Scaling (desquamation): Each of the 4 body regions is given a scaling score ranging from 0 to 4:

- 0 = none
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

9.1.2.3. Calculate the PASI score

Body region score: First sum the intensity grading for erythema, thickness and scaling for each of the body regions. The intensity score for each body region will fall within the range of 0 to 12 (see Section 9.1.2.2). Next multiply the intensity body region score by the surface area involvement score. The surface area involvement score will fall within the range of 0 to 6 (see Section 9.1.2.1). Finally, multiply by the total % of BSA accounted for by each body region and this will be the body region score.

Individual intensity and surface area involvement scores will be recorded for each body region. The eCRF will calculate the body region and total PASI scores. The total PASI score will fall within the range of 0 to 72. A PASI calculator is provided below.

Table 9-2 Psoriasis Area and Severity Index (PASI) calculator

Body Regions	
Head and Neck Body Region Score	(E + T + Sc) x surface area involvement score x 0.1 (__+__+__) x _____ x ___
Upper Extremities Body Region Score	(E + T + Sc) x surface area involvement score x 0.2 (__+__+__) x _____ x ___
Trunk (includes axillae and groin) Body Region Score	(E + T + Sc) x surface area involvement score x 0.3 (__+__+__) x _____ x ___
Lower Extremities (includes buttocks) Body Region Score	(E + T + Sc) x surface area involvement score x 0.4 (__+__+__) x _____ x ___
PASI =	Head and neck + Upper extremities + Trunk + Lower extremities _____+_____+_____+_____

PASI = Psoriasis Area and Severity Index
E = erythema; T = thickness; Sc = scaling

9.1.3. Physician's Global Assessment

The PGA will be completed by the same trained and qualified dermatologist, to the extent possible, at all study timepoints when PGA is assessed, including the screening and baseline visits. The same trained and qualified dermatologist must determine the baseline and Week 16 PGA. A 5-point scale (0 to 4) will be used and is described in Table 9-3.

Table 9-3 Physician's Global Assessment (PGA) Scoring

Score	Severity	Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin); Scaling = 0 (no evidence of scaling); Erythema = 0 (except for residual hyperpigmentation /hypopigmentation)
1	Almost clear	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin); Scaling = ± (surface dryness with some desquamation); Erythema = ± (fading, diffuse pink or slight red coloration)
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped); Scaling = fine (fine scale partially or mostly covering lesions); Erythema = mild (light red coloration)
3	Moderate	Plaque elevation = marked (marked definite elevation with rough or sloped edges); Scaling = coarser (coarser scale covering most or all of the lesions); Erythema = moderate (definite red coloration).
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges); Scaling = coarser (coarse, non-tenacious scale predominates covering most or all of the lesions); Erythema = severe (very bright red coloration)

For PGA scores recorded after initiation of treatment, the assessment of overall severity will include areas that have already been cleared (scores of 0) and will not be scored only on remaining lesions. The severity will be averaged across all areas of involvement including cleared lesions. When severities differ across the disease parameters evaluated (erythema, scaling and induration), the parameter that is the predominant feature of the disease should be used to determine the PGA score.

9.1.4. Photograph of Primary Lesion

Photography of primary lesions will be taken in a subset of participants that consent to have their photos taken. A primary lesion that is representative of the severity of the PGA and PASI scores at baseline (Day 1) will be selected and photographed at scheduled visits (Section 2). The images can be captured before or after the study medication is administered. Conditions of photography will be standardized across all photos including camera equipment, exposure, background, lighting and focal length. Ideally, the same photographer will take all required photos.

A qualified third party vendor will provide instructions for taking photographs and processing digital photographs. Photographs will be transferred to sponsor on a periodic basis and all digital images will be transferred to sponsor at the end of the study. Participants will provide consent to

be photographed and by consenting to have photographs taken, participants are indicating their understanding that they give permission for use of their study photographs for general research, education or informational purposes. Participants may decline permission for use of their study photographs for advertising, publicity, and promotional purposes.

[redacted]

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3 (Section 12.3).

AEs will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and any other study-specific terms as relevant and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment and/or study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs (serious and non-serious) from the signing of the informed consent form (ICF) until the follow-up visit will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 12.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3, Section 12.3.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and adverse events of special interest (AESI), including out of reference range laboratory test results, will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

9.2.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it, along with the IB, and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Cardiovascular and Death Events

Not applicable.

9.2.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Progression of the treatment indication (ie, the disease under investigation), including new occurrence or worsening of anticipated clinical signs or symptoms collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as an adverse event unless the disease progression is greater than anticipated in the natural course of the disease.

9.2.7. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 12.4).

Abnormal pregnancy outcomes (eg, spontaneous abortion, elective termination of a pregnancy, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 3, Section 12.3).

9.2.8. Adverse Events of Special Interest

All of the following are AESI:

- AST and/or ALT increased to ≥ 5 ULN
- AST and/or ALT increased to ≥ 3 x ULN AND TBL increased to ≥ 2 x ULN or INR > 1.5. Typically, all analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period.
- AST and/or ALT increased to ≥ 3 x ULN with symptoms believed to be related to liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia > 5%)
- For any participant who meets one of the above liver criteria resulting in study treatment discontinuation, the following must be performed (See Appendix 3, Section 12.3, for additional details regarding the reporting of AESIs):

1) The lab abnormality captured as an AESI
2) Non-serious AESIs should be reported to the sponsor within 72 hours and serious AESIs should be reported to the sponsor within 24 hours
3) The AESI form, which is the Adverse Event of Interest Abnormal Liver Function Reporting Form, should be completed and used for reporting the AESI even if a serious outcome may not apply, and

4) Every effort to determine the cause of the liver enzyme abnormalities must be made (in conjunction with the MSP and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

In addition, a potential Hy's Law case is also an AESI. Criteria for potential Hy's Law cases are as follows:

- ALT and/or AST ≥ 3 × ULN AND
- TBL ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

A laboratory alert for potential Hy's Law cases will be in place, and must notify investigators and the sponsor immediately when the above criteria have been met. A potential Hy's law case must be reported as a SAE by completing an Adverse Event of Interest Abnormal Liver Function Reporting Form and sent to IR-Clinical-SAE@allergan.com (or faxed to the SAE fax number) as soon as possible (within 24 hours of learning of the potential Hy's Law case). The eCRF for potential Hy's Law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the MSP and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Suggested actions and follow-up assessments for liver safety are described in Appendix 6 (Section 12.6).

9.2.9. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study treatment as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

Wrong study treatment/device

Wrong dose (including dosing regimen, strength, form, concentration, amount)

Wrong route of administration

Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study treatment.

Overdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is above the maximum recommended dose according to the

reference safety information or protocol for the study treatment or comparator as applicable. This also takes into account cumulative effects due to overdose. An overdose for this study treatment is any dose of AGN-242428 greater than [redacted] taken within 1 calendar day with less than 8 hours between doses will be considered an overdose.

Underdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol. An underdose for this study will be any dose of AGN-242428 less than the randomized study treatment.

9.3. Treatment of Overdose

For this study, any dose of AGN-242428 greater than [redacted] taken within 1 calendar day with less than 8 hours between doses will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the sponsor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities until study treatment can no longer be detected systemically (at least 5 days).
3. Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study medication.
4. Document the quantity of the excess dose of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the MSP based on the clinical evaluation of the participant.

9.4. Safety Assessments

All participants receiving study medication (AGN-242428 or placebo) will be included in the safety summary. Safety will be assessed by medical review of AE reports, clinical laboratory findings, ECG data, physical examinations, and vital signs. Any skin findings will be carefully assessed and reviewed.

Planned timepoints for all safety assessments are provided in the schedule of activities (Section 2).

9.4.1. Physical Examinations

A full physical examination, including but not limited to, evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, neurological status, skin, and any other notable conditions, will be performed at screening, Day 1, and Week 16.

Abbreviated physical examinations including skin, heart, chest, lungs, and abdomen will be conducted at all other scheduled visits during the study. For the skin examination performed at

screening and baseline, a careful examination for and documentation of possible pre-existing cutaneous infections, including fungal infections, or scarring will be included. Screening and baseline skin findings for psoriatic participants will be carefully noted in the eCRF.

The physical examination must be performed by a qualified healthcare professional [eg, medical doctor (MD) ie, physician, Doctor of Osteopathy (DO), physician assistant (PA)]. Whenever possible, the same qualified healthcare professional should conduct the physical examination at all scheduled times throughout the study. Skin evaluations associated with physical examinations for psoriatic participants will be completed by the same qualified dermatologist throughout the study. Assessment of PASI and PGA will follow the procedures outlined in Section 9.1.

Height and weight will be measured in full indoor clothing without shoes at the Screening Visit. A BMI will be calculated using the screening height and weight values. Additional weight measurement will be taken at baseline and the end of the study.

9.4.2. Vital Signs

All vital sign measurements will be taken after a participant has been in a sitting position for a minimum of 5 minutes (participant in a quiet setting without distractions eg, television, cell phones). Vital signs will include blood pressure, pulse, respiration rate, and body temperature. Radial or brachial pulse will be measured over a 30 second interval, if performed manually and respiration rate will be measured over a 60 second interval. Body temperature may be oral or aural. An electronic or manual sphygmomanometer or an electronic oscillometric device may be used. The method of assessment should be consistent throughout the study.

9.4.3. Electrocardiograms

Standard 12-lead ECGs will be performed after the participant has been resting quietly supine for at least 10 minutes at scheduled visits throughout the study (see Section 2).

At the time that the ECG is obtained, the investigator or medically qualified subinvestigator will inspect the ECG tracing to confirm the QT interval provided by the ECG machine is accurate so that a repeat tracing may be performed, if needed. ECG results will be classified by the investigator as normal, having a clinically significant (CS) abnormality, or having a not clinically significant (NCS) abnormality.

ECGs will be assessed by an external vendor through central reading of ECGs. Standardized equipment and instructions will be provided by the ECG vendor and data will be received and over-read by the external vendor. Central ECG over-read and interval measurements will be provided by experienced, qualified, and certified cardiac safety specialists (primary reader). The readers will be blinded to participant details and a single reader will read all ECGs of a given participant. In addition, the ECGs will also be reviewed by a US board-certified Cardiologist from the vendor who will evaluate the ECG from a morphological perspective and who will confirm the interval measurements performed by the primary reader.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using [Bazett's formula [QTcB] or Fridericia's formula [QTcF]] after

enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

The ECG printout should be kept in the source documentation file. If potentially clinically significant findings are detected by the site investigator, the MSP should be consulted. All communications and diagnoses should be filed in the source documentation file.

The investigator is responsible for maintaining participant's safety throughout the study. Investigators will review ECGs and may discontinue participants with clinically significant abnormal ECG findings.

9.4.4. Clinical Safety Laboratory Assessments

See Table 9-4 for a listing of laboratory tests utilized during the screening period to qualify patients for study participation and throughout the study to monitor participant safety. PK (Section 9.5) and PD (Section 9.6) assessments are listed separately.

Specimens for serum hematology, chemistry, coagulation and urinalysis will be drawn at the times indicated in the schedule of activities (Section 2). All clinical laboratory testing will be performed in the fasting state with the exception of laboratory testing at the Screening Visit and Week 6 and Week 10 visits, which will not require fasted samples. Additional guidance on monitoring of liver function tests is provided in Section 8 and Appendix 6, Section 12.6.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study medication should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or MSP.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the schedule of activities.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

The tests detailed in Table 9-4 will be performed by the central laboratory. All laboratory tests should be sent to the central laboratory for the study.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Table 9-4 Clinical Laboratory Tests

Category[a]	Parameters
Hematology and Coagulation[a]	Hematocrit (HCT), hemoglobin (HGB), red blood cell (RBC) count, RBC indices, total leukocyte (or white blood cell [WBC]) count including differential, and platelet count with mean platelet volume, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR)
Serum Chemistry	
Electrolytes	Sodium (Na), potassium (K), chloride, bicarbonate
Renal function	Blood urea nitrogen (BUN), creatinine (Cr)
Liver function[a]	Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total, direct, and indirect bilirubin (TBL, DBL, IBL), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH)
Pancreatic function	Lipase and amylase
Other[a] (selected tests at Week 6 and Week 10)	Calcium (Ca), magnesium (Mg), phosphorus (P), total protein[a], albumin[a], globulins, glucose, uric acid, creatine phosphokinase (CK)[a], cholesterol (total and fractionated) and triglycerides
Urinalysis	Appearance, bilirubin, color, ketones, glucose, leukocyte esterase, nitrites, pH, blood, protein, specific gravity and urobilinogen with microscopic examination of the sediment if blood, protein or leukocyte esterase is positive.
Other Analyses	Serum for hepatitis B (hepatitis B surface antigen [HbsAG] and hepatitis B core antibodies [Anti-HBc]), hepatitis C antibodies (HCV Ab), and HIV (screening only)
	Urine pregnancy (women of childbearing potential [WOCBP] only)[b]
	Urine drug and alcohol[c]
	Mycobacterium tuberculosis (TB) by QuantiFERON

[a] Visits on Week 6 and Week 10 need random blood draws. Participants can be fasting or non-fasting and only the following laboratory tests will be performed at those visits: Hematology and Coagulation, Liver function, and Other (Total protein, albumin, and CK). For example, urinalysis is not collected at these visits.
[b] Urine pregnancy tests will be done on site with kits provided by the central laboratory.
[c] As referenced in the laboratory manual.

9.4.5. Suicidal Risk Monitoring

Not applicable.

9.5. Pharmacokinetics

Blood samples for the analysis of AGN-242428 plasma concentrations will be collected at scheduled times (Section 2). Instructions for the collection and handling of biological samples will be provided by the central laboratory. The actual date and time (24-hour clock time) of each sample will be recorded. Trough and random PK blood samples will be drawn from all participants; sequential PK samples will be drawn in a subset of participants. The participants will be asked to provide the date and time of administration of the 3 doses taken prior to the visit when PK samples are to be drawn. This date and time information will be recorded in the eCRF.

Trough PK samples: Trough PK samples will be collected from all study participants. Samples that are designated as trough (Day 1 and Weeks 4, 8, 12 and 16) will be collected before on-site administration of the morning dose of study medication. In case of early termination, a blood sample for AGN-242428 plasma concentration will be drawn at the early termination visit. The date and time of PK sample collection will be recorded in the eCRF. Deviations to sample collection such as failure to collect the sample, collection of the sample after dose administration, or deviations to dose administration in the 3 days prior to sample collection will be recorded in the eCRF.

Profile (Sequential) PK samples: A subset of approximately 14 to 18 participants per treatment arm will provide sequential blood samples at the Week 4 visit to allow evaluation of PK concentration versus time profiles and PK parameters. Participants must not take the study medication at home as it will be administered on site. Participants will fast for at least 8 hours prior to dosing and continue to fast until after collection of the 0.5 hour postdose blood sample has been collected. Sequential blood samples will be obtained immediately before the administration of study medication at the Week 4 visit and at the following times after study medication administration: 0.5, 2, 6, 8, and 24 hours (Day 29). Allowable collection windows to sampling times are summarized in Table 9-5. The date and time of PK sample collection and the date and time of dosing during this visit will be recorded in the eCRF. Deviations to sample collection such as failure to collect the sample, collection of the predose sample after dose administration, or deviations to dose administration in the 3 days prior to sample collection will be recorded in the eCRF. Participants will remain at the clinical site until after collection of the 8 hour postdose sample and will return to the clinical site for collection of the 24 hour postdose sample on the following morning. The 24 hour postdose sample will be collected BEFORE the participant takes their morning dose of randomized study medication on Day 29.

Table 9-5 Allowable Windows for Pharmacokinetic (PK) Sampling Times

Scheduled Time	Allowable Collection Windows
Predose (0 hour)	Within 15 minutes prior to dose administration
0.5 hour	± 3 minutes
2 hour	± 15 minutes
6 hour	± 30 minutes
8 hour	± 30 minutes
24 hour	± 1 hour but before dose administration

Random Time PK samples: Random PK samples will be collected from all study participants. Samples that are designated as random will be collected during the Week 6 and Week 10 visits. All participants will self-administer their morning dose of study medication and then report to the clinic to have a sample collected no sooner than 1 hour, but no later than 2 hours after self-administration. The participant will self-administer their morning dose of study medication at home as normally instructed in advance of the Week 6 and Week 10 visits. The date and time that the blood sample for AGN-242428 concentration was collected will be recorded in the eCRF. Deviations to sample collection such as failure to collect the sample or deviations to dose administration in the 3 days prior to sample collection will be recorded in the eCRF.

Required blood collection tubes, processing instructions, storage instructions and processing instructions will be provided in the laboratory manual.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

9.6. Pharmacodynamics

Blood samples for the analysis of IL-17A and IL-17F plasma concentrations will be collected from all participants before dose administration at scheduled times (Section 2). The date and time of sample collection will be recorded in the eCRF. Deviations to sample collection such as failure to collect the sample, collection of the sample after dose administration or deviations to dose administration in the 3 days prior to sample collection will be recorded in the eCRF.

Additional cytokines, chemokines, or proteins may be measured from samples collected.

Required blood collection tubes, processing instructions, storage instructions and processing instructions will be provided in the laboratory manual.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

As discussed in Section 9.6, biomarkers will include, but not be limited to, the following: IL-17A and IL-17F.

9.9. Medical Resource Utilization and Health Economics

Health economics and medical resource utilization parameters are not evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

A responder is a participant with ≥ 75% reduction in PASI from baseline to Week 16. The sample size of 200 participants (50 per treatment arm) will provide 90% power to detect a response rate difference of 27% between each AGN-242428 and placebo group at Week 16, with an assumed response rate of 6% in the placebo group, a 5% type 1 error rate, and 20% dropout rate.

10.2. Populations for Analyses

The analysis populations will consist of participants as defined in Table 10-1.

Table 10-1 Analysis Populations

Population	Definition	Study Treatment
Modified intent-to-treat (mITT)	All randomized participants with at least 1 postbaseline PASI assessment. This population will be used for all efficacy analysis.	Randomized assignment
Pharmacokinetic (PK)	All participants who received AGN-242428 and had available plasma concentration data. The PK analysis set will be used for all PK analyses.	Actual received
Pharmacodynamic (PD)	All participants for whom PD measurements are available at baseline and at least one postbaseline visit.	Actual received
Safety	All participants who received ≥ 1 administration of study treatment.	Actual received

PASI = Psoriasis Area and Severity Index

10.3. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1. Disposition and Baseline Demographic Characteristics Analyses

Disposition: The number and percentage of participants screened or randomized, included in each analysis population, completing the study, and withdrawing from the study (together with the reasons for withdrawal) will be summarized by treatment group.

Baseline demographic characteristics: Demographic data (age, sex, race, ethnicity), and baseline characteristics (weight, height, BMI, Fitzpatrick skin phototype (Table 10-2), baseline PASI, % BSA, and PGA) will be summarized by treatment for the mITT analysis set.

Continuous variables will be summarized using descriptive statistics. Categorical variables will be tabulated using frequency distributions.

Table 10-2 Fitzpatrick Skin Phototype

Type	Description
I	Always burns easily; never tans (sensitive)
II	Always burns easily; tans minimally (sensitive)
III	Burns moderately; tans gradually (light brown) (normal)
IV	Burns minimally; always tans well (moderate brown) (normal)
V	Rarely burns; tans profusely (dark brown) (insensitive)
VI	Never burns; deeply pigmented (insensitive)

Source: Federal Register 1999

10.3.2. Efficacy Analyses

10.3.2.1. Primary and Secondary Endpoints

The following key primary and secondary efficacy endpoints will be analyzed for the mITT population. All other efficacy endpoints and analyses will be defined in the SAP.

The primary efficacy endpoint is the percentage of participants achieving a reduction (improvement) in PASI score of ≥ 75% from baseline to Week 16 (responder). The null hypothesis is that the population responder rates of the AGN-242428 and placebo groups are the same. The alternative hypothesis is that the rates differ:

- H_0: $r_v = r_p$
- H_a: $r_v \neq r_p$

where r_v and r_p are the population rates in the AGN-242428 and placebo groups, respectively.

The difference between each of the AGN-242428 groups and placebo in the proportion of participants with a reduction in PASI of ≥ 75% from baseline to Week 16 will be analyzed using a Chi-square test.

Frequency counts of participants achieving a 50%, 75%, and 90% reduction in PASI score relative to baseline will be tabulated by treatment at each postbaseline visit. Frequency counts of participants achieving ≥ 2-point improvement in PGA score will be tabulated by treatment at each postbaseline visit. Frequency counts of participants who achieve a PGA score of clear or almost clear will be tabulated by treatment at each postbaseline visit.

Other efficacy measures will be summarized by visit and treatment.

10.3.3. Safety Analyses

The following safety categories will be summarized as appropriate for the safety population and will be fully defined in the SAP.

AEs: A by-participant listing of all AEs and of all TEAEs, including verbatim term, preferred term, treatment, as well as severity and relationship to treatment as per investigator assessment, will be provided. The number of participants experiencing TEAEs will be summarized by treatment using frequency counts and percentages. TEAEs will also be summarized by severity, and causality. A listing of TEAEs leading to study discontinuation will be provided.

A TEAE is defined as a postbaseline AE in which:

- the onset date is on or after the date of the first study treatment, or
- the onset date is prior to the date of the first study treatment, and
  - the severity worsened on or after the date of the first study treatment, or
  - the event became serious on or after the date of the first study treatment.

Clinical laboratory evaluations: Descriptive summaries (mean, SD, median, minimum, and maximum) of changes from baseline will be presented for clinical laboratory values by treatment group and visit.

Vital signs: Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for vital signs (systolic and diastolic blood pressure, pulse and respiration rate). These summaries will be presented by treatment and by visit.

ECG: ECG data will be summarized by treatment and by visit.

10.3.4. Pharmacokinetic Analyses

Listings will be provided for trough, random, and sequential (profile) plasma concentrations for the PK population. Additionally, trough and sequential plasma concentrations will be summarized by using appropriate descriptive statistics.

Sequential PK samples will be analyzed using noncompartmental methods based on a PK analysis plan. The following PK parameters will be determined from this analysis: area under the plasma concentration versus time curve from time 0 to the end of the dosing interval, tau, at steady state ($AUC_{0\text{-}tau.ss}$), maximum plasma drug concentration at steady state ($C_{max,ss}$), minimum plasma drug concentration at steady state ($C_{min,ss}$), and time of maximum plasma drug concentration at steady state ($T_{max,ss}$). The PK parameters will be summarized using appropriate descriptive statistics.

All plasma PK samples (trough, sequential, and random) obtained in the study will be analyzed using a population PK model. Individual predictions of AGN-242428 exposure (including, but not limited to, steady state $AUC_{0\text{-}tau,ss}$ and $C_{min,ss}$) will be determined based on the population PK

model. A stand alone pharmacometric analysis plan will be written and the analyses will be reported separately from the integrated clinical trial report.

10.3.5. Pharmacodynamic and Pharmacokinetic-Pharmacodynamic Analyses

Descriptive statistics will be calculated for IL-17A and IL-17F levels in plasma for the PD population.

The relationship of systemic exposure parameters such $AUC_{0\text{-}tau,ss}$ and $C_{min,ss}$ with efficacy, safety and/or biomarker endpoints will be evaluated graphically. If graphical evaluation identifies possible trends, exploratory PK/PD analyses will be performed for the evaluation and quantification of potential relationships via nonlinear mixed effects modeling. These analyses will be prespecified in the pharmacometrics analysis plan.

10.3.6. Interim Analyses

No formal interim analyses are planned. Ongoing review of safety data will be completed along with blinded review of select safety data when approximately 10%, 30%, 60% and 80% of the total participants have completed treatment through Week 4.

11. References

Federal Register 1999: Volume 64(98); Friday, May 21, 1999
https://www.gpo.gov/fdsys/pkg/FR-1999-05-21/html/99-12643.htm

FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. https://www.fda.gov/downloads/Drugs/.../guidances/UCM174090.pdf.

12. Appendices

12.1. Appendix 1: Abbreviations and Trademarks

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration curve
AUC∞	area under the plasma concentration curve from time 0 to infinity
AUC_{tau}	area under the plasma concentration curve from 0 hours to the time of next dosing
$AUC_{0\text{-}tau.ss}$	area under the plasma concentration versus time curve from time 0 to the end of the dosing interval, tau, at steady state
BCG	Bacillus Calmette-Guérin vaccine
BCRP	Breast Cancer Resistance Protein alternately known as $ABCG_2$ (ATP binding cassette sub-family G member 2)
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations (United States of America)
CIOMS	Council for International Organizations of Medical Sciences
CK	creatinine phosphokinase – also known as CPK
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma drug concentration at steady state
$C_{min,ss}$	minimum plasma drug concentration at steady state

Abbreviation or Specialist Term	Explanation
CONSORT	Consolidated Standards of Reporting Trials
Cr	creatinine
CS	clinically significant
CYP2C8	cytochrome P450 family 2 subfamily C member 8
CYP2D6	cytochrome P450 family 2 subfamily D member 6
CYP3A4	cytochrome P450 family 3 subfamily A member 4
DDIs	drug-drug interactions
[redacted]	[redacted]
DMC	Data Monitoring Committee
DO	Doctor of Osteopathy
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GCSM	Global Clinical Supplies Management
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
IB	investigator's brochure
IBL	indirect bilirubin
IC_{50}	inhibitory concentration producing 50% inhibition
IC_{90}	inhibitory concentration producing 90% inhibition
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL-12	interleukin 12

Abbreviation or Specialist Term	Explanation
IL-17	interleukin 17 family inclusive of IL-17A and IL-17F
IL-23	interleukin 23
IND	investigational new drug application
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat population
IxRS	interactive response system
K	potassium
Ki	inhibition constant
LBD	ligand binding domain
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAD	multiple-ascending dose
MCS	Mental component summary
MD	medical doctor (physician)
Mg	magnesium
mITT	modified intent to treat population
mIU/mL	milli-international units per milliliter
MSP	Medical Safety Physician
Na	sodium
NOAEL	no observed adverse effect level
NCS	not clinically significant
OATP1B3	organic anion-transporting polypeptide 1B3 also known as SLCO1B3 (solute carrier organic anion transporter family member 1B3)
OTC	over-the-counter
P	phosphorus
PA	Physician's Assistant
PASI	Psoriasis Area and Severity Index
PCS	physical component summary

Abbreviation or Specialist Term	Explanation
PD	pharmacodynamics
[redacted]	[redacted]
PGA	Physician's Global Assessment
PK	pharmacokinetics
POC	proof-of-concept
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SF-36	36-item Short Form
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis (*mycobacterium tuberculosis*)
TBL	total bilirubin
TEAE	treatment-emergent adverse event
Th17	T helper 17
t_{max}	time at which C_{max} occurs
$T_{max,ss}$	time of maximum plasma drug concentration at steady state
TNFα	Tumor Necrosis Factor alpha
ULN	upper limit of normal
WOCBP	women of childbearing potential

12.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Committees Structure

A Data Monitoring Committee (DMC) will review select safety and exposure data (as needed) at scheduled times during the conduct of the study. Ad-hoc meetings of the DMC may be scheduled to evaluate potential safety signals, as needed. The DMC will review blinded data. If there is a significant safety signal, then unblinded data may be reviewed in a closed session by DMC members designated as unblinded reviewers. Policies, procedures, and composition of the DMC are described separately in the DMC charter for this study.

Publication Policy

Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of

multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

Study information and tabular study results will be posted to the US National Institutes of Health website .

Study data and information may be published in non-promotional, peer-reviewed publications either by or on behalf of Allergan.

Clinical study reports, safety updates and annual reports will be provided to regulatory authorities as required.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 3 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data are defined as: Original documents, data, and records (eg, hospital records, clinical and office charts, diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments (eg, ECGs), copies or transcriptions certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study). These records include, but are not limited to, original signed and dated consent forms, relevant observations including records of adverse events and records of all exposure to study treatments.

Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
 	
NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
 	
AE of Special Interest (AESI)
 	
An adverse event of special interest (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study treatment/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.
 	
The following AESI(s) have been identified for the study treatment(s) in this protocol:
 	
• AST and/or ALT ≥ 5 ULN
• AST and/or ALT ≥ 3 x ULN AND TBL ≥ 2 x ULN or INR > 1.5. Typically, all analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period.
• AST and/or ALT ≥ 3 x ULN with symptoms believed to be related to liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia > 5%)
• Changes in hepatic laboratory test results that meet potential Hy's Law
  • ALT and/or AST ≥ 3 x ULN AND
  • TBL ≥ 2 x ULN AND
  • Alkaline phosphatase < 2 x ULN
 	
Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. Non-serious AESIs should be reported to the sponsor within 72 hours and serious AESIs should be reported to the sponsor within 24 hours. The AESI form, which is the Adverse Event of Interest Abnormal Liver Function Reporting Form, should be used for reporting the AESI even if a serious outcome may not apply. Of note, all potential Hy's Law cases are to be reported as SAEs.

Events Meeting the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease)
Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study
Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae
Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition
Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an

emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

As discussed in Section 9.2.7, abnormal pregnancy outcomes (eg, spontaneous abortion, elective termination of a pregnancy, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

All events of AST and/or ALT ≥ 3 x ULN and TBL ≥ 2 x ULN and alkaline phosphatase < 2 x ULN indicate severe liver injury (potential 'Hy's Law') and must be reported as an SAE.

Recording an AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information in the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity as per Investigator

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality as per Investigator
The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment. For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

SAE Reporting to the sponsor via Paper CRF
Facsimile transmission of the SAE Reporting Form is the preferred method to transmit SAE information to the sponsor. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Reporting Form within the designated reporting time frames. Contacts for SAE reporting can be found in the protocol title page.

12.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the study and for 30 days following the last dose of study treatment:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant

Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for 30 days following the last dose of study treatment.

In addition, male participants must refrain from donating sperm for the duration of the study and for 30 days following the last dose of study treatment.

The same highly effective method of contraception must be used consistently and correctly throughout the study.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use 2 forms of birth control, in which at least 1 form must be a highly effective method of contraception, consistently and correctly as tabulated below. Of note, both forms can be highly effective if preferred, but at least 1 form must be highly effective.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent[a]
Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Etonogestrel implant (ie, Nexplanon®) Bilateral tubal occlusion Intrauterine copper contraceptive (ie, ParaGard®)
Vasectomized Partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the women of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual Abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

The list in this table is not all inclusive.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Acceptable birth control methods that result in a failure of more than 1% per year (and are thus, not classified as highly effective) include the following noted below. One of these methods can be used as the required second method of contraception, if desired:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Pregnancy Testing

WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.

Additional pregnancy testing should be performed as outlined in schedule of activities during the treatment period and at the follow-up visit or upon early termination. Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected at the investigator's discretion.

Pregnancy testing, with a sensitivity of at least 25 mIU/mL will be performed at the study site with testing materials provided by the central laboratory.

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication.

After obtaining the necessary site specific signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be

forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion and an elective termination of a pregnancy are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 9.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment immediately and be withdrawn from the study.

12.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (National Cancer Institute [NCI])
Death	The absence of life or state of being dead (NCI)
Disease relapse	The return of a disease after a period of remission
Failure to meet randomization criteria	An indication that the participant has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a participant to follow-up
Non-compliance with study treatment	An indication that a participant has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion or judgment reached after consideration by a physician with reference to participant (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth (NCI)
Progressive disease	A disease process that is increasing in extent or severity (NCI)

CDISC Submission Value	CDISC Definition
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Recovery	A healing process and/or an outcome implying relative health. The term is typically used in the context of direct and indirect effects of sickness or injury (NCI)
Screen failure	The potential participant who does not meet one or more criteria required for participation in a trial
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by parent/guardian	An indication that a study participant has been removed from the study by the parent or legal guardian
Withdrawal by participant	An indication that a study participant has removed itself from the study (NCI)

12.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessment

Phase II liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Phase II Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
AST and/or ALT-absolute	AST and/or ALT ≥ 5 x ULN
AST and/or ALT Increase	AST and/or ALT ≥ 3 x ULN persists for ≥ 4 weeks
Bilirubin or INR	AST and/or ALT ≥ 3 x ULN **and** TBL ≥ 2 x ULN or INR > 1.5
Cannot Monitor	AST and/or ALT ≥ 3 x ULN and cannot be monitored weekly for 4 weeks
Symptomatic[a]	AST and/or ALT ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Potential Hy's Law cases	
AST, ALT, and Bilirubin[b]	AST and/or ALT ≥ 3 x ULN and TBL ≥ 2 x ULN and alkaline phosphatase < 2 x ULN

Required Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study treatment. • Report the event to the sponsor **within 24 hours.** • Complete the liver event eCRF, and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE.[b] • Perform liver chemistry follow-up assessments. • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study treatment • As restart/rechallenge is **not allowed per protocol**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow-up assessments **MONITORING:** **<u>If AST and/or ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN:</u>** • Repeat liver chemistry tests (include alanine transferase (ALT), aspartate transaminase [AST], alkaline phosphatase [ALP], total, direct, and indirect, bilirubin [TBL, DBL, IBL], gamma-glutamyl transferase [GGT], and lactate dehydrogenase [LDH]) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>If AST and/or ALT ≥ 3 x ULN AND bilirubin < 2 x ULN:</u>**	• Viral hepatitis serology and other laboratory testing, as well as anti-nuclear antibody and anti-smooth muscle antibody[c] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis 48 hours after the most recent dose[d] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if TBL ≥ 2 x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF **<u>If AST and/or ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN:</u>** • Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma

• Repeat liver chemistry tests (include ALT, AST, ALP, TBL, DBL, IBL, GGT, and LDH) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	globulins. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete the Hy's Law eCRF form and the AESI Form, which is the Adverse Event of Interest Abnormal Liver Function Reporting Form.

AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form: TBL = total bilirubin; ULN = upper limit of normal

a = New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

b = All events of AST and/or ALT ≥ 3 x ULN **and** TBL ≥ 2 x ULN and alkaline phosphatase < 2 x ULN indicate severe liver injury **(potential 'Hy's Law') and must be reported as both an AESI and an SAE** by completing the AESI Form, which is the Adverse Event of Interest Abnormal Liver Function Reporting Form, and and sending it to IR-Clinical-SAE@allergan.com (or faxing it to the SAE fax number) within 24 hours of learning of the potential Hy's Law case.

c = Includes:Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B Core Antibody (HBcAb); hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); hepatitis E IgM antibody; anti-nuclear antibody; and anti-smooth muscle antibody.

d = PK sample may not be required for participants known to be receiving placebo or non-comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

Phase II Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criterion and Follow-Up	
Criterion	**Actions**
ALT ≥ 3 x ULN and < 5 x ULN **and** bilirubin < 2 x ULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 8. • If, after 4 weeks of monitoring, ALT < 3 x ULN and bilirubin < 2 x ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

12.7. Appendix 7: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	A Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of AGN-242428 in Patients With Plaque Psoriasis
	Clinical Study sponsor	Vitae Pharmaceuticals Inc., an Allergan affiliate
	Trial Phase Classification	Phase 2b Trial
	Trial Indication	Plaque psoriasis
	Trial Indication Type	Treatment
	Trial Type	Efficacy Safety
	Trial Length	22 weeks ± 3 days from screening to follow-up
	Planned Country of Investigational Sites	United States
	Planned Number of Participants	200
	FDA-Regulated Device Study Indicator	No
	FDA-Regulated Drug Study Indicator	Yes
	Pediatric Study Indicator	No
Participant information	Diagnosis Group	Moderate to severe plaque psoriasis defined as PASI ≥ 12, % BSA ≥ 10 and PGA of ≥ 3
	Healthy Participant Indicator	No
	Planned Minimum Age of Participants	18
	Planned Maximum Age of Participants	75
	Sex of Participants	Male/Female
	Stable Disease Minimum Duration	6 months

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	AGN-242428
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Selective, orally active small molecule inhibitor of RORγt activity
	Dose per Administration	[redacted]
	Dose Units	[redacted] and [redacted] capsules
	Dosing Frequency	Once-daily
	Route of Administration	Oral
	Current Therapy or Treatment	Current treatment or history of treatment with immunosuppressive therapy, for any condition, within 4 weeks of study, unless otherwise stated is prohibited. Current treatment or history of treatment with any anti-TNFα biologic therapy within 3 months or 5 half-lives of study, and/or all other biologics within 6 months of study (Day 1) is prohibited. Current treatment or history of treatment for psoriasis with non-biologic systemic medications or UV therapy within 4 weeks of Day 1 and treatment with topical agents within 2 weeks of Day 1 is prohibited.
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	Not applicable
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	4
	Trial is Randomized	Yes
	Randomization Quotient	1:1:1:1 ([redacted] AGN-242428: [redacted] AGN-242428: [redacted] AGN-242428: placebo).
	Trial Blinding Schema	Double blind
	Stratification Factor	No
	Adaptive Design	No
	Study Stop Rules	A participant will be permanently withdrawn from study treatment if any of the criteria below are met and considered related to AGN-242428:

Parameter Group	Parameter	Value
		Study Treatment-related SAE Decreased total leukocyte count; Leukopenia < 3000/µL (< 3.0 x 10^9/L) Decreased total neutrophil count; Neutropenia < 1000/µL (< 1.0 x 10^9/L) Decreased total lymphocyte count; Lymphopenia < 500/µL (< 0.5 x 10^9/L) Decreased platelet count; Thrombocytopenia < 100,000/µL (< 100 x 10^9/L) Increased serum creatinine; Serum creatinine > 2 x ULN Unspecified safety concern; Upon request by investigator or Medical Safety Physician Increased liver enzymes: •ALT and/or AST ≥ 5 x ULN •ALT and/or AST ≥ 3 x ULN AND TBL ≥ 2 x ULN or INR > 1.5 •ALT and/or AST ≥ 3 x ULN with symptoms

12.8. Appendix 8: Partial List of Prohibited Medications Which Are Sensitive Substrates for BCRP, OATP1B3, CYP2D6, and CYP2C8 and Strong Inhibitors or Inducers of CYP3A4

This list of prohibited medications is provided as a guidance. Use of these medications is prohibited unless approved by the investigator or sponsor. This list is not comprehensive and the investigators will consult with the sponsor before allowing concomitant medication use during the trial.

Partial List of Prohibited Substrates

BCRP Substrates	OATP1B3 Substrates	CYP2D6 Substrates	CYP2C8 Substrates	CYP3A4 Inhibitors	CYP3A4 Inducers
Apixaban	Atorvastatin	Amitriptyline	Amiodarone	Bitter Orange supplement	Carbamazepine
Methotrexate	Methotrexate	Aripiprazole	Pioglitazone	Clarithromycin	Guggul (Commiphora mukul)
Rivaroxaban	Pravastatin	Atomoxetine	Repaglinide	Grapefruit	Phenobarbital
Rosuvastatin	Rifampin	Carvedilol		Grapefruit Juice	Phenytoin
Sulfasalazine	Rosuvastatin	Chlorpheniramine		Itraconazole	Primidone
		Desipramine		Ketoconazole	Rifampin
		Dextromethorphan		Resveratrol	St. John's Wort
		Doxepin		Seville oranges	
		Fluoxetine		Seville orange juice	
		Imipramine			
		Metoprolol			
		Mirtazapine			
		Nortriptyline			
		Paroxetine			
		Propafenone			
		Propranolol			
		Risperidone			
		Tolterodine			

Use of drugs or substances known to be sensitive cytochrome P450 CYP2D6 or CYP2C8 substrates, strong CYP3A4 inhibitors, strong CYP3A4 inducers, or transported by specific liver transporters (ie, breast cancer resistance protein [BCRP] and/or organic anion transporting polypeptide 1B3 [OATP1B3]) is prohibited unless approved by the investigator and sponsor.

12.9. Appendix 9: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment (Amendment 2) is located directly before the table of contents.

The rationale and the protocol amendment summary of changes table for Amendment 1 is located below:

Overall Rationale for Amendment 1:

The overall rationale for the changes implemented in the protocol amendment was 1) to align the inclusion/exclusion criteria with industry precedence for similar psoriasis studies, 2) to add INR monitoring to the stopping criteria to adhere to FDA Guidance for DILI 2009, and 3) to add INR monitoring to the Adverse Events of Special Interest for additional safety surveillance.

Section No. and Name	Description of Change	Brief Rationale
6.1 Inclusion Criteria	Removed the following phrase from Inclusion Criterion 3.01: "and body mass index (BMI) within the range 18 to 35 kg/m^2 inclusive"	To align the inclusion/exclusion criteria with industry precedence for similar psoriasis studies
6.2 Exclusion Criteria	Removed the following statement from Exclusion Criterion 1.02: "Stable is defined as psoriasis that has not worsened or improved resulting in a 1% change in total body surface area (BSA) or a 2-point change in total Psoriasis Area and Severity Index (PASI) score."	To align the inclusion/exclusion criteria with industry precedence for similar psoriasis studies
Table 7-1	Deleted "Manufactured for Allergan by Frontage Laboratories, Inc."	In the event there is a change in the manufacturer
Table 8-1 Safety Criteria for Individual Participants Stopping Study Treatment	Added INR to stopping criteria here and throughout the protocol	Adhere to FDA Guidance for DILI 2009
9.1.1 Determination of Percent Body Surface Area	Added "(handprint method)"	Clarified the BSA methodology
9.1.2 Psoriasis Area and Severity Index	Added "(handprint method)" and text on the surface area involvement of each of the 4 anatomic regions and how they are scored.	Clarified the PASI methodology and aligned the PASI descriptors with industry precedents
Section 9.2.8 Adverse Events of Special Interest	Added INR to Adverse Events of Special Interest here and throughout the protocol	Additional safety surveillance
12.4 Contraceptive Guidance	Deleted footnote b from the table, which stated: "Hormonal contraception may be susceptible to interaction with the study treatment, which may	Deleted for clarity to match the text in the protocol, which states: "…agree to use 2 forms

Section No. and Name	Description of Change	Brief Rationale
	reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for 30 days after the last dose of study treatment."	of birth control, in which at least 1 form must be a highly effective method of contraception."
Throughout	Minor editorial revisions	Minor, therefore have not been summarized

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Protocol 1957-201-001 Amd 2

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]