Protocol ITN086AI

Evaluation of AMG 714 for Vitiligo: A Phase 2a Randomized Double Blind Placebo Controlled Trial

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Protocol Chair
Brett King, MD, PhD
Associate Professor of Dermatology
Yale Dermatology Department
[redacted]

ITN Clinical Trial Physician
[redacted]
Chief Medical Officer
Senior Director, Clinical and Translational Medicine
Clinical Trials Group
Immune Tolerance Network
[redacted]

NIAID Medical Monitor
[redacted]
Medical Officer
Division of Allergy, Immunology, and Transplantation / NIAID
[redacted]

NIAID Medical Monitor
[redacted]
Medical Officer | Autoimmunity and Mucosal Immunology Branch
Division of Allergy, Immunology, and Transplantation
NIAID, NIH, DHHS
[redacted]

NIAID Project Manager
[redacted]
Senior Project Manager
Division of Allergy, Immunology, and Transplantation / NIAID
[redacted]

ITN Clinical Operations Manager
[redacted]
Clinical Operations Manager
Clinical Trials Group
Immune Tolerance Network
[redacted]

NIAID Senior Regulatory Officer
[redacted]
Regulatory Affairs Officer
Division of Allergy, Immunology, and Transplantation / NIAID
[redacted]

ITN Lead Biologist
[redacted]
Immune Tolerance Network
University of Michigan
[redacted]

Rho Scientist
[redacted]
Associate Director, Biostatistics
Federal Systems Division, Rho Inc.
[redacted]

Rho Biostatistician
[redacted]
Biostatistician II
Federal Systems Division, Rho Inc.
[redacted]

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INVESTIGATOR SIGNATURE PAGE

Protocol: ITN086AI REVEAL	**Version/Date: V4.0 / November 3, 2023**
Protocol Chair: Brett King, MD, PhD	
Title: Evaluation of AMG 714 for Vitiligo: A Phase 2a Randomized Double Blind Placebo Controlled Trial	
Study Sponsor: The National Institute of Allergy and Infectious Diseases (NIAID)	
INSTRUCTIONS: *The site Principal Investigator should print, sign, and date at the indicated location below. The original of this form should be kept for your records. After signature, please return a copy of the signed form by email to:* [redacted]	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* dated March 2018. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the site Principal Investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without the written permission of the IRB and NIAID.

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Site Principal Investigator (Print)

_____ _____

Site Principal Investigator (Signature) **Date**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL SYNOPSIS

Title	Evaluation of AMG 714 for Vitiligo: A Phase 2a Randomized Double Blind Placebo Controlled Trial
Short Title	Evaluation of AMG 714 for Vitiligo
Clinical Phase	Phase 2a
Number of Sites	5-10 sites
IND Sponsor / Number	DAIT, NIAID / IND 146561
Study Objectives	The primary objective is to determine the efficacy of IL-15 inhibition with AMG 714 at inducing facial repigmentation in vitiligo. The secondary objectives are to: 1. Evaluate the safety and tolerability of AMG 714 in vitiligo. 2. Determine the efficacy of IL-15 inhibition with AMG 714 at inducing total body skin repigmentation in vitiligo. 3. Assess the durability of the skin repigmentation achieved by AMG 714 in vitiligo. 4. Evaluate the efficacy of AMG 714 followed by narrow band UVB (nbUVB) phototherapy.
Study Design	This clinical trial is a phase 2a, double blind, placebo-controlled, multi-center, proof of concept trial of AMG 714 for the treatment of vitiligo. Fifty-seven participants ages 18-75 years old with vitiligo will be randomized 2:1 to receive AMG 714 300 mg or placebo subcutaneously (SQ) every 2 weeks for 6 doses beginning at Week 0 with the last dose at Week 10. Participants will be stratified based on vitiligo activity, as defined in Section 3.6. The primary endpoint will be assessed at Week 24. Participants with < 25% improvement in the T-VASI score at Week 24 compared to Week 0 will receive nbUVB phototherapy. Participants will be followed for an additional 24 weeks after assessment of the primary endpoint to evaluate change in the F-VASI and T-VASI scores through Week 48 with or without the addition of nbUVB, and to continue to collect safety information.
Primary Endpoint	Proportion of participants achieving ≥ 35% improvement in F-VASI (F-VASI35) at Week 24 compared to Week 0.
Secondary Endpoints	**Efficacy:** 1. Proportion of participants with F-VASI35 at Weeks 12, 36, and 48. 2. Proportion of participants with F-VASI25, F-VASI50, F-VASI75, and F-VASI90 at Weeks 12, 24, 36, and 48. 3. Proportion of participants with T-VASI25, T-VASI35, T-VASI50, T-VASI75, and T-VASI90 at Weeks 12, 24, 36 and 48.

	4. Change in each of the following at Weeks 12, 24, 36, and 48 compared to Week 0: a. F-VASI b. T-VASI c. Vitiligo Extent Score (VES) d. Vitiligo Quality of Life instrument (VitiQoL) e. Vitiligo Noticeability Scale (VNS) f. Static Investigator Global Assessment (sIGA) 5. Percent change in each of the following at Weeks 12, 24, 36, and 48 compared to Week 0: a. F-VASI b. T-VASI **Safety endpoints:** 1. Grade 2 or higher adverse events (AEs). 2. Grade 3 or higher infectious AEs.
Accrual Objective	57
Study Duration	The target enrollment duration is 14 months. Participants will be followed for 48 weeks.
Treatment Description	AMG 714 300 mg or placebo injected subcutaneously every 2 weeks for 6 doses.
Inclusion Criteria	1. Adults 18-75 years of age. 2. Clinical diagnosis of active or stable vitiligo made by a dermatologist, as defined in Section 3.4.2. 3. F-VASI $\geq$ 0.25 (Appendix 2). 4. T-VASI $\geq$ 3 (Appendix 2). 5. Willingness to: a) Undergo nbUVB phototherapy, as outlined in Section 7.3. b) Stop all other treatments for vitiligo from screening through the final follow up visit as outlined in Section 7.2.
Exclusion Criteria	1. Inability or unwillingness of a participant to give written informed consent or comply with the study protocol. 2. Segmental vitiligo. 3. Contraindication to nbUVB phototherapy. 4. More than 33% leukotrichia on the face or on the total body. 5. Use of biologic immunosuppressive or immunomodulatory agents, or investigational therapy or procedure within 12 weeks or 5 half-lives prior to Visit 0 (whichever is longer), except agents authorized for prevention and treatment of SARS-CoV-2 infection according to FDA Emergency Use Authorization (EUA).

	6. Use of laser or light-based treatment (phototherapy) including tanning beds within 8 weeks prior to Visit 0. 7. Use of non-biologic systemic or topical immunosuppressive or immunomodulatory agents within 4 weeks prior to Visit 0. 8. History of melanocyte-keratinocyte transplantation procedure (MKTP) or other surgical treatment for vitiligo. 9. Current or past use of the depigmenting agents monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone). 10. Presence of skin conditions or lesions that would confound the vitiligo assessments. 11. Spontaneous repigmentation within 6 months prior to Visit 0 (repigmentation without any treatment and significant in amount as determined by the investigator). 12. Uncontrolled thyroid function at screening as determined by the investigator. If the participant has a history of thyroid disease and is on treatment, the participant must be on a stable thyroid regimen for at least three months prior to Visit 0. 13. Greater than 3 adequately treated nonmetastatic basal cell carcinomas (BCC) or squamous cell carcinomas (SCC) within 12 months prior to Visit 0; or previous history of multiple BCC or SCC which may pose additional risks from participation in the study in the opinion of the investigator. 14. Previous or current diagnosis of other cancer, except adequately treated cervical carcinoma in situ. 15. Acute or chronic infection, including current use of suppressive therapy for chronic infection, hospitalization for treatment of infection within 90 days prior to Visit 0, or parenteral anti-microbial (including anti-bacterial, anti-viral, or anti-fungal agents) use within 90 days prior to Visit 0. 16. Evidence of infection, including: a) Human immunodeficiency virus (HIV) b) Current or prior infection with hepatitis B (HBV), as indicated by positive HBsAg or positive HBcAb c) Current or prior hepatitis C (HCV), unless treated with anti-viral therapy with achievement of a sustained virologic response (undetectable viral load 12 weeks after cessation of therapy) d) Positive Quantiferon-TB Gold or Quantiferon-TB Gold Plus test. PPD or T-SPOT.TB test may be substituted for Quantiferon-TB Gold or Quantiferon-TB Gold Plus test 17. Any of the following laboratory abnormalities: a) White blood count (WBC) $< 3.5 \times 10^3/\mu L$ b) Hemoglobin < 10 g/dL c) Platelets (Plt) $< 125{,}000/mm^3$ d) Alanine aminotransferase (ALT) ≥ 2x ULN

	e) Aspartate aminotransferase (AST) ≥ 2x ULN 18. Women of child-bearing potential who are unwilling to use a medically acceptable form of contraception or be sexually inactive by abstinence until study Week 48 (Section 7.4). Contraception or abstinence is required for 2 weeks prior to Visit 0. 19. Women who are pregnant or lactating. 20. Vaccination with a live attenuated vaccine within 30 days prior to Visit 0. 21. Known drug allergy or reaction to any component of AMG 714 (Section 6.1.1) or proteins derived from mammalian cell lines. 22. Past or current medical problems or findings from physical examination or laboratory testing, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study. 23. Current, diagnosed mental illness (e.g. severe depression) or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements.
Study Stopping Rules	• Any death that occurs in the study, which is possibly related or related to study medication (Table 4). • The occurrence of a Grade 3 or higher SAE related to study treatment that is also a SUSAR in one or more of the study participants who have received study treatment. • Any occurrence of a Grade 3 or higher anaphylaxis reaction (Table 3). • Two or more events of skin malignancy in individuals who receive nbUVB during the study.

GLOSSARY OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ALP	alkaline phosphatase
BSA	body surface area
CBC	complete blood count
CDSMC	Clinical Data and Safety Management Center
CFR	Code of Federal Regulations
CRF	case report form
DAIT	Division of Allergy, Immunology, and Transplantation
DSMB	Data and Safety Monitoring Board
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FDA	US Food and Drug Administration
F-VASI	Facial Vitiligo Area Scoring Index
GCP	good clinical practice
GLP	good laboratory practice

GMP	good manufacturing practice
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonization
IEC	independent ethics committee
IEL(s)	intraepithelial lymphocyte
IFN-Ɣ	interferon-gamma
IL	interleukin
IND	Investigational New Drug application
IRB	institutional review board
ITN	Immune Tolerance Network
IV	intravenous
mITT	modified intention to treat
MKTP	melanocyte-keratinocyte transplantation procedure
nbUVB	narrow band ultraviolet B
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NK	natural killer

OHRP	Office for Human Research Protections
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PHI	personal Health Identifiers
PK	pharmacokinetics
Plt	platelets
PMEL	premelanosome protein
PoR	Pharmacist of Record
PP	per protocol
QA	quality assurance
QC	quality control
QOL	quality of life
RA	rheumatoid arthritis
TB	tuberculosis
SAE	serious adverse event
SAR	suspected adverse reaction
SCCC	Statistical and Clinical Coordinating Center
sIGA	Static Investigator Global Assessment
SOE	schedule of events
SOP	standard operating procedures
SPF	sun protection factor
SQ	subcutaneous

SUSAR	serious and unexpected suspected adverse reaction
Tcm(s)	central memory T cell(s)
TCR	T cell receptor
TEAE	treatment-emergent adverse events
TGF-ß	transforming growth factor beta
Trm(s)	resident memory T cell(s)
T-VASI	Total body Vitiligo Area Scoring Index
ULN	upper limit of normal
UVB	ultraviolet B
VASI	Vitiligo Area Scoring Index
VES	Vitiligo Extent Score
VNS	Vitiligo Noticeability Scale
VitiQoL	Vitiligo Quality of Life
WBC	white blood count

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

Vitiligo is an acquired autoimmune skin disorder characterized by T cell-mediated progressive destruction of melanocytes, which causes depigmented patches in the skin. Vitiligo is common and affects 0.5 to 2% of the world population, or approximately 3.5 million in the U.S. alone.[1] It equally affects both males and females without racial preference.

The natural course of the disease is usually progressive, causing the generalized distribution of multiple and often symmetrical well-circumscribed areas of depigmented skin. Patients with vitiligo may develop extra-cutaneous manifestations, since melanocytes are also present in the uveal tract, retinal pigment epithelium, leptomeninges, heart, and membranous labyrinth of the inner ear. The destruction of melanocytes in these organs can lead to significant symptoms including cochlear dysfunction and sensorineural hearing loss. Vitiligo is also associated with other autoimmune diseases such as autoimmune thyroid disease, type 1 diabetes mellitus, rheumatoid arthritis (RA), and pernicious anemia. Patients with vitiligo have significant psychological distress and suffer from anxiety and depression. Adverse effects of vitiligo on a person's quality of life are similar to those with psoriasis and atopic dermatitis.[2]

Currently, there are no FDA-approved medical treatments for vitiligo. Topical immunomodulatory agents and phototherapy are the most commonly used treatments. These treatments have varying efficacy, and produce results which are usually not sustained. In addition, these treatments are expensive, time consuming, and can have significant side effects.[1] Janus kinase (JAK) inhibitor creams are under investigation for the treatment of vitiligo, however trials with these agents indicate efficacy primarily in sun-exposed areas.[3-11] There is unmet medical need in vitiligo for treatment that is effective, safe, and can produce predictable, sustained, and cosmetically acceptable results.

Vitiligo represents a model of human organ-specific autoimmunity, and its pathogenesis includes the silent destruction of target cells, a role for cellular stress in initiating disease, importance of innate immunity, dependence on $CD8^+$ T cells and IFNɣ, and a role for regulatory T cells (Tregs) in controlling disease.[12] A murine model of vitiligo is available that closely resembles human disease. Affected mice develop patchy epidermal depigmentation with histological changes and gene expression profiles similar to human vitiligo.[13] The targeted antigen in the model, premelanosome protein (PMEL), is an important autoantigen in human vitiligo expressed physiologically in melanocytes.[14,15] Maintenance of vitiligo in the murine model depends on the presence of both autoreactive tissue resident memory $CD8^+$ T cells (Trms), as well as recirculating memory T cells. Autoreactive Trms are observed in vitiligo lesions in the skin of affected mice, and also in the interstitial skin fluid from human patients with vitiligo. These skin-infiltrating T cells are largely $CD69^+CD103^+$, and thus express phenotypic markers of Trm in skin.[16-19]

Resident memory $CD8^+$ T cells are generated in response to epidermal viral infections and remain in the tissue long-term to "raise an alarm" if infection returns.[20-24] These cells cooperate with recirculating memory T cells and depend on CXCR3 chemokines to

efficiently clear reinfection.[22,24] They depend on both TGF-β and IL-15 for their generation, and possibly for survival.[22,24-28] Thus, targeting Trm survival could be an effective durable treatment strategy for vitiligo, as it would eliminate autoreactive memory within the tissue, requiring any return of disease to that location to begin *de novo*.

The impact of anti-IL15 blockade was examined by using an antibody blocking IL-15Rβ in the murine model of vitiligo. Mice were exposed to this antibody for 8 weeks, which resulted in the depletion of autoreactive Trms in the skin and significant, durable treatment responses in the mice. A shorter 2-week treatment was also associated with long-lasting responses, but resulted primarily in altered Trm function (IFNɣ and granzyme B production) without significant depletion.[16] While IL-15Rβ is a shared receptor subunit between IL-15 and IL-2, the effect is most likely due to the block in IL-15 signaling, since IL-15 more potently generates $CD8^+$ Trm pools than residual IL-2 signaling in skin tissue,[27] and IL-15 is required for the generation of $CD8^+$ Trm in viral models in mice.[23] Further, $CD8^+$ T cells often express IL-15Rβ without CD25 (IL2Rα).[29] Mice lacking IL-2 or CD25 develop autoimmunity, whereas mice lacking IL-15 are protected from autoimmunity.[30] This preliminary study found that targeting IL-15 signaling through antibody treatment even after the generation of Trm in the tissue was effective at clearing these cells from the epidermis, and was associated with repigmentation of affected skin.[16]

Overall, these findings suggest that blocking the IL-15 pathway may be a novel therapeutic strategy for vitiligo treatment that may induce immune tolerance by depleting autoreactive Trms in the skin. Therefore, the goal of this trial is to conduct a proof of concept study examining the ability of IL-15 blockade with AMG 714 to induce immune tolerance and treat vitiligo. After assessment of AMG 714 efficacy, standard-of-care nbUVB treatment will be provided for participants who do not sufficiently improve, since phototherapy might enhance melanocyte recovery and repigmentation in non-sun exposed areas of skin.

1.2 RATIONALE FOR SELECTION OF INVESTIGATIONAL DRUG

IL-15 is a pro-inflammatory cytokine that promotes the development, homeostasis, and activation of memory $CD8^+$ T cells and NK cells. It also stimulates the production of IL-1, IL-6, and TNFα. IL-15 is produced by monocytes, macrophages, epithelial and fibroblastic cells, as well as bone marrow stromal cells.[31] Increased IL-15 expression has been observed in many immune-mediated conditions, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, celiac disease, and solid organ transplant rejection.[32]

AMG 714 is a fully human $IgG1_K$ monoclonal antibody that binds IL-15.[32,33] It is under clinical development by Amgen, Inc., and has been evaluated in Phase I and Phase II studies as a potential treatment for rheumatoid arthritis, psoriasis, and celiac disease (Section 1.4). AMG 714 was chosen as the investigational drug for this study given its ability to neutralize the effects of IL-15 (Section 1.3), a key pro-inflammatory pathogenic mediator in vitiligo. AMG 714 also has an acceptable safety profile (Section 5).

1.3 PRECLINICAL EXPERIENCE

Preclinical studies show that AMG 714 recognizes an epitope of human IL-15 that is essential for its interaction with its receptor complex.[33] AMG 714 neutralizes IL-15, and inhibits the IL-15 induced proliferation of peripheral blood T cells, as well as IL-15 induced TNFα production, in a dose-dependent fashion.

Hu714MuXHu, a monoclonal anti-macaque-IL-15 antibody, neutralizes macaque IL-15 with a similar potency as AMG 714 neutralizing human IL-15, and was judged to be an appropriate surrogate of AMG 714 in studies of macaques.[34] In a toxicity study of Hu714MuXHu in cynomolgus monkeys, there was no mortality and no effect on body weight, ophthalmoscopy, or electrocardiographic assessments. Administration of Hu714MuXHu was associated with histological signs of minimal to slight inflammation at injection sites without a clinical correlate.

In addition, Hu714MuXHu administration was associated with marked reduction in individual absolute and relative NK cell counts with a progressive decrease in NK cell activity in all animals during the dosing phase. This was an expected pharmacodynamic response, given the known role of IL-15 in NK cell biology. The NK cell depletion was not accompanied by microscopic findings indicative of other systemic immunomodulatory effects. Of note, human NK cells are not dependent on IL-15 for their survival,[33] possibly due to the redundant role of IL-2 on human NK cells. This difference in effect on NK cells may be related to a differential sensitivity of human versus cynomolgus monkey NK cells to IL-15.

The most common clinical signs included non-formed, discolored, mucoid, or liquid feces, which was not dose dependent. These cases were attributed to *Campylobacter* or *Shigella* infection, and responded well to antibiotic therapy. Of the six animals treated for diarrhea, five were infected with *Shigella* and successfully treated with enrofloxacin.

In studies to assess off-target binding, AMG 714 was found to bind to several cell types in human tissues including epithelial, fibroblast, glial, muscle, peripheral nerve, endothelial, and mononuclear cells. This binding pattern is consistent with IL-15Rα expression patterns and the high affinity of IL-15 for its receptor. No studies evaluating the genotoxicity, carcinogenicity, or reproductive or development toxicity have been conducted.

1.4 CLINICAL STUDIES

1.4.1 Safety Data for AMG 714

According to the current version of the AMG 714 Investigator's Brochure (IB),[32] 256 individuals have received AMG 714, including 200 individuals who were dosed biweekly for 12 weeks. These individuals participated in six completed clinical trials in healthy participants and participants with psoriasis, rheumatoid arthritis, celiac disease, and refractory celiac disease. In these six trials,[32] treatment-emergent adverse events (TEAEs) were reported in 190 (74.2%) individuals receiving AMG 714 and in 70 (64.8%) individuals receiving placebo. Most TEAEs were non-serious and were mild to moderate in severity. Nineteen serious adverse events (SAEs) were reported, of which 15 occurred in individuals receiving

AMG 714. These SAEs included sepsis and deep vein thrombosis (80 mg AMG 714); hip fracture, nerve compression, C5-C6 nerve compression, and asthma (280 mg AMG 714); flare of rheumatoid arthritis (0.15 mg/kg single dose AMG 714 SQ); and peroneal nerve palsy, hepatitis, tuberculosis, pneumococcal infection, balance disorder and cerebellar syndrome (8 mg/kg AMG 714). None of these SAEs was assessed as related to AMG 714.

Injection site reactions were the most commonly reported adverse event. No injection reactions were classified as an SAE. No deaths and no anaphylaxis events were reported in individuals treated with AMG 714.

Anti-AMG 714 antibodies were detected in 8 of the 256 individuals treated with AMG 714 and in 1 individual receiving placebo. Anti-drug antibodies (ADAs) were detected in 4 of the 8 subjects before receiving any dose of AMG 714. Neutralizing antibodies were observed in 1 subject who received a single dose of AMG 714. There were no effects on pharmacokinetics in any subject with detectable ADAs. The presence of ADAs does not appear to be associated with increased risk of adverse events or laboratory abnormalities.

In summary, AMG 714 was well tolerated in the completed clinical trials and has demonstrated an acceptable safety profile.

1.4.2 Clinical Efficacy Data

Two studies of AMG 714 were conducted in patients with rheumatoid arthritis (RA). In a Phase 1 study (Hx-IL15-001), 24 participants with RA received a single dose (0.15, 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg SQ injection) of AMG 714, while 6 participants received placebo. Twenty-four participants completed the second stage, an open-label extension study of repeated doses (0.5, 1.0, 2.0, or 4.0 mg/kg SQ injection; a total of 5 doses over 8 weeks).[35] Efficacy was assessed using the American College of Rheumatology (ACR) response criteria. In a pooled analysis of all dose cohorts, ACR20 response was achieved by week 8 in 15 of 24 patients (63%), ACR50 in 9 patients (38%), and ACR70 in 6 patients (25%).[32,35]

In a Phase 2 study, 180 participants with RA were randomized to receive placebo or AMG 714 (40, 80, 160, 280 mg SQ injection dose every 2 weeks for 12 weeks with an initial 200% loading dose).[32] Primary endpoint was the 14-week ACR20 response rate. At 14 weeks, the ACR20 response rate was higher in the AMG 714 280 mg group compared to placebo (54% vs. 38%), but the difference was not statistically significant (p=0.10). However, the difference in ACR20 responses was statistically significant between the AMG 714 280 mg and placebo groups at 12 weeks (64% vs. 34%, p=0.003) and at 16 weeks (66% vs. 38%, p=0.003). The DAS28, a measure of rheumatoid arthritis disease activity, was also reduced in the AMG 714 280 mg group compared to placebo at weeks 8, 12, and 16 (p = 0.02, p = 0.005, and p = 0.01, respectively). Also, inflammatory biomarkers such as C-reactive protein and erythrocyte sedimentation rate also decreased.

In a Phase 1b/2a dose escalation study in psoriasis, the primary endpoint of improvement in PASI scores was not met.[32]

Two studies of AMG 714 were completed for celiac disease. A Phase 2a double-blind, placebo-controlled, parallel group study was conducted in adult celiac disease participants on

a gluten-free diet. The study randomized 64 participants to placebo, AMG 714 150 mg, or AMG 714 300 mg SQ once every two weeks for six doses over 10 weeks. Primary efficacy endpoint was difference in the relative reduction in villous height to crypt depth ratio (VH:CD) between the AMG 714 and placebo groups after gluten challenge. The attenuation in reduction in VH:CD after gluten challenge was 11% compared to placebo but was not statistically significant. However, AMG 714 may ameliorate the effects of gluten challenge in this population compared to placebo, since the AMG 714 group had a statistically significant 38% attenuation in the increase in intraepithelial lymphocytes (IELs) and improvement in clinical symptoms. No patient in the AMG 714 300 mg group had clinical disease activity despite high dose gluten challenge.[32]

A Phase 2 study of Type II refractory celiac disease randomized 28 patients to receive 7 doses of AMG 714 8 mg/kg IV or placebo over 10 weeks. The primary endpoint of reduction in aberrant IELs vs. total IELs between baseline and week 12 was not met. However after 12 weeks of study treatment, the AMG 714 group saw improvement in diarrhea and T cell receptor clonality compared to the placebo group, which worsened.[32]

Clinical studies of AMG 714 for the treatment of vitiligo have not been conducted.

2. STUDY HYPOTHESES / OBJECTIVES

2.1 HYPOTHESIS

The primary clinical hypothesis is that inhibition of the IL-15 pathway with AMG 714 will deplete autoreactive resident memory T cells in the skin and modulate pro-inflammatory mediators, resulting in durable repigmentation of skin affected by vitiligo.

2.2 PRIMARY OBJECTIVE

The primary objective is to determine the efficacy of IL-15 inhibition with AMG 714 at inducing facial skin repigmentation in vitiligo.

2.3 SECONDARY OBJECTIVES

The secondary objectives are to:

1. Evaluate the safety and tolerability of AMG 714 in vitiligo.
2. Determine the efficacy of IL-15 inhibition with AMG 714 at inducing total body skin repigmentation in vitiligo.
3. Assess the durability of the skin repigmentation achieved by AMG 714 in vitiligo.
4. Evaluate the efficacy of AMG 714 followed by narrow band UVB (nbUVB) phototherapy.

2.4 EXPLORATORY OBJECTIVES

Exploratory mechanistic objectives are described in Section 9.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY DESIGN

This clinical trial is a phase 2a, double blind, placebo-controlled, multi-center, proof of concept trial of AMG 714 for the treatment of vitiligo. Fifty-seven participants ages 18-75 years old with vitiligo will be randomized 2:1 to receive AMG 714 300 mg or placebo subcutaneously every 2 weeks for 6 doses beginning at Week 0 with the last dose at Week 10. Participants will be stratified based on vitiligo activity, as defined in Section 3.4. The primary endpoint will be assessed at Week 24. Participants with < 25% improvement in the T-VASI score at Week 24 compared to Week 0 will receive nbUVB phototherapy. Participants will be followed for an additional 24 weeks after assessment of the primary endpoint to evaluate change in the F-VASI and T-VASI scores through Week 48 with or without the addition of nbUVB, and to continue to collect safety information. The target enrollment duration is 14 months. Figure 1 provides a schematic of the study design for this trial and Figure 2 provides an overview of individual study participation.

Figure 1. Study Design

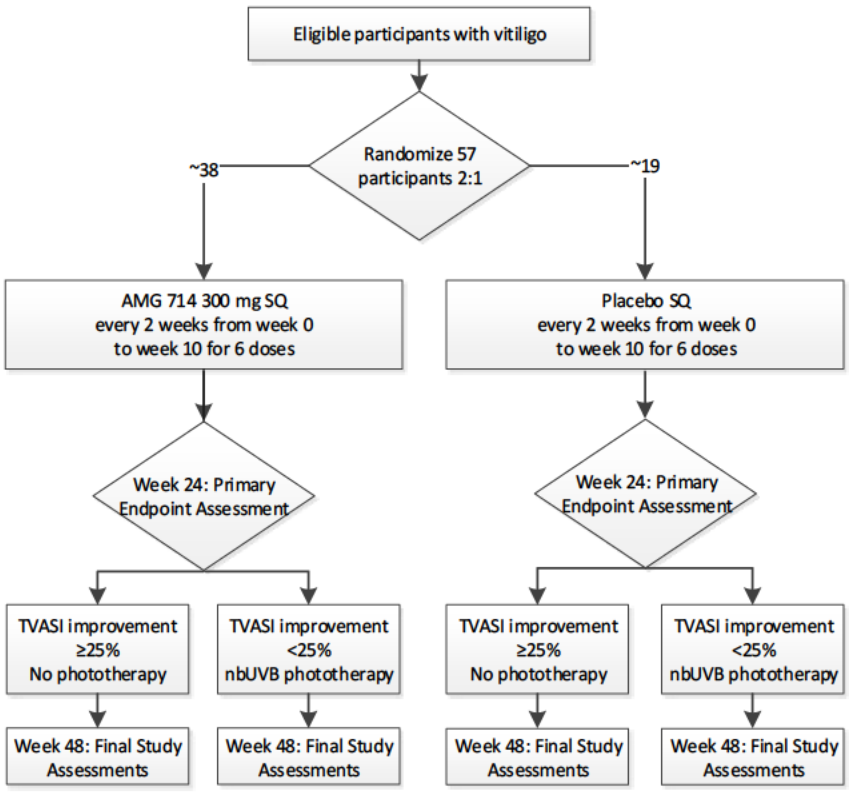
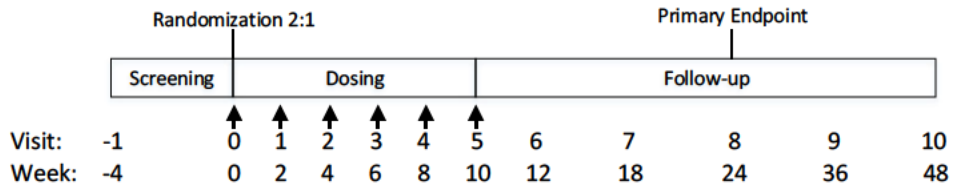


Figure 2. Individual Study Participation



3.2 PRIMARY ENDPOINT

Proportion of participants achieving ≥ 35% improvement in F-VASI (F-VASI35) at Week 24 compared to Week 0.

3.3 SECONDARY ENDPOINTS

3.3.1 Secondary Efficacy Endpoints

1. Proportion of participants with F-VASI35 at Weeks 12, 36, and 48.
2. Proportion of participants with F-VASI25, F-VASI50, F-VASI75, and F-VASI90 at Weeks 12, 24, 36, and 48.
3. Proportion of participants with T-VASI25, T-VASI35, T-VASI50, T-VASI75, and T-VASI90 at Weeks 12, 24, 36 and 48.
4. Change in each of the following at Weeks 12, 24, 36, and 48 compared to Week 0:
    a. F-VASI
    b. T-VASI
    c. Vitiligo Extent Score (VES)[36]
    d. Vitiligo Quality of Life instrument (VitiQoL)[37]
    e. Vitiligo Noticeability Scale (VNS)[38]
    f. Static Investigator Global Assessment (sIGA)
5. Percent change in each of the following at Weeks 12, 24, 36, and 48 compared to Week 0:
    a. F-VASI
    b. T-VASI

3.3.2 Secondary Safety Endpoints

1. Grade 2 or higher adverse events (AEs).
2. Grade 3 or higher infectious AEs.

3.4 DEFINITIONS

3.4.1 F-VASI35

F-VASI35 is defined as ≥ 35% improvement in the F-VASI score compared to Week 0, according to the following formula:

$$\text{F-VASI} < 0.65\ (\text{F-VASI at Week 0})$$

3.4.2 Vitiligo Activity

1. Active vitiligo: New or expanding vitiligo lesions with or without the presence of confetti, trichrome, or inflammatory vitiligo lesion patterns, Koebner phenomenon, or other clinical signs of active vitiligo in the past 3 months.
2. Stable vitiligo: No new depigmented lesions, and no confetti, trichrome, or inflammatory vitiligo lesion patterns, Koebner phenomenon, or other clinical signs of active vitiligo in the past 3 months.

3.5 STRATIFICATION, RANDOMIZATION, AND BLINDING/MASKING

Participants who sign the informed consent form and meet the eligibility criteria will be randomly assigned 2:1 in favor of treatment with AMG 714 versus treatment with placebo. Random assignment will be stratified by active versus stable vitiligo, as defined in Section 3.4.2.

Randomization will be accomplished through a password-protected, web-based, randomization system.

Randomization will occur at least one day prior to Visit 0.

3.5.1 Blinding

Blinding will be maintained for all study participants and trial personnel throughout the study, except for the study site Pharmacist of Record (PoR). As an extra blinding precaution, AMG 714 or placebo will be administered by qualified personnel not involved in the vitiligo assessment of the study participant.

3.5.2 Procedure for Unblinding / Unmasking

Before the study is complete, the blind for an individual participant should only be broken when appropriate medical management of the participant necessitates knowledge of treatment assignment.

In the event of a medical emergency, when the immediate knowledge of the actual treatment is essential for the management of the participant, the site PI, or designee, can automatically obtain the participant's treatment assignment from the randomization system. The site PI is encouraged to discuss the emergency unblinding with the NIAID Medical Monitor prior to unblinding the participant, if possible.

If the randomization system is not available, the site PI can contact the Clinical Data and Safety Management Center (CDSMC) Client Support Services to obtain treatment assignment information. For more information and other unblinding pathways, please refer to the study Manual of Procedures (MOP).

As soon as possible, the site investigator will provide a full account of unblinding to the NIAID Medical Monitor, Protocol Chair, and the Statistical and Clinical Coordinating Center (SCCC) of the unblinding event. The NIAID Medical Monitor will then notify the Data and Safety Monitoring Board (DSMB). A full account of the event will be recorded, including the date and time of the unblinding, the names of the individual(s) who made the decision, the

reason(s), the participant(s) affected, and individual(s) who were unblinded, and individual(s) who were notified.

Unblinding the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analysis will require written approval from NIAID.

IND safety reports will be reported to the FDA, DSMB, and IRBs in an unblinded fashion.

The final study report will contain any instances of unblinding prior to completion of the study along with the reason(s) for unblinding.

4. SELECTION OF PARTICIPANTS

4.1 RATIONALE FOR STUDY POPULATION

This study will recruit adults with vitiligo from age 18 to 75 years. Clinical diagnosis of vitiligo by a dermatologist is required to ensure vitiligo is correctly diagnosed. Vitiligo involvement of the face is required since facial repigmentation is the primary endpoint. Individuals with vitiligo that is segmental, or who have more than 33% leukotrichia on the face or total body will be excluded since these lesions are not expected to repigment. Some prior treatments for vitiligo within specific time periods will be excluded to avoid confounding of the results by prior therapy.

4.2 INCLUSION CRITERIA

Individuals must meet all of the following criteria to be eligible for enrollment as study participants:

1. Adults 18-75 years of age.
2. Clinical diagnosis of active or stable vitiligo made by a dermatologist, as defined in Section 3.4.2.
3. F-VASI ≥ 0.25 (Appendix 2).
4. T-VASI ≥ 3 (Appendix 2).
5. Willingness to:
    a) Undergo nbUVB phototherapy, as outlined in Section 7.3.
    b) Stop all other treatments for vitiligo from screening through the final follow up visit as outlined in Section 7.2.

4.3 EXCLUSION CRITERIA

Individuals who meet any of the following criteria are not eligible for enrollment as study participants:

1. Inability or unwillingness of a participant to give written informed consent or comply with the study protocol.
2. Segmental vitiligo.
3. Contraindication to nbUVB phototherapy.

4. More than 33% leukotrichia on the face or on the total body.
5. Use of biologic immunosuppressive or immunomodulatory agents, or investigational therapy or procedure within 12 weeks or 5 half-lives prior to Visit 0 (whichever is longer), except agents authorized for prevention and treatment of SARS-CoV-2 infection according to FDA Emergency Use Authorization (EUA).
6. Use of laser or light-based treatment (phototherapy) including tanning beds within 8 weeks prior to Visit 0.
7. Use of non-biologic systemic or topical immunosuppressive or immunomodulatory agents within 4 weeks prior to Visit 0.
8. History of melanocyte-keratinocyte transplantation procedure (MKTP) or other surgical treatment for vitiligo.
9. Current or past use of the depigmenting agent monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone).
10. Presence of skin conditions or lesions that would confound the vitiligo assessments.
11. Spontaneous repigmentation within 6 months prior to Visit 0 (repigmentation without any treatment and significant in amount as determined by the investigator).
12. Uncontrolled thyroid function at screening as determined by the investigator. If the participant has a history of thyroid disease and is on treatment, the participant must be on a stable thyroid regimen for at least three months prior to Visit 0.
13. Greater than 3 adequately treated nonmetastatic basal cell carcinomas (BCC) or squamous cell carcinomas (SCC) within 12 months prior to Visit 0; or previous history of multiple BCC or SCC which may pose additional risks from participation in the study in the opinion of the investigator.
14. Previous or current diagnosis of other cancer, except adequately treated cervical carcinoma in situ.
15. Acute or chronic infection, including current use of suppressive therapy for chronic infection, hospitalization for treatment of infection within 90 days prior to Visit 0, or parenteral anti-microbial (including anti-bacterial, anti-viral, or anti-fungal agents) use within 90 days prior to Visit 0.
16. Evidence of infection, including:
    a) Human immunodeficiency virus (HIV)
    b) Current or prior infection with hepatitis B (HBV), as indicated by positive HBsAg or positive HBcAb
    c) Current or prior hepatitis C (HCV), unless treated with anti-viral therapy with achievement of a sustained virologic response (undetectable viral load 12 weeks after cessation of therapy)
    d) Positive Quantiferon-TB Gold or Quantiferon-TB Gold Plus test. PPD or T-SPOT.TB test may be substituted for Quantiferon-TB Gold or Quantiferon-TB Gold Plus test
17. Any of the following laboratory abnormalities:
    a) White blood count (WBC) < 3.5 x $10^3/\mu L$

b) Hemoglobin < 10 g/dL

c) Platelets (Plt) < 125,000/mm^3

d) Alanine aminotransferase (ALT) ≥ 2x ULN

e) Aspartate aminotransferase (AST) ≥ 2x ULN

18. Women of child-bearing potential who are unwilling to use a medically acceptable form of contraception or be sexually inactive by abstinence until study Week 48 (Section 7.4). Contraception or abstinence is required for 2 weeks prior to Visit 0.
19. Women who are pregnant or lactating.
20. Vaccination with a live attenuated vaccine within 30 days prior to Visit 0.
21. Known drug allergy or reaction to any component of AMG 714 (Section 6.1.1) or proteins derived from mammalian cell lines.
22. Past or current medical problems or findings from physical examination or laboratory testing, which, in the opinion of the investigator, may pose additional risks from participation in the study, may interfere with the participant's ability to comply with study requirements or that may impact the quality or interpretation of the data obtained from the study.
23. Current, diagnosed mental illness (e.g. severe depression) or current, diagnosed or self-reported drug or alcohol abuse that, in the opinion of the investigator, would interfere with the participant's ability to comply with study requirements.

5. KNOWN AND POTENTIAL RISKS AND BENEFITS TO PARTICIPANTS

5.1 RISKS OF INVESTIGATIONAL DRUG AS CITED IN INVESTIGATOR'S BROCHURE

Precautions for hypersensitivity events are required. Hypersensitivity events such as injection site reaction (13.3%), injection site pain (2%), rash (4.7%), and eczema (3.1%) were reported in individuals receiving AMG 714.[32] All hypersensitivity reactions were mild and transient. There are no reports of anaphylaxis to AMG 714. All individuals who receive AMG 714 or AMG 714 placebo will be monitored for 1 hour after injection to detect any possible injection site reaction, hypersensitivity, and/or anaphylactic reaction (Section 6.1.3.4). AMG 714 is contraindicated in individuals with a known sensitivity to proteins derived from mammalian cell lines or other components of this drug.

The effect of AMG 714 on pregnancy, breast-feeding, pediatric participants, or geriatric participants is not known. No clinical studies have been conducted in individuals with renal or hepatic impairment. The effects of an overdose of AMG 714 are not known, and an antidote is not available. There is no evidence that AMG 714 use is habit forming.

5.2 RISKS OF INVESTIGATIONAL DRUG CITED IN MEDICAL LITERATURE

The results of study Hx-IL15-001 with AMG 714 in rheumatoid arthritis have been published.[35] Related adverse events reported in this study (n=30) include influenza-like symptoms, transient pyrexia, myalgia, injection site reactions, upper respiratory site infection (managed with antibiotics), herpes simplex virus, and aphthous stomatitis. None were

moderate or severe. In addition, fluorescence-activated cell sorting for T cell and NK cell subsets did not show significant changes from baseline up to 28 days after treatment.

5.3 RISKS OF OTHER PROTOCOL SPECIFIED MEDICATIONS

There are no other protocol specified medications.

5.4 RISKS OF STUDY PROCEDURES

The risks of the study procedures are as follows:

1. Study drug administration: Injection site reactions such as pain, redness, or swelling at the injection site are common.
2. Blood draw: Low risk of hemorrhage, hematoma, or infection at the venipuncture site.
3. Skin biopsies: Low risk of hemorrhage, hematoma or infection at the biopsy site. Scarring at the biopsy site is expected, however the biopsy diameter will be small and every effort will be made to collect biopsies from non-exposed areas of the body.
4. Narrow band UVB phototherapy: Low risk of erythema, xerosis, pruritus, folliculitis, sunlight-induced rash, or worsening of vitiligo.
5. Questionnaires: Low risk of discomfort due to questions that may be sensitive in nature.

5.5 RISK OF SARS-COV-2

Participants will be educated and advised about the importance of adherence to recommendations of the Center for Disease Control and Prevention (CDC) and other public health authorities for reducing the risk of SARS-CoV-2 infection, including vaccination.

5.6 POTENTIAL BENEFITS

The overall goal of this study is to examine whether inhibition of the IL-15 pathway can induce immune tolerance in vitiligo by depleting autoreactive T-cells, leading to the repigmentation of vitiligo lesions. Participants themselves may not directly benefit from the trial since the active study medication may not be an effective treatment for vitiligo. In addition, some participants will receive placebo instead of active study medication. However, the insight gained from studying the clinical efficacy of IL-15 blockade in the treatment of vitiligo may improve the understanding of the pathogenesis of vitiligo and help identify novel therapeutic targets for future study. All participants whose T-VASI score does not improve by at least 25% by Week 24 will undergo 24 weeks of nbUVB phototherapy, a standard treatment for vitiligo.

6. INVESTIGATIONAL DRUG

6.1 INVESTIGATIONAL DRUG

6.1.1 AMG 714

AMG 714 is the investigational drug used in the study and will be given at a dose of 300 mg SQ every 2 weeks for a total of 6 doses. AMG 714 is not FDA-approved and is in clinical development by Amgen.

Each sterile 10 cc vial of AMG 714 is filled with a 2 mL deliverable volume of 100 mg/mL AMG 714 formulated in 10 mM sodium acetate, 9.0% w/v sucrose, and 0.004% w/v polysorbate 20, pH 5.2. AMG 714 is stored as a frozen liquid at ≤ -30°C ± 10°C and protected from light.

6.1.2 AMG 714 Placebo

The AMG 714 placebo used in clinical trials contains the same liquid formulation as AMG 714. Each sterile vial of AMG 714 placebo contains 1 ml volume of 10 mM sodium acetate, 9% w/v sucrose, and 0.004% w/v polysorbate 20, pH 5.2 without the active ingredient. The placebo solution is not visually distinguishable from AMG 714.

AMG 714 placebo is stored in the same fashion as AMG 714.

6.1.3 Dosage, Preparation, Administration, and Treatment of Hypersensitivity or Anaphylaxis

6.1.3.1 Dosage

The dose of AMG 714 to be used in this study is 300 mg every 2 weeks for a total of 6 doses. Each dose will be administered as 2 subcutaneous (SQ) injections (1.5 mL each). Placebo will also be administered as 2 SQ injections (1.5 mL each).

6.1.3.2 Preparation

Doses of AMG 714 or placebo will be prepared by the unblinded study site PoR according to the investigational pharmacy manual. After preparation, AMG 714 or placebo may be stored for up to 72 hours at 2-8°C, and no longer than 12 hours at room temperature. Prolonged exposure to light during storage should be avoided.

AMG 714 should be warmed to room temperature for a minimum of 1 hour before administration. Light exposure should continue to be avoided. The syringe should be inspected by the study staff member responsible for administering study drug for any visible foreign particles. If the study drug is not suitable for injection, it should be returned to the unblinded study PoR and replaced.

6.1.3.3 Administration

Temperature, blood pressure, pulse and respirations will be obtained immediately before study drug administration and 60 minutes after study drug administration. Study participants will be monitored for 1 hour after study drug administration to detect any possible injection site reaction, hypersensitivity, and/or anaphylaxis (Section 6.1.3.4).

AMG 714 or placebo will be administered subcutaneously by trained health care staff not otherwise involved in the vitiligo assessment of the participant (Section 3.5.1). Each dose will be comprised of two separate syringes, each containing 1.5 ml of AMG 714 or placebo. The SQ injections should be administered on the participant's anterior abdominal wall in a consecutive fashion approximately 2 cm apart. The side of the abdominal wall should be alternated at every visit (i.e., left side at one visit, right side at the next visit).

If more than one participant is scheduled to receive study drug on the same day at the same investigational site, at least 15 minutes must elapse between study drug administration to each participant.

6.1.3.4 Treatment of Hypersensitivity and/or Anaphylaxis

Participants will be monitored as specified in Section 6.1.3.3 for 1 hour after administration of the study treatment for hypersensitivity and anaphylaxis reactions. Administration of AMG 714 or placebo will be stopped immediately if any of the following hypersensitivity/anaphylaxis reactions occurs (Table 3 Section 12.3.1):

- Any grade 2 or higher hypersensitivity/anaphylaxis reaction, or
- A generalized pruritus or urticaria grade 1 hypersensitivity/anaphylaxis reaction.

Appropriate treatment for the reaction per institution's guidance will be instituted. Appropriate treatment may include corticosteroids, antihistamines, epinephrine, bronchodilators, or oxygen.

All participants should be instructed to seek immediate medical attention if they experience any delayed onset hypersensitivity or anaphylaxis symptoms as listed in Table 3 (Section 12.3.1).

6.2 DRUG ACCOUNTABILITY

Under Title 21 of the Code of Federal Regulations (21CFR §312.62) the investigator is required to maintain adequate records of all investigational drug storage and disposition. For all DAIT-sponsored clinical trials, these responsibilities are delegated to the site's PoR. The PoR must maintain all records related to storage and disposition of AMG 714 active and placebo vials including:

1. Ensure drugs are stored in a secured area, with access limited to authorized pharmacy personnel and stored under appropriate temperature range as specified in the protocol and pharmacy manual.
2. Date and quantity of the drug received.
3. Date and quantity of the drug dispensed.
    a. A drug dispensing log will be kept current for each drug and participant. These logs will contain the drug information, identification of each participant, the date, and quantity of drug dispensed. Please see pharmacy manual for more detailed information.
4. Detailed accountability of any unused (un-dispensed) AMG 714 active and placebo vials for return to DAIT/NIAID investigational drug distributor.
    a. All remaining unused and/or expired AMG 714 active and placebo vials will be returned to DAIT/NIAID investigational drug distributor during study and after study termination.

All records regarding drug disposition will be maintained by the study site's investigational pharmacy and available for inspection.

6.3 ASSESSMENT OF PARTICIPANT COMPLIANCE WITH INVESTIGATIONAL DRUG

Study treatment will be administered by trained health care staff. Compliance, therefore, will be monitored by the site and documented on the eCRF.

6.4 TOXICITY PREVENTION AND MANAGEMENT

Study treatment must be suspended if the participant develops an infection or other AE that the investigator judges to be significant. Study treatment must be suspended if the participant develops a confirmed SARS-CoV-2 infection.

If the infection or AE resolves, AMG 714 or placebo may be restarted at the next scheduled dose.

Clinically significant laboratory abnormalities should be repeated within 48 hours of awareness.

6.4.1 Hypersensitivity or Anaphylaxis

Administration of AMG 714 or placebo will be permanently discontinued if the participant develops a hypersensitivity/anaphylactic reaction, as described in section 6.1.3.4.

6.4.2 Liver Chemistry Abnormalities

Participants will be monitored for drug induced liver injury. The recommended dose modifications for elevations in ALT and AST are summarized in Table 1.

Table 1. Dose Modification for Liver Chemistry Abnormalities

ALT/AST	Action
≤ 3xULN	Maintain dose
>3xULN to ≤5xULN with serum total bilirubin ≤ 2x ULN	Suspend AMG 714 or placebo. Resume AMG 714 or AMG 714 placebo at the next expected dose if ALT and AST decrease to ≤3xULN. If AMG 714 or AMG 714 placebo is resumed, permanently discontinue AMG 714 or placebo if ALT or AST increases to >3xULN a second time.
>3xULN with serum total bilirubin > 2xULN (Hy's Law)	Discontinue AMG 714 or placebo
> 5xULN	Discontinue AMG 714 or placebo

6.5 PREMATURE DISCONTINUATION OF INVESTIGATIONAL DRUG

AMG 714 or placebo will be permanently discontinued for any participant for any of the following reasons:

1. A grade 3 or greater AE occurs that the investigator judges to be possibly or definitely related to study treatment.
2. A grade 2 or greater cardiovascular AE occurs that the investigator judges to be possibly or definitely related to study treatment.
3. A grade 2 or greater hematologic AE occurs that meets all of the following:
    a. ≥ 5% change from Visit 0, and
    b. Confirmed by repeat testing prior to the next scheduled dose of study medication, and
    c. Site investigator judges the AE to be possibly or definitely related to study treatment.
4. The study participant becomes pregnant.
5. The study participant develops a hypersensitivity or anaphylaxis reaction (Section 6.4.1, Section 12.3.1).
6. The study participant receives a prohibited biological agent, systemic immunosuppressive agent or live-attenuated vaccine (Section 7.2), except as described in Section 7.1.2.
7. The study participant develops liver chemistry abnormalities according to Table 1 (Section 6.4.2).
8. The investigator believes that the study treatment is no longer in the best interest of the participant.

Participants who discontinue study treatment will return for the Week 6 visit if it has not already occurred, and then will be followed per the Post-treatment follow-up schedule beginning at Week 12 as outlined in the Schedule of Events (Appendix 1).

If study treatment is discontinued, the NIAID Medical Monitor should be notified.

7. OTHER MEDICATIONS

7.1 CONCOMITANT MEDICATIONS

7.1.1 Protocol Mandated

There are no protocol mandated concomitant medications for this study.

7.1.2 Permitted Concomitant Medications

All skin products and medication should remain stable during the study. The following medications and therapies are permitted during the study:

1. Oral vitamins, minerals and dietary supplements.
2. Camouflage make-up, except during nbUVB treatments.
3. Sunscreen with SPF of at least 30 is recommended if participants will be exposed to sun for greater than 30 minutes.
4. Corticosteroids:
    - Prednisone (or equivalent dose of other corticosteroid) for one course only at a maximum daily dose of ≤ 30 mg/day for up to 2 weeks.
    - One course of topical corticosteroids for up to 2 weeks.
    - One course of intra-articular corticosteroids.
    - Inhaled and nasal corticosteroids.

7.1.3 Prophylactic Medications

There are no prophylactic medications required for this study.

7.2 PROHIBITED MEDICATIONS AND THERAPIES

The following medications and therapies are prohibited during the study:

1. Investigational agents other than the study drug, except agents authorized for prevention and treatment of SARS-CoV-2 infection according to FDA EUA.
2. Immunosuppressive or immunomodulatory biologic, systemic, and topical agents. Except as described in Section 7.1.2, these include, but are not limited to:
    a) Corticosteroids
    b) Calcineurin inhibitors
3. Tanning beds.
4. Medications that are contraindicated in the setting of phototherapy are prohibited while participants are receiving phototherapy.
5. The depigmenting agent monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone).
6. Live-attenuated vaccines during treatment with study medication and for 12 weeks after treatment.

7.3 NARROW BAND UVB PHOTOTHERAPY

Light or laser-based treatments (phototherapy) are prohibited for all study participants except as described below:

Participants will undergo narrow band ultraviolet B (nbUVB) phototherapy if T-VASI does not improve by ≥ 25% at Week 24 compared to Week 0. Phototherapy will be administered in

accordance with the Vitiligo Working Group expert recommendations.[39] Narrow band UVB phototherapy must be started within 28 days of the Week 24 study visit.

7.4 CONTRACEPTION USE

All female participants of childbearing potential must not become pregnant during the course of the study and must either be sexually inactive by abstinence or use a medically acceptable form of contraception for the duration of the study. Women who are abstinent must have complete abstinence from intercourse from 2 weeks prior to the administration of the first dose of the study drug until Week 48. Periodic abstinence and withdrawal are not acceptable methods of contraception.

Medically acceptable forms of birth control include oral contraceptive pills (combined hormone or progestin alone), injectable or implantable progestogens, intrauterine devices, estrogen vaginal rings, male partner sterilization, or double barrier methods (e.g., condom and occlusive cap with spermicidal agent). If using male partner sterilization (vasectomy with documentation of azoospermia), sterilization must occur prior to the female participant's entry into the study, and the male must be the sole partner for the participant. Documentation of male partner sterilization is required.

Contraception use must start at least 2 weeks prior to the administration of the first dose of study drug and must continue until Week 48. If terminating study participation prior to Week 48, participants will be instructed to continue contraception for at least 16 weeks after their last dose of study drug.

7.5 RESCUE MEDICATIONS

Not applicable.

8. STUDY PROCEDURES / ASSESSMENTS

8.1 ENROLLMENT

The research study will be explained in lay terms to each potential research participant. The potential participant will sign an informed consent form before undergoing any study procedures. Participants who meet the eligibility criteria will be randomly assigned to a study treatment group, either AMG 714 or placebo, in a 2:1 fashion. Enrollment is defined as the time of randomization.

8.2 SCREENING/BASELINE VISIT

8.2.1 Screening Visit

The purpose of the screening period is to confirm eligibility to continue in the study. Screening of study participants will take place at Visit -1. Participants will be assessed for the eligibility criteria listed in Sections 4.2 and 4.3.

8.2.2 Baseline Visit

Baseline is defined as Week 0 (Visit 0).

8.3 STUDY ASSESSMENTS AND PROCEDURES

The study assessments to be performed at each study visit are listed in Appendix 1.

8.3.1 General Assessments

- Informed consent: Written informed consent will be obtained before any study assessments or procedures are performed
- Eligibility criteria: Eligibility for study participation will be assessed during the screening period
- Demographics: Age, sex, and ethnicity
- Medical history: A history will be taken to determine if the participant has had any clinically significant diseases or medical procedures other than the disease under study
- Vital signs: Height will be obtained at screening (V-1); weight, temperature, pulse, blood pressure, and respiration will be obtained at all visits
- Comprehensive physical examination includes the following body systems: Skin, respiratory, cardiovascular, gastrointestinal, neurologic, and renal/urinary
- Limited physical examination includes the skin and focuses on the body systems relevant to the participant's clinical complaints and clinical status at the study visit
- Vitiligo history, including date of diagnosis, type (active or stable), and previous treatments
- Adverse events: Participants will be assessed for AEs. All adverse events will be graded, recorded on the case report forms (CRFs), and reported per Section 12
- Concomitant medications: All concomitant medications and their indications for use will be recorded
- Treatment Assignment Survey (Appendix 6)

8.3.2 Study Drug Administration

- Subcutaneous injection of study treatment (AMG 714 300 mg or placebo)

8.3.3 Narrow Band UVB Phototherapy

- NbUVB phototherapy for participants meeting the criterion described in Section 7.3

8.3.4 Clinical Laboratory Assessments

- Hematology: CBC with differential
- Chemistry: Creatinine, total bilirubin, AST, ALT, alkaline phosphatase, and albumin
- TSH, unless test has been performed within 30 days of Visit -1 and documented test results are available.
- HIV (antibody), unless test has been performed within 30 days of Visit -1 and documented test results are available.
- Hepatitis B (surface antigen and core antibody), unless test has been performed within 30 days of Visit -1 and documented test results are available.

- Hepatitis C (antibody with RNA confirmation if indicated), unless test has been performed within 30 days of Visit -1 and documented test results are available.
- Quantiferon-TB Gold or Quantiferon-TB Gold Plus (PPD skin test or T-SPOT.TB test may be substituted), unless test has been performed within 30 days of Visit -1 and documented test results are available.
- Serum pregnancy (for women of child bearing potential)
- STAT urine pregnancy (for women of child bearing potential)

8.3.5 Disease Specific Assessments

- Vitiligo assessments (T-VASI, F-VASI, VES) (Appendices 2 and 3)
- Static Investigator Global Assessment (sIGA) (Appendix 7)
- Patient reported outcome measures (VitiQoL, VNS) (Appendices 4 and 5)
- Digital skin photography

8.3.6 Mechanistic Assessments

- Skin biopsies
    - Lesional punch. If the lesion has resolved, the punch biopsy will be taken from the previously lesional area.
    - Non-lesional punch
- Peripheral blood mononuclear cells (PBMCs)
- Serum
- Whole blood DNA and whole blood RNA

See Section 9 for detailed discussion of mechanistic assays.

8.4 TELEPHONE VISITS

Visit 7 (Week 18) will be conducted as a telephone visit.

After Week 12, remote follow-up contact will occur at least once between each visit to facilitate participant retention, and to discuss phototherapy in participants receiving this treatment after Week 24.

8.5 WITHDRAWAL VISIT

Participants who withdraw from the study as described in Section 11.2 will be asked to complete the assessments outlined in the withdrawal (WD) visit in Appendix 1.

8.6 UNSCHEDULED VISITS

If disease activity increases or other concerns arise between regularly scheduled visits, participants should contact study personnel and may be asked to return to the study site for an "unscheduled" visit to assess vitiligo disease activity or adverse events. Assessments obtained during an unscheduled visit are outlined in Appendix 1. Some assessments for an unscheduled visit may be omitted at the discretion of the investigator if not indicated.

8.7 VISIT WINDOWS

Study visits should take place within the time limits specified in Table 2. Visit 0 must occur within 28 days of Visit -1. All other scheduled study visits must occur within the time limits specified in Table 2.

Table 2. Visit Windows

Visit	Timepoint	Visit Window
Screening: Visit -1	Within 28 days of Day 0	
Baseline: Visit 0	Day 0	n/a
Visits 1 to 6	Every 2 weeks through week 12	+/- 3 days
Visits 7 to 10	Weeks 18, 24, 36, and 48	+/- 7 days

9. MECHANISTIC ASSAYS

Similar to other ITN studies, peripheral blood mononuclear cells and serum will be obtained at pre-specified time points (Appendix 1) for immunophenotyping and characterization of proinflammatory mediators to complement assessments of immune cells, melanocytes, and functional profiles from lesional and nonlesional skin biopsies. Whole blood will be collected to support future genomic, epigenomic, and transcriptomic studies.

9.1 MECHANISTIC HYPOTHESES AND RATIONALE

Vitiligo is a chronic, progressive, autoimmune skin disease driven by the continued recruitment of autoreactive $CXCR3^+$ T cells by the IFNγ-dependent chemokines, CXCL9, and CXCL10. Recent preclinical studies show that maintenance of vitiligo depends on the presence of both autoreactive resident memory $CD8^+$ T cells (Trm), as well as recirculating memory T cell populations.[16] $CD8^+$ Trm cells are generated in response to epidermal viral infections and remain in the tissue long-term to "raise an alarm" if infection returns.[20-24,40,41] These cells cooperate with recirculating memory T cells and depend on CXCR3 chemokines to efficiently clear reinfection.[22,24]

Trm cells depend on both TGF-β and IL-15 for their generation, and possibly for survival.[25-28] Thus, targeting Trm survival by blocking IL-15 signaling with AMG 714 could be an effective and durable treatment strategy for vitiligo, as it would eliminate autoreactive memory within the tissue, requiring any return of disease to that location to begin de novo. Indeed, targeting IL-15Rβ systemically with an antibody effectively depleted autoreactive Trms in the skin, and resulted in significant, durable treatment responses in a murine model of vitiligo.[16] Another recent study found that IL-15Rβ antibody administration in rhesus macaques greatly reduced tissue effector memory T cell populations, while recirculating populations bounced back.[42]

Thus, the primary mechanistic hypothesis is that short-term treatment with AMG 714 will reduce autoreactive $CD8^+$ Trm cells within vitiligo lesions. Given the pleiotropic effects of IL-15, AMG 714 treatment may also alter frequencies and/or functional properties of effector

and regulatory T, NK, NKT, B, monocyte, and/or dendritic cell populations not eliminated by treatment in skin or blood.[43,44] In addition, keratinocytes may also be directly or indirectly modulated by AMG 714.[45-47] Mechanistic studies will address multiple questions, but will be prioritized based on the amount of tissue and blood available.

In this study, serial skin and blood samples will be collected at the same time points. The objective is to analyze the frequencies, phenotypes, and functional profiles of immune cell populations in skin and blood, enumerate melanocytes in skin, and quantify soluble mediators in serum associated with vitiligo and blockade of IL-15R signaling. These studies will explore immune signatures that correlate with clinical response outcomes, and will help determine what, if any, immunological changes in skin are paralleled in blood by systemic IL-15 antibody treatment with AMG 714 compared to placebo.

9.2 PROPOSED MECHANISTIC ASSAYS

9.2.1 Skin Biopsies

This study will collect skin biopsies of lesional and nonlesional skin.

Previous analyses indicate that vitiligo lesional skin contains increased numbers of $CD103^+CD69^+CD8^+$ T cells that express GrzmB, CD49a, CXCR3 that produce IFNγ compared to nonlesional skin from patients with and without vitiligo.[18,19] Elevated expression of pro-inflammatory chemokines CXCL9 is also increased in vitiligo lesions compared to nonlesional skin from patients with and without vitiligo.[48] Therefore, punch skin biopsies will be used to determine the impact of AMG 714 on autoreactive Trm (e.g. $CD103^+CD69^+$ $GrzmB^+CD49a^+CXCR3^+$), and recirculating memory T cells (e.g. $CD103^-CD69^+CD44^+$). We will also determine if immune phenotypes and/or functional profiles in lesional skin correlate with clinical response outcomes.

9.2.2 PBMC-Based Assays

9.2.2.1 Peripheral Blood Mononuclear Cell (PBMC) Preparation

All blood samples collected for PBMC isolation will be shipped from the clinical sites to the ITN core facility for processing using ITN standard operating procedures (SOPs) for PBMC separation and freezing. This will ensure that standardized procedures are used and that high-quality material is obtained for testing. PBMCs will be stored in the vapor phase of liquid nitrogen until use.

9.2.2.2 Multi-parameter Immunoprofiling of PMBCs

Flow cytometry or mass cytometry may be done at ITN laboratories to analyze the impact of AMG 714 treatment on the frequency and functional status of specific immune cell populations in viably cryopreserved PBMC. Proposed immunophenotyping panels will be finalized and validated by the ITN prior to starting batched analysis. Levels of circulating cells will be compared between the baseline and various time points following treatment. Additional comparisons will be made between treatment groups to evaluate the effect of treatment on specific cell phenotypes, and to identify phenotypes that correlate with clinical response outcomes.

Since vitiligo is an autoimmune skin disease characterized by IFNγ+, granzyme B+, and $CXCR3^+$ T cell infiltration in lesional skin, it may be important to determine the effects of AMG 714 compared to placebo treatment on global and skin-homing effector (e.g. $IFN\gamma+GZMB^+CXCR3^+$) and regulatory (e.g. $Foxp3^+CD127^{low}CD45RO^+$) T cell subsets in the peripheral pool of CD8 and CD4 T cells. Tetramer staining may also be applied to HLA compatible participants to evaluate the impact of treatment on autoreactive T cells in blood capable of trafficking to lesional skin (CLA^+ and $CXCR3^+$) as previously reported.[16,49]

9.2.3 Serum Assays

Participant serum may be analyzed using validated immunoassay platforms to investigate the impact of AMG 714 treatment on circulating levels of cytokines and inflammatory mediators associated with vitiligo, such as CXCL9, CXCL10, and IL-15. Treatment-induced changes in mediators in serum may be evaluated for correlations with treatment-induced changes in Trm in lesional skin and recirculating memory T cell subsets in lesional skin and blood. In addition, AMG 714 serum levels may be assessed.

9.2.4 Whole Blood Assays

9.2.4.1 Whole Blood DNA Genotyping

It is reasonable to assume that AMG 714 treatment may not be equally effective in all individuals, and that genetic differences in IL-15 signaling pathway genes may influence response outcomes. DNA may be isolated from whole blood collected from all consenting participants, and the ITN may perform genotyping for HLA Class I/II alleles or single nucleotide polymorphisms (SNPs) in selected immune response genes to investigate correlations with disease progression and therapeutic response. HLA typing may be performed to identify HLA-compatible participants for tetramer-based evaluation of T cell autoreactivity in cryopreserved PBMC.

9.2.4.2 Gene Expression in Peripheral Blood

Systemic treatment with biologic medications has been shown to modulate gene expression in autoimmune disease; therefore, whole blood can be used to evaluate changes in the peripheral circulation due to immunomodulation of the disease or the systemic nature of the treatment with AMG 714. Whole blood will be collected from enrolled participants and may be used to evaluate global changes in gene expression during and after treatment. Gene expression of molecules found to be modulated by treatment in skin biopsies and/or PBMC may be investigated in whole blood using quantitative methods.

10. BIOSPECIMEN STORAGE

A major priority of the Immune Tolerance Network, in partnership with the National Institute of Allergy and Infectious Diseases of the NIH, USA, is the development of novel immunoassays in order to better understand mechanisms of tolerance and to develop biomarkers to predict the development and maintenance of clinical tolerance. As in all Immune Tolerance Network-funded clinical trials, informed consent will be obtained from all participants for their samples to be stored for use in future studies. Biological specimens collected in this trial will be stored long-term in order to re-evaluate biologic responses as

new research tools to study tolerance become available. The specimens will therefore be stored at the ITN sample repository for a minimum of 10 years. Residual specimens may be used by the investigators for development of new immunologic assays or for cross-trial comparisons. Although specimens in this protocol are described in the context of assays to be performed, it should be noted that not necessarily all assays will be performed for all participants at each time point. Decisions to perform assays will be made based on statistical and scientific planning, hypotheses to be tested, and technologies available. Finally, clinical outcomes will be considered to determine the potential value of the assays. For example, if a clinical effect fails to occur, it may be decided that there is minimal value in performing certain mechanistic assays. The ITN sample sharing policy will apply for the provision of samples to study or outside investigators (www.immunetolerance.org).

11. CRITERIA FOR PARTICIPANT STUDY COMPLETION AND PREMATURE STUDY TERMINATION

11.1 PARTICIPANT COMPLETION

A participant is considered to have completed the study if s/he is enrolled and completes the last visit at Week 48 (Visit 10).

11.2 PARTICIPANT STOPPING RULES AND WITHDRAWAL CRITERIA

Participants may be prematurely terminated from the study for the following reasons:

1. The participant elects to withdraw consent from all future study activities, including follow-up.
2. The participant is “lost to follow-up” (i.e., no further follow-up is possible because attempts to reestablish contact with the participant have failed).
3. The participant dies.
4. The Site Investigator believes that participation is no longer in the best interest of the participant.

11.3 PARTICIPANT REPLACEMENT

Randomized participants will be replaced if they do not receive any part of any dose of study medication.

11.4 FOLLOW-UP AFTER STUDY WITHDRAWAL

If a participant withdraws or is withdrawn from the study as described in Section 11.2, the participant will be asked to return for a final visit where the assessments outlined in the withdrawal (WD) visit in Appendix 1 will be performed. No additional follow-up will be requested from participants after early study withdrawal.

11.5 STUDY STOPPING RULES

If any of the events described in Section 12.8.2.2 occur, an *ad hoc* DSMB review will occur. After review of the data, the DSMB will make recommendations regarding the study conduct and/or continuation.

12. SAFETY MONITORING AND REPORTING

12.1 OVERVIEW

This section defines the types of safety data that will be collected under this protocol and outlines the procedures for appropriately collecting, grading, recording, and reporting those data. Adverse events that are classified as serious according to the definition of health authorities must be reported promptly (Section 12.5) to the Sponsor (DAIT/NIAID). Appropriate notifications will also be made to the IRBs and health authorities.

Information in this section complies with ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH Guideline E-6: Guideline for Good Clinical Practice, 21CFR Parts 312 and 320, and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

12.2 DEFINITIONS

12.2.1 Adverse Event

An adverse event (AE) is any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events [1/15/07]", http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with AMG 714 administration or any study mandated procedure (Section 5.4).

12.2.1.1 Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the investigational study drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction (SAR) implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a)).

12.2.2 Unexpected Adverse Event

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the current AMG 714 IB or is not listed at the specificity, severity or rate of occurrence that has been observed.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the current IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (21 CFR 312.32(a)).

12.2.3 Serious Adverse Event

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor (DAIT/NIAID), it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or Sponsor (DAIT/NIAID), its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Elective hospitalizations or hospital admissions for the purpose of conduct of protocol-mandated procedures are not to be reported as an SAE unless hospitalization is prolonged due to complications.

12.2.4 Adverse Events of Special Interest (AESI)

Any occurrence of malignancy will be considered an Adverse Event of Special Interest (AESI) and must be reported to the IND Sponsor within 24 hours, according to the procedure for SAEs described in Section 12.5.1.

12.3 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

12.3.1 Grading of Hypersensitivity and Anaphylaxis

For this study, hypersensitivity and anaphylaxis reactions will be graded according to Table 3 below. The final grade of the reaction will not be determined until the event is over. Any reaction that results in the permanent discontinuation of the AMG 714 (Section 6.4.1) should be reported according to the procedure for SAEs described in Section 12.5.1.

Table 3. Grading of Hypersensitivity and Anaphylaxis Reactions

(Modified from World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System[50]).

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/ sign(s) of one organ system present Cutaneous Generalized pruritus, urticaria, flushing or sensation of heat or warmth or Angioedema (not laryngeal, tongue or uvular) or Upper respiratory Rhinitis (e.g., sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) or Throat-clearing (itchy throat) or Cough perceived to come from the upper airway, not the lung, larynx, or trachea or Conjunctival Conjunctival erythema, pruritus or tearing or Other Nausea, metallic taste, or headache	*Symptom(s)/ sign(s) of more than one Grade 1 organ system present* or Lower respiratory Asthma: cough, wheezing, shortness of breath (e.g., less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator) or Gastrointestinal Abdominal cramps, vomiting, or diarrhea or Other Uterine cramps	Lower respiratory Asthma (e.g., 40% PEF or FEV1 drop, NOT responding to an inhaled bronchodilator) or Upper respiratory Laryngeal, uvula or tongue edema with or without stridor	Lower or Upper respiratory Respiratory failure with or without loss of consciousness or Cardiovascular Hypotension with or without loss of consciousness	Death

12.3.2 Grading of Liver Chemistry Abnormalities

For this study, liver function abnormalities will be graded using protocol specific criteria, and are defined relative to the upper limit of normal (ULN) as follows:

- Aspartate aminotransferase [AST] increased
  - Grade 1: > ULN - 3.0x ULN
  - Grade 2: > 3.0x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN
- Alanine aminotransferase [ALT] increased

- Grade 1: > ULN - 3.0x ULN
- Grade 2: > 3.0x ULN - 5.0x ULN
- Grade 3: > 5.0x ULN - 20.0x ULN
- Grade 4: > 20.0x ULN

- Alkaline phosphatase [ALP] increased
  - Grade 1: > ULN - 2.5x ULN
  - Grade 2: > 2.5x ULN - 5.0x ULN
  - Grade 3: > 5.0x ULN - 20.0x ULN
  - Grade 4: > 20.0x ULN

- Blood bilirubin increased
  - Grade 1: > ULN - 1.5x ULN
  - Grade 2: > 1.5x ULN - 3.0x ULN
  - Grade 3: > 3.0x ULN - 10.0x ULN
  - Grade 4: > 10.0x ULN

12.3.3 Grading Criteria

For all other adverse events not related to hypersensitivity, anaphylaxis or liver chemistry abnormalities, the study site will grade the severity of adverse events experienced by the study participants according to the criteria set forth in the NCI-CTCAE (version 5.0, November 27, 2017). This document (here in referred to as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. The NCI-CTCAE manual has been reviewed by the Protocol Chair, ITN Clinical Trial Physician and NIAID Medical Monitor and has been deemed appropriate for the participant population to be studied in this protocol.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

Grade 1 = mild adverse event.

Grade 2 = moderate adverse event.

Grade 3 = severe adverse event.

Grade 4 = life-threatening or disabling adverse event.

Grade 5 = death.

For grading an abnormal value or result of a clinical or laboratory evaluation (including, but not limited to, a radiograph, an ultrasound, an electrocardiogram etc.), a treatment-emergent adverse event is defined as an increase in grade from baseline or from the last post-baseline value that doesn't meet grading criteria. Changes in grade from screening to baseline will also be recorded as adverse events, but are not treatment-emergent. If a specific event or result from a given clinical or laboratory evaluation is not included in the NCI-CTCAE manual, then an abnormal result would be considered an adverse event if changes in therapy or monitoring are implemented as a result of the event/result.

For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.

12.3.4 Attribution Definitions

The relationship, or attribution, of an adverse event to the study drug or study procedure(s) will initially be determined by the site investigator and recorded on the appropriate AE/SAE eCRF. Final determination of attribution for safety reporting will be determined by DAIT/NIAID. The relationship of an adverse event to study drug or procedures will be determined using the descriptors and definitions provided in Table 4.

Table 4. Attribution of Adverse Events

Code	Descriptor	Relationship (to primary investigational drug and/or other concurrent mandated study drug or study procedure)
Unrelated Category		
1	Not Related	The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
Related Categories		
2	Possibly Related	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3	Related	The adverse event is clearly related.

12.4 COLLECTION AND RECORDING OF ADVERSE EVENTS

12.4.1 Collection Period

All adverse events will be collected from the time the participant signs the informed consent until the participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study.

12.4.2 Collecting Adverse Events

Details regarding all AEs and SAEs will be collected in the source documents. Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant
- Interviewing the participant
- Receiving an unsolicited complaint from the participant
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3.

12.4.3 Recording Adverse Events

Grade 2 or higher AEs will be recorded on the appropriate AE case report form (eCRF) for this study. A generalized pruritus or urticaria Grade 1 hypersensitivity/anaphylaxis reaction,

or confirmed Grade 1 SARS-CoV-2 infection will also be recorded (Section 6.1.3.4). The investigator will record these adverse events and serious adverse events (Section 12.2) on the appropriate AE/SAE eCRF regardless of the relationship to study treatment or study procedure.

Once recorded, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent) or is withdrawn from the study, whichever occurs first.

12.5 REPORTING OF SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS

12.5.1 Reporting of Serious Adverse Events to Sponsor

This section describes the responsibilities of the site investigator to report serious adverse events to the Sponsor (DAIT/NIAID) via the eCRF. Timely reporting of adverse events is required by 21 CFR and ICH E6(R2) guidelines.

Site investigators will report all serious adverse events (Section 12.2.3), regardless of relationship or expectedness within 24 hours of discovering the event. Any AESI (Section 12.2.4) or a hypersensitivity/anaphylactic reaction that results in permanent discontinuation of study medication (Section 6.4.1 and Section 12.3.1) will also be reported within 24 hours.

For serious adverse events, all requested information on the AE/SAE eCRF will be provided. However, unavailable details of the event will not delay submission of the known information. As additional details become available, the SAE eCRF should be updated and submitted.

For additional information regarding SAE reporting, contact Rho Product Safety:

Rho Product Safety

[redacted]

12.5.2 Reporting to Health Authority

After an adverse event requiring 24-hour reporting (Section 12.5.1) is submitted by the site investigator and assessed by DAIT/NIAID, there are two options for DAIT/NIAID to report the adverse event to the appropriate health authorities:

12.5.2.1 Annual Reporting

DAIT/NIAID will include in the annual study report to health authorities all adverse events classified as:

- Serious, expected, suspected adverse reactions (Section 12.2.1.1)

- Serious and not a suspected adverse reaction (Section 12.2.2)
- Pregnancies.

Note that all adverse events (not just those requiring 24-hour reporting) will be reported in the Annual IND Report.

12.5.2.2 Expedited Safety Reporting

This option, with 2 possible categories, applies if the adverse event is classified as one of the following:

Category 1: **Serious and unexpected suspected adverse reaction** (**SUSAR)** (see Section 12.2.1.1, Section 12.2.2, and 21 CFR 312.32(c)(1)(i)).

The Sponsor shall report any suspected adverse reaction that is both serious and unexpected. The Sponsor shall report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
3. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Category 2: Any findings from studies that suggests a significant human risk

The Sponsor shall report any findings from other epidemiological studies, analyses of adverse events within the current study or pooled analysis across clinical studies or animal or *in vitro* testing (e.g. mutagenicity, teratogenicity, carcinogenicity) that suggest a significant risk in humans exposed to the drug that would result in a safety-related change in the protocol, informed consent, current IB or other aspects of the overall conduct of the study.

DAIT/NIAID shall notify the FDA and all participating investigators of expedited Safety Report within 15 calendar days; unexpected fatal or immediately life-threatening suspected adverse reaction(s) shall be reported as soon as possible or within 7 calendar days.

12.5.3 Reporting of Adverse Events to IRB/IECs

All investigators shall report adverse events, including expedited reports, in a timely fashion to their respective IRBs/IECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA shall be distributed by DAIT/NIAID or designee to all participating institutions for site IRB/IEC submission.

12.6 PREGNANCY REPORTING

The investigator shall be informed immediately if a female study participant becomes pregnant, or if a male participant becomes aware of a pregnancy in a female partner. A pregnant participant shall be instructed to stop taking study medication. The investigator shall counsel the participant, and discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of a pregnant participant shall continue until the conclusion of the pregnancy.

The investigator shall report to DAIT/NIAID all pregnancies that occur in female study participants within 1 business day of becoming aware of the event using the Pregnancy eCRF. All female participant pregnancies identified during the study shall be followed to conclusion and the outcome of each must be reported. The Pregnancy eCRF shall be updated and submitted to the CDSMC when details about the outcome are available.

Information requested about the delivery shall include:

- Gestational age at delivery
- Birth weight, length, and head circumference
- Gender
- Appearance, pulse, grimace, activity, and respiration (APGAR) score at 1 minute, 5 minutes, and 24 hours after birth, if available
- Any abnormalities.

For all pregnancy complications that result in a congenital abnormality, birth defect, miscarriage, and medically indicated abortion, an SAE shall be submitted to DAIT/NIAID using the SAE reporting procedures described above.

The investigator shall also report to DAIT/NIAID all male participant partner pregnancy outcomes by eCRF when this information can be obtained. Specific information collected will include number of infants; gender, weight, length, and head circumference of each infant; any infant complications, medical problems, or congenital anomalies.

12.7 REPORTING OF OTHER SAFETY INFORMATION

An investigator shall promptly notify the site IRB as well as DAIT/NIAID when an "unanticipated problem involving risks to participants or others" is identified, which is not otherwise reportable as an adverse event.

12.8 REVIEW OF SAFETY INFORMATION

12.8.1 Medical Monitor Review

The DAIT/NIAID Medical Monitor shall receive monthly reports from the SCCC compiling new and accumulating information on AEs, SAEs, and pregnancies recorded by the study site(s) on appropriate eCRFs.

In addition, the Medical Monitor shall review and make decisions on the disposition of the SAE (Section 12.5.1) and pregnancy reports (Section 12.6) received by the CDSMC.

12.8.2 DSMB Review

12.8.2.1 Planned DSMB Reviews

The NIAID Autoimmune DSMB will review safety data and make recommendations regarding the continuation, termination, or modification of the study. The DSMB shall review safety data at least yearly during planned DSMB Meetings. Data for the planned safety reviews will include, at a minimum, a listing of all reported AEs and SAEs. The DSMB will also review F-VASI and T-VASI results through Week 12 by treatment group in a closed session to monitor for an unexpected drug-induced worsening of vitiligo.

The DSMB will be informed of an Expedited Safety Report in a timely manner.

12.8.2.2 Ad hoc DSMB Reviews

In addition to the pre-scheduled data reviews and planned safety monitoring, the DSMB may be called upon for *ad hoc* reviews. The DSMB will review any event that potentially impacts safety at the request of the protocol chair or DAIT/NIAID. In addition, the following events will trigger an *ad hoc* comprehensive DSMB Safety Review:

- Any death that occurs in the study, which is possibly related or related to study medication (Table 4).
- The occurrence of a Grade 3 or higher SAE related to study treatment that is also a SUSAR in one or more of the study participants who have received study treatment.
- Any occurrence of a Grade 3 or higher anaphylaxis reaction (Table 3).
- Two or more events of skin malignancy in individuals who receive nbUVB during the study.

The DSMB will review the data within 2 weeks of the event being identified. If the DSMB has not reviewed the data within 2 weeks, study enrollment, as defined in Section 8.1, will be suspended and no additional participants will sign consent. Participants already in screening may continue with screening assessments, and participants already enrolled in the trial will continue as planned, pending completion of the DSMB *ad hoc* review. After review of the data, the DSMB will make recommendations regarding study conduct and/or continuation.

13. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

13.1 OVERVIEW

ITN086AI is a Phase 2a, randomized, double-blind, placebo controlled trial in which participants with vitiligo will receive AMG 714 or placebo. The primary objective is to determine the efficacy of IL-15 inhibition with AMG 714 at inducing facial skin repigmentation compared to placebo. The study also aims to evaluate safety and assess the durability of repigmentation with AMG 714.

13.2 ENDPOINTS

Primary and secondary endpoints are listed in Sections 3.2 and 3.3.

13.3 MEASURES TO MINIMIZE BIAS

This study has a randomized, double-blind, placebo-controlled, prospective design with well-defined entry criteria. Participants and site personnel who manage participants will be blinded to treatment assignment throughout the trial. In addition, site personnel, including investigators, will not have access to any mechanistic data until completion of the study.

13.4 ANALYSIS PLAN

13.4.1 Analysis Populations

Safety sample (SS): All participants who receive any amount of AMG 714 or placebo. The safety analyses will be based on the actual treatment the participants receive.

Modified Intent to treat (mITT) sample: All randomized participants who receive any dose of study treatment. The efficacy analyses will be based on the mITT sample according to the group to which the participants are assigned.

Per protocol (PP) sample: All participants in the mITT sample with no major protocol deviations that impact efficacy assessments, who received at least 5 of the 6 doses of the expected study treatment, and who have the Week 24 F-VASI assessment. The reported major deviations will be reviewed during a masked data review after the last participant's primary endpoint visit to determine which participants should be excluded from the per-protocol population.

13.4.2 Primary Analysis of Primary Endpoint

The primary endpoint is the proportion of participants achieving an F-VASI35 response at Week 24.

The primary analysis of the primary endpoint will be performed on the mITT sample and is designed to test the following hypotheses:

- Null hypothesis: The proportion achieving an F-VASI35 at Week 24 does not differ between the AMG 714 and placebo groups
- Alternate hypothesis: The proportion achieving an F-VASI35 at Week 24 differs between the AMG 714 and placebo groups.

The proportion of F-VASI35 responders will be estimated for each treatment group. Groups will be compared using two-sided Fisher's Exact test evaluated using a Type 1 error rate of α=0.05.

Missing Data. For a participant who is missing the baseline F-VASI, the screening F-VASI will be used. Participants for whom the Week 24 F-VASI cannot be evaluated will be deemed non-responders.

13.4.3 Supportive Analyses of the Primary Endpoint(s)/Outcome(s)

At a minimum, the following sensitivity analyses for the primary analyses will be performed:

- An analysis analogous to the primary endpoint analysis using only mITT participants with observed F-VASI data at Week 24 (i.e., dropping participants with missing Week 24 F-VASI rather than assuming non-response)
- An analysis analogous to the primary endpoint analysis using the PP participants
- A stratified analysis of F-VASI35 response using the Cochran-Mantel-Haenszel statistic to compare treatment groups after controlling for active versus stable vitiligo at baseline.

13.4.4 Analyses of Secondary Endpoints

All secondary inferential analyses are considered supportive; p-values for test of differences among groups will be presented without adjustment for multiple comparisons. The mITT population will be used for all secondary analyses. For secondary response indices (e.g. F-VASI25 at Week 12, F-VASI25 at Week 36, F-VASI25 at Week 48, T-VASI25 at Week 12, etc.), participants for whom endpoint data is unavailable will be deemed response failures. Otherwise, data will not be imputed for analyses of secondary endpoints.

The null hypothesis proposes that there are no differences in the secondary endpoints (measured either as means or proportions) between study groups. The alternative hypothesis proposes that there are differences between groups.

The following analyses are planned to evaluate the impact of treatment over the course of the study:

1. For secondary dichotomous response variables including F-VASI25, F-VASI35, F-VASI50, F-VASI75, F-VASI90, T-VASI25, T-VASI35, T-VASI50, T-VASI75, and T-VASI90 at each indicated secondary analysis time point, analyses will be analogous to those described for the primary endpoint.
2. Estimated response rates for each dichotomous F-VASI and T-VASI responder variable (i.e. 25%, 35%, 50%, 75%, 90%) at each indicated analysis time point will be presented for subgroups defined by treatment and active/stable vitiligo status.
3. For the change (and % change) in F-VASI, change (and % change) in T-VASI, change in VES, and change in VitiQoL at each indicated secondary analysis time point, the treatment group distributions will be compared using Mann-Whitney tests (2-sided).
4. For the ordinal VNS endpoint at each secondary analysis time point,
    a. Treatment groups will be compared at each indicated secondary analysis time point using an extension of the Fisher's Exact test.
    b. Shifts in distributions from baseline to each time point will be evaluated for each treatment arm using Bowker's exact test of symmetry.

5. To evaluate treatment group differences longitudinally, separate general mixed linear models will be fit to the F-VASI, T-VASI, VES, and VitiQoL, over all time points from day 0 through Week 24 with fixed effects for time point (fit as categorical), treatment group and the time*treatment interaction. A 1-banded unstructured within-subject covariance matrix will be assumed and fit separately for each treatment arm. Appropriate contrasts will evaluate trends over time and changes from baseline.

After Week 24, participants who do not achieve a T-VASI25 response will receive nbUVB phototherapy. For T-VASI25 responders (who will not receive nbUVB phototherapy), the post-Week 24 analyses will evaluate durability of response. In contrast, for T-VASI25 non-responders, the aim will be to evaluate improvement following the addition of nbUVB phototherapy. The following analyses are planned:

1. Durability of response: For the subset of participants who achieve a T-VASI25 response at Week 24 (and receive no nbUVB phototherapy), the null hypothesis of no change from Week 24 to Week 48 will be evaluated by treatment arm against the 1-sided alternative of worsening from Week 24 to Week 48.

    a. For each treatment arm, descriptive statistics and p-values derived from Wilcoxon tests will be presented for change (and % change) in F-VASI, change (and % change) in T-VASI, change in VES, and change in VitiQoL from Week 24 to Week 48.

    b. For the VNS ordinal endpoint, shifts in distributions from Week 24 to Week 48 will be evaluated for each treatment arm using Bowker's exact test of symmetry.

2. Improvement after nbUVB phototherapy: For the subset of participants who do not achieve a T-VASI25 response at Week 24 and receive nbUVB phototherapy, analyses will assess improvement in repigmentation and other key scales in the AMG 714 and placebo arms following nbUVB phototherapy.

    a. For each treatment arm, descriptive statistics and p-values derived from Wilcoxon tests will be presented for change (and % change) in F-VASI, change (and % change) in T-VASI, change in VES, and change in VitiQoL from baseline to Week 48.

    b. For dichotomous response indices defined by % improvement from baseline to Week 48 (i.e. F-VASI25, F-VASI35, F-VASI50, F-VASI75, F-VASI90, T-VASI25, T-VASI35, T-VASI50, T-VASI75, and T-VASI90), estimated response rates will be presented for subgroups defined by treatment.

    c. For the VNS ordinal endpoint at Week 48,

        i. Shifts in distributions from baseline to Week 48 will be evaluated for each treatment arm using Bowker's exact test of symmetry.

Treatment group differences for the incidence of AEs and the incidence of grade 3 or higher infectious AEs occurring over the first 24 weeks will be compared using a Fisher's exact test.

13.4.5 Descriptive Analyses

Descriptive statistics will be provided by treatment group for participant disposition, baseline and demographic characteristics, and use of concomitant medications. Continuous measures will be summarized using n, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts and percentages.

13.5 INTERIM ANALYSES

No formal interim analyses for stopping the trial early for futility or efficacy are planned.

13.6 STATISTICAL HYPOTHESES

Statistical hypotheses are provided in Sections 13.4.2 and 13.4.4.

13.7 SAMPLE SIZE CONSIDERATIONS

The underlying F-VASI35 response rate at Week 24 was assumed to be 5% for the placebo arm based on clinical trial results with ruxolitinib cream for vitiligo.[6,7] For the AMG 714 arm, the minimal clinically meaningful response rate was assumed to be 45%. Under this scenario, a study of 57 individuals randomized 2:1 to AMG 714 and placebo, respectively, will provide 88% power using a 2-sided Fisher's Exact test at α=0.05. If the placebo response rate is actually 7.5% (i.e. 50% higher than expected), power will still 81%. For the secondary PP analysis, if sample size drops to 48 (16% loss), then power is still 80%.

14. IDENTIFICATION AND ACCESS TO SOURCE DATA

14.1 SOURCE DATA

Source documents and source data are considered to be the original documentation where participant information, visits consultations, examinations and other information are recorded. Documentation of source data is necessary for the reconstruction, evaluation and validation of clinical findings, observations and other activities during a clinical trial.

14.2 ACCESS TO SOURCE DATA

The site investigators and site staff will make all source data available to the Sponsor (DAIT/NIAID), ITN, and relevant health authorities. Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals.

15. QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management. Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the

database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

16. PROTOCOL DEVIATIONS

16.1 PROTOCOL DEVIATION DEFINITIONS

Protocol Deviation – The investigators and site staff will conduct the study in accordance to the protocol; no deviations from the protocol are permitted. Any change, divergence, or departure from the study design or procedures constitutes a protocol deviation. As a result of any deviation, corrective actions will be developed by the site and implemented promptly.

Major Protocol Deviation (Protocol Violation) – A Protocol Violation is a deviation from the IRB approved protocol that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. In addition, protocol violations include willful or knowing breaches of human participant protection regulations, or policies, any action that is inconsistent with the NIH Human Research Protection Program's research, medical, and ethical principles, and a serious or continuing noncompliance with federal, state, local or institutional human subject protection regulations, policies, or procedures.

Non-Major Protocol Deviation – A non-major protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that does not have a major impact on the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

16.2 REPORTING AND MANAGING PROTOCOL DEVIATIONS

The study site principal investigator has the responsibility to identify, document and report protocol deviations as directed by the study Sponsor. However, protocol deviations may also be identified during site monitoring visits or during other forms of study conduct review.

17. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

17.1 STATEMENT OF COMPLIANCE

This clinical study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB.

Any amendments to the protocol or to the consent materials will also be approved by the IRB before they are implemented.

17.2 INFORMED CONSENT PROCESS

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The principal investigator or licensed physician designee listed on the FDA 1572 will review the consent and answer questions. The prospective participant will be told that being in the trial is voluntary and that he or she may withdraw from the study at any time, for any reason. All participants will read, sign, and date a consent form before undergoing any study procedures. Consent materials will be presented in participants' primary language. A copy of the signed consent form will be given to the participant.

The consent process will be ongoing. The consent form will be revised when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

17.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique identification number and these numbers rather than names will be used to collect, store, and report participant information. Site personnel will not transmit documents containing personal health identifiers (PHI) to the study Sponsor or their representatives.

18. PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN internet website at http://www.immunetolerance.org.

19. REFERENCES

1. Picardo M, Dell'Anna ML, Ezzedine K, et al. Vitiligo. *Nat Rev Dis Primers.* 2015;1:15011.
2. Linthorst Homan MW, Spuls PI, de Korte J, Bos JD, Sprangers MA, van der Veen JP. The burden of vitiligo: patient characteristics associated with quality of life. *J Am Acad Dermatol.* 2009;61(3):411-420.
3. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol.* 2017;77(4):675-682 e671.
4. McKesey J, Pandya AG. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. *J Am Acad Dermatol.* 2019;81(2):646-648.
5. Rothstein B, Joshipura D, Saraiya A, et al. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib. *J Am Acad Dermatol.* 2017;76(6):1054-1060 e1051.
6. Romarin D. Efficacy and Safety of Ruxolitinib Cream for the Treatment of Vitiligo: Results of a 24-Week Randomized, Double-Blind, Dose-Ranging, Vehicle-Controlled Study. Paper presented at: World Congress of Dermatology2019; Milan, Italy.
7. Incyte Announces Positive Results from a Phase 2 Study of Ruxolitinib Cream in Patients with Vitiligo. 2019; https://investor.incyte.com/news-releases/news-release-details/incyte-announces-positive-results-phase-2-study-ruxolitinib. Accessed July 17, 2019, 2019.
8. Relke N, Gooderham M. The Use of Janus Kinase Inhibitors in Vitiligo: A Review of the Literature. *J Cutan Med Surg.* 2019;23(3):298-306.
9. Joshipura D, Alomran A, Zancanaro P, Rosmarin D. Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib: A 32-week open-label extension study with optional narrow-band ultraviolet B. *J Am Acad Dermatol.* 2018;78(6):1205-1207 e1201.
10. Craiglow BG, King BA. Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy. *JAMA Dermatol.* 2015;151(10):1110-1112.
11. Rosmarin D, Pandya AG, Lebwohl M, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. *Lancet.* 2020;396(10244):110-120.
12. Harris JE. Cellular stress and innate inflammation in organ-specific autoimmunity: lessons learned from vitiligo. *Immunol Rev.* 2016;269(1):11-25.
13. Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-gamma for autoreactive CD8(+) T-cell accumulation in the skin. *J Invest Dermatol.* 2012;132(7):1869-1876.
14. Palermo B, Campanelli R, Garbelli S, et al. Specific cytotoxic T lymphocyte responses against Melan-A/MART1, tyrosinase and gp100 in vitiligo by the use of major histocompatibility complex/peptide tetramers: the role of cellular immunity in the etiopathogenesis of vitiligo. *J Invest Dermatol.* 2001;117(2):326-332.
15. Lang KS, Caroli CC, Muhm A, et al. HLA-A2 restricted, melanocyte-specific CD8(+) T lymphocytes detected in vitiligo patients are related to disease activity and are predominantly directed against MelanA/MART1. *J Invest Dermatol.* 2001;116(6):891-897.

16. Richmond JM, Strassner JP, Zapata L, Jr., et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. *Sci Transl Med.* 2018;10(450).

17. Malik BT, Byrne KT, Vella JL, et al. Resident memory T cells in the skin mediate durable immunity to melanoma. *Sci Immunol.* 2017;2(10).

18. Cheuk S, Schlums H, Gallais Serezal I, et al. CD49a Expression Defines Tissue-Resident CD8(+) T Cells Poised for Cytotoxic Function in Human Skin. *Immunity.* 2017;46(2):287-300.

19. Boniface K, Jacquemin C, Darrigade AS, et al. Vitiligo Skin Is Imprinted with Resident Memory CD8 T Cells Expressing CXCR3. *J Invest Dermatol.* 2018;138(2):355-364.

20. Jiang X, Clark RA, Liu L, Wagers AJ, Fuhlbrigge RC, Kupper TS. Skin infection generates non-migratory memory CD8+ T(RM) cells providing global skin immunity. *Nature.* 2012;483(7388):227-231.

21. Mackay LK, Stock AT, Ma JZ, et al. Long-lived epithelial immunity by tissue-resident memory T (TRM) cells in the absence of persisting local antigen presentation. *Proc Natl Acad Sci U S A.* 2012;109(18):7037-7042.

22. Shin H, Iwasaki A. A vaccine strategy that protects against genital herpes by establishing local memory T cells. *Nature.* 2012;491(7424):463-467.

23. Mackay LK, Rahimpour A, Ma JZ, et al. The developmental pathway for CD103(+)CD8+ tissue-resident memory T cells of skin. *Nat Immunol.* 2013;14(12):1294-1301.

24. Schenkel JM, Fraser KA, Vezys V, Masopust D. Sensing and alarm function of resident memory CD8(+) T cells. *Nat Immunol.* 2013;14(5):509-513.

25. Mackay LK, Wynne-Jones E, Freestone D, et al. T-box Transcription Factors Combine with the Cytokines TGF-beta and IL-15 to Control Tissue-Resident Memory T Cell Fate. *Immunity.* 2015;43(6):1101-1111.

26. Zhang N, Bevan MJ. Transforming growth factor-beta signaling controls the formation and maintenance of gut-resident memory T cells by regulating migration and retention. *Immunity.* 2013;39(4):687-696.

27. Adachi T, Kobayashi T, Sugihara E, et al. Hair follicle-derived IL-7 and IL-15 mediate skin-resident memory T cell homeostasis and lymphoma. *Nat Med.* Vol 212015:1272-1279.

28. Mohammed J, Beura LK, Bobr A, et al. Stromal cells control the epithelial residence of DCs and memory T cells by regulated activation of TGF-beta. *Nat Immunol.* 2016;17(4):414-421.

29. Zhang X, Sun S, Hwang I, Tough DF, Sprent J. Potent and selective stimulation of memory-phenotype CD8+ T cells in vivo by IL-15. *Immunity.* 1998;8(5):591-599.

30. Nelson BH. IL-2, regulatory T cells, and tolerance. *J Immunol.* 2004;172(7):3983-3988.

31. Fehniger TA, Caligiuri MA. Interleukin 15: biology and relevance to human disease. *Blood.* 2001;97(1):14-32.

32. AMG 714 Investigator's Brochure. Amgen Edition 9.0. November 6, 2018.

33. Lebrec H, Horner MJ, Gorski KS, et al. Homeostasis of human NK cells is not IL-15 dependent. *J Immunol.* 2013;191(11):5551-5558.

34. Pan WJ, Li H, Xiao JJ, et al. Modeling the pharmacokinetic-pharmacodynamic relationship of the monoclonal anti-macaque-IL-15 antibody Hu714MuXHu in cynomolgus monkeys. *Pharmacol Res Perspect.* 2015;3(6):e00199.

35. Baslund B, Tvede N, Danneskiold-Samsoe B, et al. Targeting interleukin-15 in patients with rheumatoid arthritis: a proof-of-concept study. *Arthritis Rheum.* 2005;52(9):2686-2692.

36. van Geel N, Lommerts J, Bekkenk M, et al. Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. *J Invest Dermatol.* 2016;136(5):978-984.

37. Lilly E, Lu PD, Borovicka JH, et al. Development and validation of a vitiligo-specific quality-of-life instrument (VitiQoL). *J Am Acad Dermatol.* 2013;69(1):e11-18.

38. Batchelor JM, Tan W, Tour S, Yong A, Montgomery AA, Thomas KS. Validation of the Vitiligo Noticeability Scale: a patient-reported outcome measure of vitiligo treatment success. *Br J Dermatol.* 2016;174(2):386-394.

39. Mohammad TF, Al-Jamal M, Hamzavi IH, et al. The Vitiligo Working Group recommendations for narrowband ultraviolet B light phototherapy treatment of vitiligo. *J Am Acad Dermatol.* 2017;76(5):879-888.

40. Zaid A, Mackay LK, Rahimpour A, et al. Persistence of skin-resident memory T cells within an epidermal niche. *Proc Natl Acad Sci U S A.* 2014;111(14):5307-5312.

41. Carbone FR, Mackay LK, Heath WR, Gebhardt T. Distinct resident and recirculating memory T cell subsets in non-lymphoid tissues. *Curr Opin Immunol.* 2013;25(3):329-333.

42. DeGottardi MQ, Okoye AA, Vaidya M, et al. Effect of Anti-IL-15 Administration on T Cell and NK Cell Homeostasis in Rhesus Macaques. *J Immunol.* 2016;197(4):1183-1198.

43. Mishra A, Sullivan L, Caligiuri MA. Molecular pathways: interleukin-15 signaling in health and in cancer. *Clin Cancer Res.* 2014;20(8):2044-2050.

44. Waldmann TA. The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders. *J Investig Dermatol Symp Proc.* 2013;16(1):S28-30.

45. Jones AM, Griffiths JL, Sanders AJ, et al. The clinical significance and impact of interleukin 15 on keratinocyte cell growth and migration. *Int J Mol Med.* 2016;38(3):679-686.

46. Luo X, Jin R, Wang F, et al. Interleukin-15 inhibits the expression of differentiation markers induced by Ca(2+) in keratinocytes. *Exp Dermatol.* 2016;25(7):544-547.

47. Ruckert R, Asadullah K, Seifert M, et al. Inhibition of keratinocyte apoptosis by IL-15: a new parameter in the pathogenesis of psoriasis? *J Immunol.* 2000;165(4):2240-2250.

48. Strassner JP, Rashighi M, Ahmed Refat M, Richmond JM, Harris JE. Suction blistering the lesional skin of vitiligo patients reveals useful biomarkers of disease activity. *J Am Acad Dermatol.* 2017;76(5):847-855.e845.

49. Rashighi M, Agarwal P, Richmond JM, et al. CXCL10 is critical for the progression and maintenance of depigmentation in a mouse model of vitiligo. *Sci Transl Med.* 2014;6(223):223ra223.

50. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. *The Journal of allergy and clinical immunology.* 2010;125(3):569-574, 574.e561-574.e567.

APPENDIX 1. SCHEDULE OF EVENTS

Phase of Trial	SCRN	Dosing						Post-treatment (FU)[1]					WD[2]	UN[3]
Week		0	2	4	6	8	10	12	18	24	36	48	WD	U
Visit[4]	V-1	V0	V1	V2	V3	V4	V5	V6	V7[5]	V8	V9	V10	WD	U
GENERAL ASSESSMENTS														
Informed consent	X													
Eligibility criteria	X													
Randomization[6]		X												
Medical history & demographics	X													
Vitiligo history	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive physical examination	X							X		X		X	X	
Limited physical examination		X	X	X	X	X	X				X			X
Vital signs	X	X	X	X	X	X	X	X		X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Assignment Survey								X					X	
STUDY DRUG ADMINISTRATION														
Study drug (AMG 714 or placebo)		X	X	X	X	X	X							
PHOTOTHERAPY														
nbUVB phototherapy[7]										X	X	X		

[1] After Week 12, remote follow-up contact will occur at least once between each visit to facilitate participant retention, and to discuss phototherapy in participants receiving this treatment after Week 24.

[2] See Sections 11.2 and 11.4 for additional information related to the early study withdrawal visit.

[3] Some assessments for an unscheduled visit may be omitted at the discretion of the principal investigator if not indicated.

[4] Remote visit allowable if indicated at V1, V2, V4, and V5.

[5] V7 will be conducted as a telephone visit (Section 8.4).

[6] Randomization must occur at least one day prior to V0.

[7] Participants will undergo narrow band ultraviolet B (nbUVB) phototherapy if T-VASI does not improve by ≥ 25% at Week 24 compared to Week 0.

Phase of Trial	SCRN	Dosing						Post-treatment (FU)[1]					WD[2]	UN[3]
Week		0	2	4	6	8	10	12	18	24	36	48	WD	U
Visit[4]	V-1	V0	V1	V2	V3	V4	V5	V6	V7[5]	V8	V9	V10	WD	U
CLINICAL LABORATORY ASSESSMENTS														
Hematology (CBC w/diff and plt)	X	X			X			X		X	X	X	X	X
Chemistry (Cr, T bili, AST, ALT, ALP, albumin)	X	X			X			X		X	X	X	X	X
TSH	X													
HIV	X													
Hepatitis B (core Ab & surface Ag)	X													
Hepatitis C (RNA or antibody)	X													
Quantiferon-TB Gold/Quantiferon-TB Gold Plus[8]	X													
Serum pregnancy	X													
STAT urine pregnancy		X	X	X	X	X	X	X		X	X	X	X	
VITILIGO ASSESSMENTS														
F-VASI	X	X			X			X		X	X	X	X	X
T-VASI	X	X			X			X		X	X	X	X	X
VES		X			X			X		X	X	X	X	
VitiQoL		X			X			X		X	X	X	X	
VNS					X			X		X	X	X	X	
sIGA		X						X		X	X	X	X	
Digital skin photography		X						X		X		X	X	

[8] PPD skin test may be substituted.

Phase of Trial	SCRN	Dosing						Post-treatment (FU)[1]					WD[2]	UN[3]
Week		0	2	4	6	8	10	12	18	24	36	48	WD	U
Visit[4]	V-1	V0	V1	V2	V3	V4	V5	V6	V7[5]	V8	V9	V10	WD	U
MECHANISTIC ASSESSMENTS														
Skin biopsy – lesional[9]		X						X		X		X	X	
Skin biopsy – non-lesional		X						X						
PBMCs		X			X			X		X	X	X	X	
Serum		X			X			X		X	X	X	X	
Whole blood RNA		X			X			X		X	X	X	X	
Whole blood DNA		X			X			X		X	X	X	X	

[9] If the lesion has resolved, the punch biopsy will be taken from the previously lesional area.

APPENDIX 2. VASI

Vitiligo Area Scoring Index (VASI)

The vitiligo area scoring index (VASI) is a quantitative clinical tool to assess the area affected by vitiligo. The body is divided into 6 separate regions:

- Head and neck (includes face)
- Upper extremities (excluding hands). The axillae are considered part of the upper extremities.
- Hands
- Torso (excluding axillae). The genitalia are not included in the VASI assessment.
- Lower extremities (excluding feet). The buttocks and inguinal area are considered part of the lower extremities.
- Feet

For each body region, the VASI is determined by the product of the area of vitiligo in hand units and the extent of depigmented skin within each hand unit-measured patch (estimated to the nearest of the following percentages: 0%, 10%, 25%, 50%, 75%, 90% or 100%).

Body Surface Area (BSA)

The percentage of the body surface area (BSA) affected with vitiligo can be estimated by the hand unit or thumb unit to the tenth decimal (0.1%). A hand unit encompasses the palm plus five digits, with fingers and thumb apposed. The hand unit is approximately 1% of the total BSA and the thumb is approximately 0.1% of the total BSA. The hand unit is based on each individual participant's own hand size.

Calculation of the T-VASI

The total body VASI is then calculated using a formula that includes a contribution from all body sites, with a possible range of 0-100%.

$$\textbf{VASI} = \sum_{\text{All body sites}} [\text{Hand Units}] \times [\text{Residual Depigmentation}]$$

The evaluable area for the T-VASI assessment is all of the following:

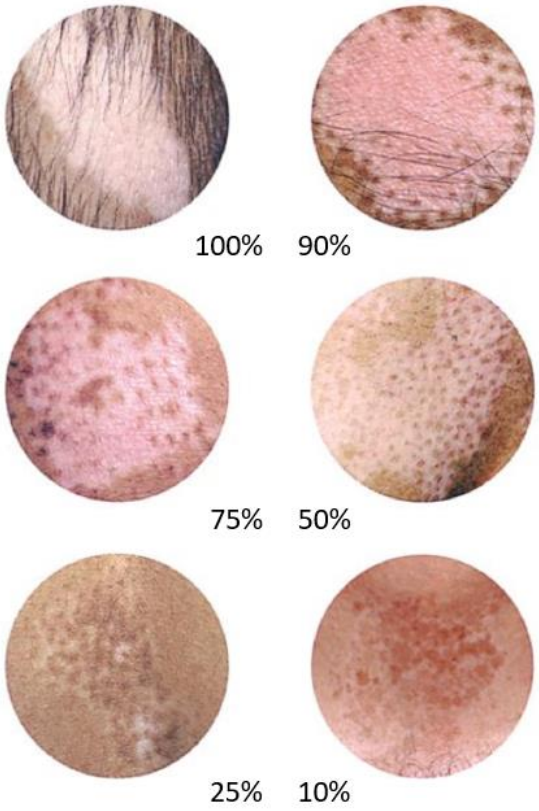
1. The total body including the face and neck, and excluding the genitalia.
2. Vitiligo lesions on fingers including and distal to the proximal interphalangeal joints, toes, palms, and soles will not be included in the T-VASI assessment.

Calculation of the F-VASI

The F-VASI will be calculated separately. The F-VASI will be calculated in the same fashion as the T-VASI, except that the evaluable area is limited to the face only (see above). The %BSA will be measured to the tenth decimal (0.1%). The evaluable area is all of the following:

1. From the top of the forehead at the hairline down to the jawline, and from the right to the left tragus anteriorly, excluding mucosal lips. For participants who have a receding hairline, the original hairline should be used as the border for the face.

Illustrations of Percent Depigmentation for the Vitiligo Area Scoring Index for the F-VASI and the T-VASI



1.0 (100%)	Completely depigmented skin
0.90 (90%)	Specks of pigmented skin present
0.75 (75%)	Depigmented area exceeds the pigmented area
0.50 (50%)	Pigmented and depigmented areas are equal
0.25 (25%)	Pigmented area exceeds depigmented area
0.10 (10%)	Only specks of depigmented skin present
0.00 (0%)	No depigmented skin present

VASI Calculation Methods

F-VASI

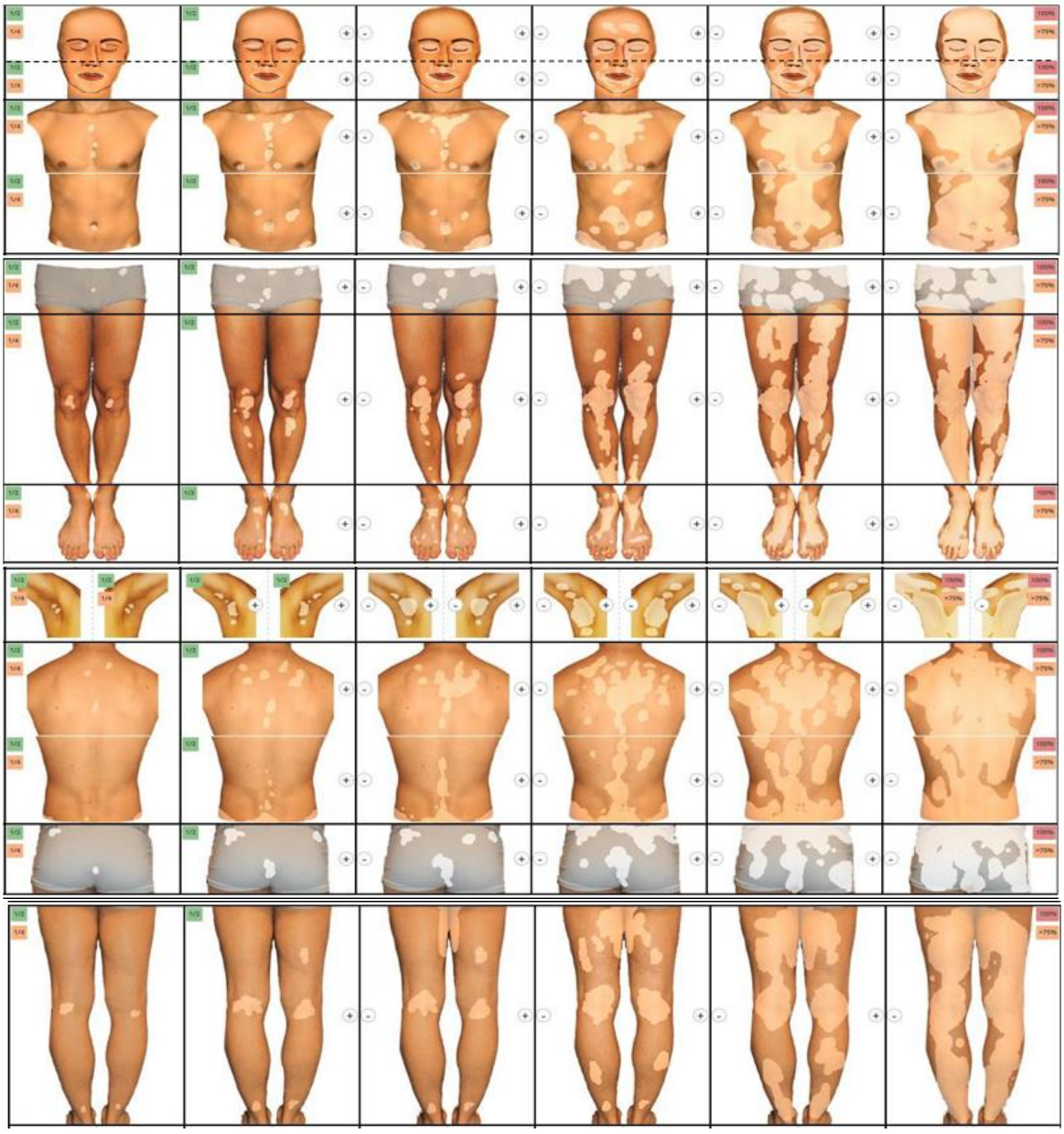
Maximum BSA for Face	%BSA (Hand/Thumb Units) rounded to the nearest tenth	Residual Depigmentation % (0.0 – 1.0)	F-VASI Score (Hand/Thumb Units) x Residual Depigmentation
3.5%			

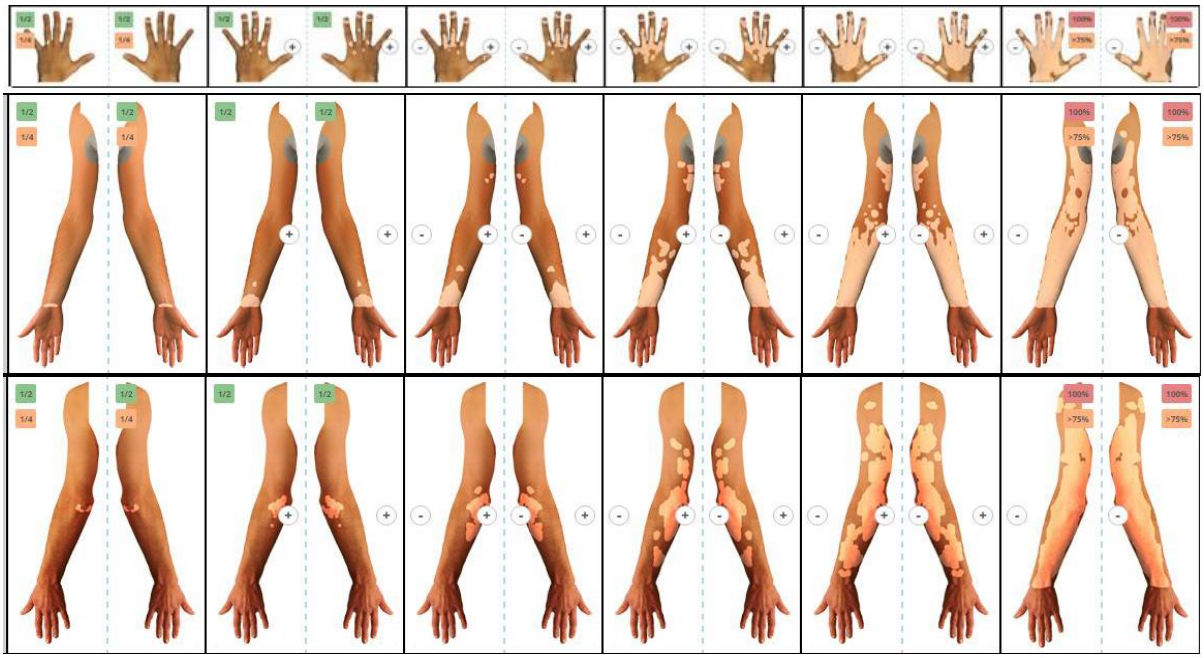
T-VASI

Total Body	Maximum BSA per Body Area	%BSA (Hand/Thumb Units) rounded to the nearest tenth	Residual Depigmentation % (0.0 – 1.0)	% Area Involved (Hand/Thumb Units) x Residual Depigmentation
Head and neck (includes face)	9%			
Upper extremities, including axillae (excluding hands)	14%			
Hands	4%			
Torso (excluding axillae and genitalia)	32%			
Lower extremities, including buttocks and inguinal area (excluding feet)	36%			
Feet	4%			
T-VASI = $\sum$ [Hand/Thumb Units] **x** [Residual Depigmentation] *All body regions*				

APPENDIX 3. VES

The Vitiligo Extent Score (VES) is determined *during* the patient encounter using the calculator at www.vitiligo-calculator.com as follows: For each area, select 1 picture which best represents the extent of the vitiligo lesions. There are additional options for quantifying the extent, e.g. if the extent is half (½) or a quarter (¼) of the involved area in the picture or slightly less (-) or slightly more (+) than the involved area in the picture. The ">75%" option can be selected if the involved area is more than shown in the last picture, but less than 100% (i.e. complete depigmentation). The calculator will use the selected images to calculate the percentage of the body surface area (BSA) involved or grade of extent per region (Grade 0 to 6).





APPENDIX 4. VITIQOL

Vitiligo-specific Health-related Quality-of-life Instrument (VitiQoL) is a validated instrument that asks participants to rate various aspects of their vitiligo during the past month. Assessment will be conducted at the baseline visit, as well as visits during and after treatment per Appendix 1. The response to each question will be scored on a 0 (not at all) to 6 (all of the time) scale.

During the past month,	Not at all ↓			•			All of the time ↓
1. Have you been bothered by the appearance of your skin condition?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Have you felt frustrated about your skin condition?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Has your skin condition made it hard to show affection?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Has your skin condition affected your daily activities?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. When you were talking to someone, have you worried about what they may be thinking of you?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. Have you been afraid that people will find fault with you?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. Have you felt embarrassed or self-conscious because of your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. Has your skin condition influenced the clothes you wear?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. Has your skin condition affected your social or leisure activities?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. Has your skin condition affected your emotional well-being?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. Has your skin condition affected your overall physical health?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. Has your skin condition affected your grooming practices (i.e. hairstyle, use of cosmetics)?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. Has your skin condition affected your sun protection efforts during recreation (i.e. limiting exposure time during peak sun hours, seeking shade, wearing hat, long sleeves or pants)?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Has your skin condition affected your chances for making new friends?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. Have you worried about progression or spread of disease to new areas of the body?	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Please check how severe you currently feel your skin condition is:	No skin involvement ↓			•			Most severe case ↓
16. Severity of skin condition.	☐0	☐1	☐2	☐3	☐4	☐5	☐6

APPENDIX 5. VNS

Vitiligo Noticeability Scale (VNS) is a validated patient-reported outcome measure of vitiligo treatment.[38] Participants will be presented with one pre-treatment photograph of their face at different visits (see Schedule of Events, Appendix 1) and asked to answer the question below. The same pre-treatment photograph must be used at each visit.

Question	Response option (Score)	Success criteria
Compared with before treatment, how noticeable is the vitiligo now?	More noticeable (1) As noticeable (2) Slightly less noticeable (3) A lot less noticeable (4) No longer noticeable (5)	Score of 4 or 5

APPENDIX 6. STUDY TREATMENT ASSIGNMENT SURVEY

The following survey will be administered to assess the extent of blinding among study investigators, and is to be completed by the investigator as outlined in the Schedule of Events (Appendix 1).

Question	Answer
1. Did this participant receive clinical benefit from the experimental drug treatment he/she received during this research study?	☐ Yes ☐ No
2. What treatment do you think the participant likely received during this study?	☐ AMG 714 ☐ Placebo ☐ Can't tell

The following survey will be administered to assess the extent of blinding among study participants, and is to be completed by the participant as outlined in the Schedule of Events (Appendix 1).

Question	Answer
1. Did you receive benefit from the experimental drug treatment you received during this research study?	☐ Yes ☐ No
2. What treatment do you think you likely received during this study?	☐ AMG 714 ☐ Placebo ☐ Can't tell

APPENDIX 7. STATIC INVESTIGATOR GLOBAL ASSESSMENT (sIGA)

Score	Short descriptor	Detailed descriptor
0	Clear	▪ No loss of pigmentation with natural light or with Woods lamp examination
1	Almost clear	▪ Faint, barely detectable loss of pigmentation mainly located on dorsal hands, feet, bony prominences, and/or limited areas ▪ Approximately 90% pigmentation within lesions ▪ No or rare signs of Koebner phenomenon, confetti-like or trichrome lesions may be present
2	Mild vitiligo	▪ Mild loss of pigmentation mainly located on dorsal hands, feet, bony prominences, and/or limited areas ▪ Approximately 75% pigmentation within lesions ▪ Few signs of Koebner phenomenon, confetti-like or trichrome lesions may be present
3	Moderate vitiligo	▪ Moderate loss of pigmentation affecting several areas of the body with large patches ▪ Approximately 50% pigmentation within lesions ▪ Moderate number of signs of Koebner phenomenon, confetti-like or trichrome lesions may be present
4	Severe vitiligo	▪ Extensive loss of pigmentation affecting most areas of the body ▪ Approximately 25% or less pigmentation within lesions ▪ Many signs of Koebner phenomenon, confetti-like or trichrome lesions affecting several areas of the body may be present