CLINICAL TRIAL PROTOCOL

A Phase 2, Double-blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of MRG-201 Following Intradermal Injection in Subjects with a History of Keloids

Protocol Number: MRG201-30-201

(NCT03601052)

Version 1.0, Final

16 March 2018

miRagen Therapeutics, Inc.
6200 Lookout Road
Boulder, CO 80301

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and clinical research guidelines established by the United States Code of Federal Regulations (21 CFR Parts 50, 56, and 312) and the International Conference on Harmonization (ICH) E6(R1) Guideline for Good Clinical Practice (GCP).

PROTOCOL APPROVAL PAGE

By signing below, I affirm that this protocol and the attachments are approved by the clinical trial Sponsor, miRagen Therapeutics, Inc.

Protocol Approved by:

[redacted]

Date

miRagen Therapeutics, Inc.

[redacted]

Date

miRagen Therapeutics, Inc.

[redacted]

Date

miRagen Therapeutics, Inc.

[redacted]

Date

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor, and agree to the following:

- To conduct this trial in accordance with the design and provisions of this protocol;
- To await Institutional Review Board (IRB) approval for the protocol and informed consent document before initiating enrollment into the study;
- To ensure that the requirements for obtaining informed consent are met and to obtain informed consent from subjects before their enrollment into the study;
- To provide sufficient and accurate financial disclosure and to update this information if any relevant changes occur during the investigation and for one year following the completion of the study;
- To collect and record data as required by this protocol into the case report form;
- To maintain the confidentiality of all information received or developed in connection with this protocol;
- To conduct this trial in accordance with the ICH GCP, the Declaration of Helsinki, and applicable regulatory requirements;
- To permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents;
- To prepare annual, final and safety reports as required by this protocol and by regulation under 21 CFR 312.64;
- To maintain study documentation for the period of time required as stipulated in the protocol;
- To report all adverse events to miRagen Therapeutics, Inc. within the timeframe specified;
- To report all serious adverse events within 24 hours after becoming aware of the event as directed in the protocol;
- To comply with the provisions of the Clinical Trial Agreement to which I will be a signatory, including but not limited to, the disclosure or publication of data collected during this trial, as stipulated in that agreement.

Signature of Investigator	Date
Investigator Name (print or type)	Site Number

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the curve extrapolated to infinity
°C	Degree(s) Celsius
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
Cl	Clearance
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ECM	Extracellular matrix
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
mRNA	Messenger ribonucleic acid
mVSS	Modified Vancouver Scar Scale
NCI	National Cancer Institute
PI	Principal Investigator
PK	Pharmacokinetic
POSAS	Patient and Observer Scar Assessment Scale

PP	Per Protocol
PT	Prothrombin time
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
$t_{1/2}$	Half-life
TGF-β	Transforming growth factor beta
TEAE	Treatment-emergent adverse event
Th1	T helper 1
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UTR	Untranslated region
V_z/F	Volume of distribution of the terminal phase
WHO-DD	World Health Organization Drug Dictionary

PROTOCOL SYNOPSIS

Sponsor:	miRagen Therapeutics, Inc.
Protocol No.:	MRG201-30-201
Title:	A Phase 2, Double-blind, Placebo-Controlled Study to Investigate the Efficacy, Safety and Tolerability of MRG-201 Following Intradermal Injection in Subjects with a History of Keloids
Phase:	Phase 2
Investigational Product and Comparators:	Investigational Product: MRG-201 The sponsor will provide MRG-201 (66 mg/mL active moiety) in sterile, single-use glass vials with a rubber closure and an aluminum flip-off overseal, each containing 0.3 mL of a clear to slightly yellow liquid formulation in isosmotic phosphate buffer, pH 7.4. The study drug is stored at -20 ± 5°C. MRG-201 will be administered by intradermal injections at the site of a sutured excisional wound, as instructed in study materials. The study sites will provide placebo comparator (0.9% sodium chloride injection, United States Pharmacopeia [USP]) for intradermal injection at the site of a second sutured excisional wound.
Population:	Males/females, ≥ 18 years of age, with a history of a significant number of keloids (e.g., ≥ 10 individual keloids) or large keloids (e.g., ≥ 4 cm), where new keloids are likely to form with a punch biopsy
Number of Participants Planned:	Up to 6 cohorts of 12-16 subjects each (a total of 96 subjects) may be enrolled in this study to evaluate different doses and regimens of MRG-201 given intradermally. Approximately 12 subjects are anticipated for enrollment in the first cohort. Subjects who drop out for reasons other than safety or study treatment tolerability may be replaced with sponsor approval (up to 16 total including replacements).
Duration of Participation:	Up to 393 days, including an up to 28-day screening period, a 12-day to 26-day active treatment period (first treatment cycle of study dosing), and a 52-week (± 7 days) follow-up period after

	Day 1 (i.e. the initiation of the first treatment cycle of study dosing).
Anticipated Study Duration:	18 months
Clinical Sites:	Approximately 4 centers in the United States (US)

Objectives:

Safety Objective:

Investigate the safety and tolerability of multiple intradermal administrations of MRG-201 in subjects with a history of keloids.

Pharmacodynamic Objective:

Investigate the activity of MRG-201 in prevention or reduction of keloid formation, in subjects with a history of keloids.

Other Objectives:

- Evaluate additional pharmacodynamic endpoints of MRG-201 in subjects with a history of keloids.
- Evaluate the effect of MRG-201 on skin-specific Patient Reported Outcomes.
- Characterize the pharmacokinetics of MRG-201 in subjects with a history of keloids.

Endpoints:

Safety and Tolerability:

- The safety and tolerability of MRG-201 will be assessed by determining the incidence and severity of clinically significant adverse events (AEs), (including Grade 3 and 4 AEs, treatment-related AEs, serious adverse events [SAEs], and AEs requiring discontinuation of MRG-201), and physical examination findings, changes in vital signs, electrocardiograms (ECGs), and laboratory parameters.
- AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Pharmacodynamic:

- Proportion of confirmed keloid formation across subjects for treated vs. untreated lesions at 24 weeks.
- Proportion of subjects with improvement, which is defined as no confirmed keloid formation in the treated lesion vs. confirmed keloid formation in the untreated lesions.
- Proportion of subjects forming confirmed keloids with MRG-201 treatment vs. placebo treatment at 12 weeks, 36 weeks, 52 weeks, and at the time of study withdrawal (if

subjects do not complete the study).

Other Pharmacodynamic:

- Proportion of subjects forming confirmed keloids regardless of treatment application.
- Time to keloid formation.
- Volume of keloid at 24 weeks, 52 weeks and at time of triamcinolone injection (if applicable).

Exploratory:

- Modified Vancouver Scar Scale (mVSS; Fearmonti et al 2010) score at visits occurring every 4 weeks from Day 29 to Day 365 after excisional wound creation.
- Patient and Observer Scar Assessment Scale (POSAS) scores at visits occurring every 4 weeks from Day 29 to Day 365 after excisional wound creation.
- Keloid volume and keloid severity (per mVSS and POSAS) at visits occurring every 4 weeks following a second cycle of dosing with MRG-201 or placebo in subjects exhibiting evidence that a keloid may be forming at one or both biopsy sites within 12 weeks after initiation of the first cycle of study dosing.

Pharmacokinetic:

- Plasma concentration of MRG-201 will be assessed at multiple time points on Day 1 and Day 12 (or Day 26 for cohorts dosing for 4 weeks), and at single time points on Day 2 and Day 13 (or Day 27 for cohorts dosing for 4 weeks). Voided urine samples for PK analyses will also be collected on Day 1 and 12 (or day 26 for cohorts dosing for 4 weeks) predose and 3 hours postdose, and Day 2 and Day 13 (or day 27 for cohorts dosing for 4 weeks).

Study Design:

This is a double-blind, placebo-controlled, multi-center, exploratory safety and efficacy study in subjects with a high frequency of keloid formation (i.e., history of ≥ 10 keloids or history of large keloids, ≥ 4 cm), with MRG-201 and placebo administered by intradermal injection around the site of two separate punch biopsies.

A minimum of 12 subjects are anticipated for enrollment in the first cohort of the study to attain at least 10 subjects who complete study participation through 24 weeks after excisional wound creation. Subjects who drop out for reasons other than safety or study treatment tolerability may be replaced with sponsor approval (up to 16 total including replacements). The sponsor may enroll up to 5 additional cohorts of 12 to 16 subjects each (up to 80 total additional subjects) to assess lower doses and/or additional regimens.

Subjects will receive a maximum of twelve doses of 5.3 mg MRG-201 throughout the duration of the study.

Methodology:

Subjects in the initial cohort will undergo a screening period lasting up to 28 days, followed by a double-blind, 12-day active treatment period (first cycle of study dosing) conducted in the outpatient setting, a possible second 12-day cycle of study dosing, and a follow-up period of up to 52 weeks (± 7 days) after initiation of the first cycle of study dosing.

On Day 1 of the study, subjects will be seen at the clinic in the morning to confirm study eligibility and for their baseline assessments, punch biopsy procedures, baseline photography of the biopsy sites, and administration of study treatments. Subjects will undergo two 6-mm punch biopsies bilaterally in the upper back/shoulder region in areas that can be covered with clothing and are likely to form keloids. The locations for the biopsies must be at least 10 cm from each other and far enough away from existing keloids that new keloid formation may be assessed. The punch biopsy excisional wound sites will be closed with sutures. One wound site will be treated with MRG-201 and the other wound site will be treated with placebo. The treatment for each wound site will be randomized (left versus right) and blinded but consistent throughout dosing. MRG-201 and placebo will each be administered as four 20-µL injections around one wound site, with subjects receiving approximately 5.3 mg of the MRG-201 active moiety on each dosing day (approximately 1.3 mg per 20-µL injection). After all Day 1 assessments and procedures are complete, subjects will be discharged to home.

Subjects will return to the clinic on Days 3, 5, 8, 10, and 12 to receive repeat injections with the same blinded study treatment that was administered at each wound site on Day 1. Subjects will return to the clinic on Day 19 for additional assessments and safety monitoring, and the Principal Investigator (PI) will determine whether any tolerability concerns are present and warrant consultation and safety data review with the sponsor's Medical Monitor. If at any point clinically significant safety or tolerability issues are observed by the investigator and are thought to be possibly related or related to MRG-201, the subject will not receive further administration of MRG-201 pending follow-up with the Medical Monitor. In this event, the investigator must notify the sponsor's Medical Monitor by email or phone within 24 hours, and a meeting with the sponsor Medical Monitor may be convened.

On Day 8, Day 12, Day 19, Day 29 (4 weeks ± 3 days after completion of the punch biopsies) and then every 4 weeks for 1 year (Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, each ± 7 days), excisional wound sites will be assessed for keloid formation, photographic evaluations, and other study assessments.

For subjects receiving 6 doses of MRG-201 in the initial treatment cycle, if there is evidence that a keloid may be forming (defined as meeting a score of 1 or 2 on the mVSS and having an appearance consistent with an area likely to form a keloid according to investigator judgement) within 12 weeks after initiation of the first cycle of study dosing, and following the initial 29-day treatment and assessment period, subjects will undergo a second cycle of study dosing in one or both biopsy sites (depending on keloid formation). Subjects will be treated with MRG-201 or

placebo according to the original treatment assignments (blinding will be maintained during the second treatment regimen). The treatment regimen for the second cycle of study dosing will be the same as for the first cycle, i.e., an initial dose followed by additional doses 2, 4, 7, 9, and 11 days after the initial dose, with follow-up visits at Days 19 and 29 after the re-start of dosing. After these follow-up visits, the subject will resume the original study schedule, with visits occurring every 28 days until the Day 365 visit. If the wound site scar(s) progress to an mVSS score of 3 to 5 (with a score of at least 1 in the height sub-domain) after the 12-week observation period and/or to an mVSS score of ≥ 6 (with a score of at least 1 in the height sub-domain) at any time, the scar(s) will be considered confirmed keloid(s). At the time of keloid confirmation, the investigator, in consultation with the subject, may elect to attempt local treatment of the keloid with triamcinolone as a standard of care therapy after consultation with the sponsor.

Additional cohorts may be enrolled to test lower doses or an extended dosing schedule. Study procedures for the extended dosing cohorts will be identical to the cohort described above, with the following exceptions: 1) subjects in these cohorts may receive a total of 12 intradermal doses of MRG-201 and placebo on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26; 2) subjects will not undergo a second cycle of treatment if the 4-week dosing schedule is used; and 3) pharmacokinetic assessments will be performed on study Day 1, 2, 26 and 27 if the 4-week dosing schedule is followed.

Pharmacodynamic Endpoint Assessment:

Subjects will be evaluated for the incidence, timing and physical characteristics of keloid formation. The punch biopsy wound sites will be evaluated for keloid formation, photographic assessment, and clinical response during the active treatment and follow-up periods of the study, which will last 52 weeks (± 7 days) after initiation of the first cycle of study dosing. Scars that form at one or both punch biopsies wound sites will be considered unconfirmed keloid(s) if they exhibit a score of 3 to 5 on the mVSS, with a score of at least 1 in the height sub-domain. Unconfirmed keloid(s) with a score of 3 to 5 on the mVSS will be re-evaluated at the subsequent monthly visits for up to 12 weeks. Keloid(s) that persist after this 12-week observation period and/or progress to an mVSS score of ≥ 6 (with a score of at least 1 in the height sub-domain) at any time will be considered confirmed keloid(s). At the time of keloid confirmation, the investigator, in consultation with the subject, may elect to attempt local treatment of the keloid with triamcinolone as a standard of care therapy after consultation with the sponsor.

Biopsy samples will be saved for future protein and/or nucleic acid analysis to assess MRG-201 effects in subjects who form keloids.

Safety and PK Assessments:

Subjects in all cohorts will be continuously monitored for safety through evaluations of AEs, vital signs, physical examination findings, clinical laboratory measurements, and ECG monitoring.

Samples will be collected for plasma pharmacokinetic(s) on Days 1, 2, 12, and 13 (or study Days 1, 2, 26, and 27 for subjects receiving an initial 26-day treatment cycle).

Main Criteria for Inclusion:

1. Must provide written informed consent (signed and dated), and any authorizations required by law, and be able to comply with all study requirements.
2. Males or females, ≥ 18 years of age at the time of informed consent.
3. Females must have a negative serum pregnancy test at screening and a negative urine pregnancy test on their first dosing day.
4. Females must not be or planning to be pregnant or lactating during the study. Females must be post-menopausal (confirmed by follicle-stimulating hormone [FSH] test for subjects whose last menstrual cycle was within the last 2 years before screening), abstinent, in a monogamous same sex relationship, surgically sterile or, if of child bearing potential, must use two acceptable methods of contraception with at least one being a barrier method throughout their study participation and for at least 6 months following the last dose of study treatment. Acceptable methods of contraception include oral, injectable or implantable hormonal contraception, intrauterine device, or medically-confirmed vasectomized partner.
5. Males must be surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, must be using two acceptable methods of contraception with at least one being a barrier method for at least 6 months following the last dose of study treatment. Contraception for male subjects could include a condom and a highly effective second method during and for at least 6 months after the last dose of study treatment.
6. History of a high frequency of keloid formation (history of ≥ 10 keloids), or a history of large keloids (≥ 4 cm) and Investigator feels that the subject is likely to form keloids in the upper back/shoulder area after punch biopsy.
7. Must have bilateral 2 cm × 2 cm areas, where skin punch biopsy may be performed in the upper back/shoulder region and can be covered by clothing, that are free of keloids, acne, striae or other skin pathologies or complications (e.g., tattoos, excessive hair) that may obstruct the ability to evaluate the biopsy sites.
8. Subject is currently clinically stable and is likely to remain clinically stable for a minimum of 14 months from screening.
9. Subject is not anticipated to require systemic corticosteroids during participation in the study.
10. Must be able to communicate effectively with study personnel.

Main Criteria for Exclusion:

1. Recent history of alcoholism (within the past 1 year).
2. History of drug abuse or use of illicit drugs (such as cocaine, methamphetamines, or heroin) within 1 year prior to screening. Subjects must also agree to refrain from illegal drug use during the study.
3. Systemic use of steroids within 4 weeks of Day 1, or local use of steroids within 1 week of Day 1.
4. An active or uncontrolled infection at screening or Day 1.
5. Positive at the time of screening for human immunodeficiency virus (HIV), Hepatitis B (surface antigen), or Hepatitis C.
6. Liver dysfunction, as defined by alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or alkaline phosphatase > 1.5 × upper limit of normal (ULN) at screening or Day 1.
7. Renal dysfunction defined as serum creatinine > 2 mg/dL at screening or Day 1.
8. Clinically significant anemia, neutropenia, or thrombocytopenia at screening or Day 1.
9. History of bleeding diathesis or coagulopathy.
10. Genetic disorders that predispose to keloids. These include, among others, Ehlers-Danlos syndrome, Ullrich congenital muscular dystrophy, and Rubenstein-Taybi syndrome.
11. Prior malignancies within the past 3 years (allowing squamous cell and basal cell carcinomas with free margins at excision, or other malignancies considered cured by surgical resection).
12. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec or > 480 msec if concomitant bundle branch block, at screening or Day 1.
13. Use of an investigational small molecule drug during the 30 days prior to screening or use of an investigational oligonucleotide or biologic drug during the prior 90 days.
14. History of allergy or severe adverse reaction to an oligonucleotide.
15. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
16. Clinically significant abnormalities in medical history, physical examination, or laboratory values that, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the study.

Statistical Methods: Safety Endpoints:

- Descriptive analysis of safety endpoints will be listed per patient for each assessment, and descriptive statistics may

	be tabulated for select criteria. Pharmacodynamic endpoints: • Proportion of keloid formation across subjects for treated vs. untreated lesions. Other pharmacodynamic endpoints: • Proportion of subjects forming keloids. • Intra-patient and aggregated time from initial treatment on Day 1 to unconfirmed and confirmed keloid formation subjects in treated vs. untreated lesions. • Intra-patient and aggregated keloid volume between treated and untreated lesions at 6 months, 12 months, and at the time of triamcinolone intervention (if applicable) for subjects in treated vs. untreated lesions. Exploratory endpoints: • Difference in mVSS and POSAS scores within subjects and across subjects for treated vs. untreated lesions. Pharmacokinetic Endpoints: • PK parameters (C_{max}, T_{max}, Terminal half-life (t1/2), volume of distribution at steady state (Vss), clearance (Cl), $AUC_{0-\infty}$) will be derived from plasma concentrations of MRG-106 using the actual sampling times. Concentration data and all PK parameters will be listed per patient and summarized descriptively per dose. Details of any statistical testing and data summaries will be described in the Statistical Analysis Plan, which will be finalized prior to the database lock and the clinical study report.
Sample Size Justification:	Approximately 12 subjects are anticipated for enrollment in the first cohort to attain approximately 10 subjects who complete study participation through at least 24 weeks. A sample size of 10 subjects on active treatment is considered to be adequate for analysis of safety in this early Phase 2 study. Additional subjects may be enrolled, up to a total of 16, if fewer than 10 subjects complete study participation through 24 weeks for reasons other than the safety or tolerability of study treatment, or if dosing is not completed per protocol for an individual subject for reasons other than the safety or tolerability of study treatment.

	The sponsor may enroll up to 5 additional cohorts of 12 to 16 subjects each (up to 80 total additional subjects) to assess lower doses or alternative regimens. As with the first cohort, additional subjects may be enrolled in the additional cohorts, up to a total of 16 each, if fewer than 10 subjects in a given cohort complete the study through 24 weeks for reasons other than the safety or tolerability of study treatment, or if dosing is not completed per protocol for an individual subject for reasons other than the safety or tolerability of study treatment.
Planned Interim Analysis:	Aggregated blinded interim analyses will be completed when at least 50% of the study subjects reach 12 weeks, 24 weeks, 36 weeks and 52 weeks after study Day 1.
Trial-specific Committees:	No independent safety or data review committee will be used. The Sponsor and investigator will oversee subject safety based on results of the safety and local tolerability assessments.
Protocol Version and Date:	Version 1.0, Final, 16 March 2018

1 KEY STUDY CONTACTS

A contact information list for the Sponsor, Contract Research Organization (CRO), and selected service providers will be provided to each site. General advice on protocol procedures should be obtained through the monitor assigned to each trial site. Information on service providers is given in the study reference manual provided to each site.

The following table lists contact information for investigator reports of serious adverse events (SAEs) and pregnancies occurring in study participants, as well as responsible personnel representing the Sponsor and the CRO.

Table 1: Key Study Contacts

Role	Name and Affiliation	Phone	Email
Sponsor Study Lead	[redacted] miRagen Therapeutics, Inc.	[redacted]	[redacted]
Serious Adverse Event and Pregnancy Reporting	[redacted]	[redacted]	[redacted]
Responsible Medical Officer or Medical Lead	[redacted] miRagen Therapeutics, Inc.	[redacted]	[redacted]

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Keloids

Keloids are abnormal wound responses characterized by local fibroblast proliferation and overproduction of collagen in predisposed individuals, and represent an excessive connective tissue response to dermal trauma, inflammation, surgery, or burns (English et al 1999; Nemeth 1993; Teofoli et al. 1999). Fibroblasts and myofibroblasts are believed to be responsible for the deposition of dense extracellular matrix consisting of collagen and glycosaminoglycans. Attempts to clinically differentiate keloids from hypertrophic scars have proved to be difficult in the early phases of formation. Both scar types demonstrate overproduction of multiple fibroblast proteins, including fibronectin, suggesting either pathological persistence of wound healing signals or a failure of the appropriate downregulation of wound-healing cells (Sephel et al. 2001). However, keloids seem to be a more sustained and aggressive fibrotic disorder than hypertrophic scars (Brown et al 2009). Evidence to date suggests a more prolonged inflammatory period, with immune cell infiltrate present in the scar tissue of keloids, which may contribute to increased fibroblast activity and more sustained extracellular matrix (ECM) deposition (Brown et al 2009). As a result, the keloid scar tissue by definition extends beyond the borders of the original wound into the normal skin and is frequently pruritic and painful. Unlike hypertrophic scars, keloids do not usually regress spontaneously and tend to recur after excision.

2.1.2 Human MicroRNA miR-29

2.1.2.1 Role of miR-29 in Tissue Homeostasis

miRNAs are small, non-coding RNAs of approximately 22-nucleotides in length that act as negative regulators of gene expression. miRNAs interact through homologous base pairing with the 3' untranslated regions (UTR) of specific mRNA targets to inhibit translation or promote mRNA degradation (Bartel 2009). The human genome is predicted to encode more than 2000 miRNAs, which as a class are estimated to regulate as many as 60% of mRNA transcripts (Friedman et al. 2009). To date, the functions of only a handful of miRNAs have been characterized, but their powerful effects on cellular phenotypes, impact on a substantial fraction of the genome, and evolutionary conservation point to miRNAs as key regulators of physiological processes.

The miR-29 family contains four miR-29 genes, located in two bi-cistronic clusters in the genome. miR-29a and miR-29b-1 are one cluster and miR-29c and miR-29b-2 make up the other. miR-29b-1 and miR-29b-2 have identical mature miRNA sequences. Collectively, these four genes result in three mature miRNAs, miR-29a, miR-29b, and miR-29c (Figure 1), which are 100% conserved from human to non-human primate to laboratory animals, nearly 100% conserved across other mammals, and have a high degree of homology to other vertebrates such as frog and chicken (http://people.csail.mit.edu/akiezun/microRNAviewer/all_mir-29.html). The miR-29 family members share a common seed region sequence and are predicted to target largely overlapping sets of genes. The miR-29 family is expressed in fibroblasts and other cell types in humans (Liang et al. 2007) and mice (Thomson et al. 2004; van Rooij et al. 2008).

Figure 1 : Sequence of Mature Human miR-29 Family MicroRNAs

miR-29a	5'-UAGCACCAUCUGAAAUCGGUUA -3'
miR-29b	5'-UAGCACCAUUUGAAAUCAGUGUU -3'
miR-29c	5'- UAGCACCAUUUGAAAUCGGUUA -3'

The seed region (nucleotides 2-8) is underlined in each sequence.

Predicted targets for miR-29 suggest important roles for this microRNA in connective tissue maintenance and repair, hematological function and cancer, and in the cardiovascular and nervous systems (Liston et al. 2012). The regulation of extracellular matrix by the miR-29 family is a dramatic example of a single microRNA family regulating a large set of functionally related genes. miR-29 family members target key proteins involved in the physiological or pathological formation of extracellular matrix including collagen genes, lamininγ1, fibrillin 1, elastin, matrix metalloproteinase 2, and integrin β1 (Li et al. 2009; Liu et al. 2010; Sengupta et al. 2008; van Rooij et al. 2008). The ECM is a highly dynamic structure, undergoing continuous remodeling, including the deposition, degradation, and modification of its components. The capacity of miR-29 to modulate many distinct components of the extracellular matrix indicates a role for this microRNA in ECM homeostasis in a variety of tissue contexts, including skin (Cheng et al. 2013; Maurer et al. 2010; Zhang et al. 2016), bone (Li et al. 2009), eye (Villarreal et al. 2011), heart (Boon et al. 2011; van Rooij et al. 2008), vasculature and circulation (Fort et al. 2010; Ott et al. 2011), liver (Roderburg et al. 2011), lung (Montgomery et al. 2014), and kidney (Liu et al. 2010; Qin et al. 2011). Production of extracellular matrix is also important for the integrity and structural support of the aortic wall, and dysregulation of miR-29 has been linked to aortic aneurysm disease (Boon et al. 2011; Maegdefessel et al. 2012).

The miR-29 family has multiple functions in the hematopoietic system, including both adaptive and innate immunity. miR-29 maintains hematopoietic stem cell renewal through regulation of DNMT3a (Hu et al. 2015). miR-29 supports a critical function in T cell production in a T cell-extrinsic manner, by preventing inappropriate thymic atrophy (Papadopoulou et al. 2012). The miR-29 family is highly expressed in adaptive immune cells and has a critical T cell-intrinsic function in determining polarization into different effector T cell fates. miR-29a and b were identified as critical suppressors of the T helper 1 (Th1) cell fate, setting the threshold for Th1/Th2 balance and being able to correct the Th1 bias of DGCR8$^{-/-}$ miR-deficient CD4 T cells (Steiner et al. 2011). In agreement with these findings, miR-29 inhibition in mice removed this counterbalancing force and led to an increase in the number of Th1 cells and interferon-γ production (Ma et al. 2011). miR-29 is induced in myeloid and lymphoid cells in response to immune signals, and it down-regulates multiple immune modulators including interleukins (Brain et al. 2013), interferon-γ (Smith et al. 2012), and the immunomodulatory glycoprotein B7-H3 (Xu et al. 2009).

The importance of miR-29 function in maintenance of tissue homeostasis is demonstrated by the fact that loss of miR-29 function is associated with fibrosis and cancer. Decreased expression of miR-29 has been reported for a majority of cancers (Jiang et al. 2014) and diverse cancer types including leukemia (Calin et al. 2005; Garzon et al. 2008; Garzon et al. 2009; Pekarsky et al. 2000), melanoma (Nguyen et al. 2011), and cancers of the liver (Xiong et al. 2010), colon (Cummins et al. 2006), and lung (Yanaihara et al. 2006), and down-regulation of miR-29 has been associated with more aggressive forms of cancer or relapse (Calin et al. 2005; Pekarsky et al. 2000; Zhao et al. 2010). As a tumor suppressor, miR-29 constrains cancer progression by promoting apoptosis, increasing chemosensitivity, reducing proliferation, and suppressing DNA methylation of tumor-suppressor genes. However, up-regulation of miR-29 has been reported in a minority of cancers and might promote metastasis of breast and colon cancer by mediating epithelial-mesenchymal transition (Jiang et al. 2014).

2.1.2.2 Role of miR-29 in Fibrotic Disease

Of all the studied miRNAs in fibrotic disease, the miR-29 family is the most consistently dysregulated during disease progression. All three family members are reduced in different types of tissue fibrosis, and therapeutic benefit of increasing miR-29 levels has been shown for heart (van Rooij et al. 2008), kidney (Qin et al. 2011; Wang et al. 2012; Xiao et al. 2012), liver (Roderburg et al. 2011; Sekiya et al. 2011; Zhang et al. 2012), lung (Cushing et al. 2015;

Xiao et al. 2012), and systemic sclerosis (Maurer et al. 2010). The microRNAs in the miR-29 family are understood to play a role in the regulation of key processes that contribute to fibrosis, including the initiation and maintenance of fibrosis through transforming growth factor beta (TGF-β) signaling (Li et al. 2009; Peng et al. 2012) and ECM deposition (Cheng et al. 2013; Kawashita et al. 2011; Peng et al. 2012; Zhu et al. 2012). Furthermore, both fibrotic ECM and TGF-β can down-regulate miR-29 expression, leading to a feed-forward loop for increased TGF-β expression and uncontrolled ECM production (Parker et al. 2014; Peng et al. 2012). miR-29 expression is reduced in multiple fibrotic indications (Liu et al. 2010; Maurer et al. 2010; Pandit et al. 2011; Qin et al. 2011; Roderburg et al. 2011; Sekiya et al. 2011; van Rooij et al. 2008), and miR-29 expression level has been inversely correlated with the severity of fibrosis (Cushing et al. 2015). Expression of miR-29b in a mouse model of lung fibrosis resulted in protection against, and reversal of, fibrosis (Montgomery et al. 2014), demonstrating the therapeutic potential of mimicking miR-29 function.

In addition to organ fibrosis, several studies have shown a role for miR-29 in dermal fibrosis, systemic sclerosis and keloid fibrogenesis. Fibroblasts and skin sections obtained from patients with systemic sclerosis, and primary fibroblasts derived from patients with keloids, were lower in miR-29 levels compared to healthy controls (Maurer et al. 2010; Zhang et al. 2016). Bleomycin-treated skin showed a significant reduction in miR-29 as well, suggesting miR-29 down-regulation is a common feature of cutaneous fibrosis regardless of etiology (Maurer et al. 2010). When overexpressed in systemic sclerosis fibroblasts or keloid fibroblasts, miR-29 was able to robustly reduce the expression of type I and III collagens, at both the RNA and protein level. Conversely, inhibition of miR-29 in normal fibroblasts resulted in an increase in these collagens. Additionally, miR-29 overexpression in dermal fibroblasts decreased secreted TIMP-1 and increased collagen gel degradation. Collectively, these studies point to miR-29 mimicry as having therapeutic potential in the prevention or treatment of organ fibrosis, including in the dermis.

2.1.3 Investigational Product: MRG-201

miRagen has designed a mimic of miR-29b, MRG-201, with the objective of correcting the deficiency of miRNA-29 in fibrotic disease states. The structure of MRG-201 was selected by screening a panel of synthetic oligonucleotides for activity as measured by miR-29b target gene repression in cultured cells *in vitro* and in animals *in vivo*. The safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of MRG-201 have been evaluated in nonclinical studies, as well as in a Phase 1 clinical trial in healthy human volunteers.

Of note, all the completed nonclinical and clinical studies of MRG-201, summarized below, defined the selected dose of the investigational product based on the mass of the sodium salt form of the active pharmaceutical ingredient. In this Phase 2 protocol, the dose of MRG-201 is defined based on the mass of the active moiety (protonated or free acid form) of MRG-201. A conversion factor of 0.94 must be applied to convert a dose based on the mass of the sodium salt to the same dose based on the mass of the active moiety.

2.1.3.1 Nonclinical Background

miRagen has conducted *in vitro* and *in vivo* studies to investigate the pharmacology, PK, and toxicology of MRG-201. Complete details of nonclinical studies conducted to date are provided in the MRG-201 Investigator's Brochure.

The pharmacology of MRG-201 has been assessed in single and multiple dose studies in intact skin and acute skin incisions in mouse and rat, in hypertrophic scars in rabbits, and in human skin fibroblasts in culture. Evidence of reciprocal regulation of mRNA levels by a miR-29b mimic and a miR-29 antagonist was used to identify direct and indirect targets of miR-29b in mouse skin. A similar pattern of gene expression changes was observed in response to MRG-201 treatment in incised skin of rats and hypertrophic scars in rabbits and in cultured human skin fibroblasts, consistent with the conservation of the miR-29b sequence across species and the ubiquitous role of miR-29 in regulation of extracellular matrix production. These data were used to select a panel of 24 mRNAs to be monitored as PD biomarkers of MRG-201 activity in human clinical trials. In these pharmacology studies, distribution of MRG-201 along the margin of an incision using multiple, small volume injections was found to reduce the local inflammation associated with intradermal administration of MRG-201 while preserving its effects on gene expression. The microinjection strategy was therefore used for dose administration in Good Laboratory Practice (GLP) toxicology studies performed in rats and rabbits and was used for administration of MRG-201 to Phase 1 clinical study participants.

The pharmacokinetics and biodistribution of MRG-201 have been studied in mice, rats and rabbits following intradermal or intravenous injection, and in monkeys following subcutaneous injection. The non-clinical studies suggest MRG-201 has low bioavailability (≤ 20%) when administered as a local intradermal dose. In rats and rabbits dosed at 0.8, 2.5 or 7 mg MRG-201 using 8 intradermal microinjections around a 1.5 cm incision, MRG-201 plasma concentrations peaked between 15 minutes and 2 hours and cleared quickly, with half-lives typically under 5 hours. Though there was some evidence of increased C_{max} (rat and rabbit) and accumulation (rat only) between Days 1 and 26 of dosing, the levels of MRG-201 at 48 hours post-dosing were

generally below the limit of quantitation. Data from the Phase 1 clinical study suggest a similarly low level of systemic exposure to MRG-201 in healthy volunteers administered repeat intradermal injections at doses ranging from 4 to 14 mg per dose. In addition, dose range-finding embryo-fetal development studies in rats and rabbits demonstrated very low tissue uptake and/or rapid clearance from tissues, even after high, sustained plasma exposure of MRG-201.

MRG-201 is rapidly metabolized following intradermal or subcutaneous administration in rats, rabbits and monkeys into a number of smaller species that are likely to correspond to nucleotide truncations from the 5′ or 3′ end of the antisense strand of the oligonucleotide duplex. The largest of these metabolites are biologically active *in vitro* and *in vivo* and may contribute to the pharmacological activity of the drug in humans. Structural characterization of the metabolites is ongoing, and further work is needed to determine if the same metabolites are formed in humans.

The safety of MRG-201 has been assessed in repeat intradermal dose studies (0.8-7 mg) in rats and rabbits and with single subcutaneous escalating doses (2 and 20 mg/kg) in cynomolgus monkeys. The primary safety concern observed in the rabbit studies was a mixed cell inflammatory reaction at the injection site at a dose of ≥ 2.5 mg, although neither erythema nor edema were reported. In the thymus, there was mild to moderate lymphoid depletion characterized by a decreased number of lymphocytes in the cortex accompanied by diminished cortical-medullary demarcation in male and female rabbits at doses ≥ 0.8 mg. This change was interpreted to be a minor stress reaction to inflammation at the dose site. In the rat, erythema and edema were reported at the injection site but the histological findings included only a minor monocyte infiltration at the highest dose tested (7 mg). Safety pharmacology studies using cynomolgus monkeys dosed subcutaneously with 2 or 20 mg/kg MRG-201 demonstrated no effects on any of the measured respiratory or cardiovascular parameters with the exception of transient, non-significant changes in blood pressure and heart rate at 60 minutes, but not at 45 minutes or 2 hours after a dose of 20 mg/kg. MRG-201 administration produced no clinical signs or injection site reactions and there were no effects on electrocardiogram waveform, or morphology at any dose level tested.

In the embryo/fetal development dose range-finding toxicity studies in rats and rabbits, there was no relevant MRG-201 exposure in the fetal homogenates tested, and no external fetal malformations or variations at any dose level in either species. In addition, MRG-201 did not show mutagenic activity in the bacterial mutagenicity assay (Ames test), nor any clastogenic or aneugenic effect in the micronucleus assay in human lymphocytes.

The starting dose selected for this Phase 2a study is 5.3 mg (active moiety) MRG-201 (0.09 mg/kg based on a 60 kg person) administered initially as 6 intradermal doses over 2 weeks. This dose level is essentially equivalent to the calculated no-observed-adverse-effect level (NOAEL) identified in rabbits [0.8 mg or 0.26 mg/kg for 3.1 kg rabbit, scaled to the human equivalent dose based on body surface area: 0.26 mg/kg × 0.32 (body surface area scaling factor) = 0.08 mg/kg, or 5 mg for 60 kg person]. Therefore, the results of nonclinical and clinical studies discussed below indicate that this dose and dosing regimen should be safe and well-tolerated.

2.1.3.2 Clinical Background

MRG-201 was evaluated in a Phase 1, first-in-man, double-blind, placebo-controlled, single-center, single and multiple dose-escalation study (protocol MRG201-30-001) to investigate the safety and tolerability of intradermal injections of MRG-201 in intact and sutured skin of normal healthy volunteers. The starting dose of MRG-201 (administered to the first sentinel subject and cohort) was 0.5 mg (sodium salt form), which was calculated from the NOAEL identified in rabbits, and then adjusted by a 10-fold safety margin to 0.5 mg/dose.

Fifty-four male subjects were enrolled, 47 of whom received MRG-201, across 4 study parts: Part A (untreated sutured incisions, N = 6), Part B (single-ascending dose of MRG-201 and placebo injected into intact skin, N = 19), Part C (single-ascending dose of MRG-201 and placebo injected into sutured incisions, N = 9), and Part D (multiple-ascending dose of MRG-201 and placebo injected into sutured incisions, N = 20). Subjects were monitored for safety (including local skin reactions), drug biodistribution, PD, and histologic and photographic assessments.

Overall, 32 subjects (59%) experienced at least 1 AE, including 2 subjects (33%) in Part A, 11 subjects (58%) in Part B, 4 subjects (44%) in Part C, and 15 subjects (75%) in Part D. Approximately one-half of subjects (28 subjects [52%]) experienced Grade 1 AEs, and 7 subjects (13%) experienced Grade 2 AEs. Two subjects (4%) experienced AEs of Grade 4 blood creatine phosphokinase increased that were considered to be most likely attributable to increased physical activity and changes in diet. These laboratory abnormalities were not associated with symptoms, were considered to be not related to MRG-201 and returned to baseline values without sequelae.

The most common individual treatment-emergent AEs (TEAEs) following study injections (i.e., AEs reported in Parts B, C, and D; N = 48) were injection site edema and nasopharyngitis (each 8 subjects [17%]) and injection site erythema and headache (each 6 subjects [13%]). The majority of MRG-201-related TEAEs were injection site erythema or edema, consistent with the intradermal route of administration of the product. The incidence of TEAEs following

single-dose administration of MRG-201 (Part B and Part C) and multiple-dose administration of MRG-201 (Part D) was similar and relatively low across MRG-201 dose levels, with no direct relationship observed between dose level and incidence of TEAEs.

No deaths or SAEs were reported. One subject enrolled in Part D withdrew consent from the study after experiencing 2 concurrent TEAEs: Grade 1 injection site edema and Grade 1 injection site pruritus.

The Phase 1 study results indicate that MRG-201 was safe and well tolerated at all tested concentrations following single and multiple intradermal injections, with no safety signals identified.

2.2 Scientific Rationale

Based on the nonclinical and clinical data collected to date, MRG-201 is hypothesized to offer clinical benefit to patients with a history of keloid formation. In study MRG201-30-001, analysis of the Part A subjects demonstrated that endogenous miR-29b expression was downregulated and MRG-201 PD biomarker expression was modulated with cutaneous injury (e.g., incisional wounds). Direct target genes of miR-29b that are implicated in multiple fibrotic diseases (e.g., multiple collagen genes) were upregulated following incision, and their expression inversely correlated with miR-29b expression. Indirect, downstream targets that were previously determined to be upregulated by MRG-201 in mouse skin were downregulated following incision (e.g., SDC4, SNX27). A single administration of MRG-201 resulted in a downregulation of direct targets and an upregulation of downstream targets in a dose-dependent fashion, consistent with preclinical observations in mice, rats, and rabbits. These studies support the use of the selected PD biomarkers and demonstrate the PD activity of MRG-201 in humans. Multiple administrations of MRG-201, administered either starting on Day 1 or on Day 4 resulted in PD biomarker regulation (e.g., repression of collagen expression) and repression of normal fibroplasia both at the site of dosing and, in at least one-half of subjects, at a distal site. Though normal fibroplasia was decreased, MRG-201 did not adversely affect wound closure. These results indicate that MRG-201 exerts anti-fibrotic effects in the skin and support its further clinical development for cutaneous fibrosis indications.

The current protocol is a double-blind, placebo-controlled, multi-center, outpatient study designed to determine the safety, efficacy, and PK of MRG-201 compared with placebo when administered following excisional wound creation and suturing. This study will provide further evidence regarding the safety and tolerability of MRG-201 in a patient population predisposed to

forming keloids during wound healing and will investigate the activity of MRG-201 in reducing keloid formation over an approximately 1-year post-excision period.

The dose selected for the first cohort in the proposed Phase 2a study is 5.3 mg MRG-201 (active moiety), or 0.09 mg/kg in a 60 kg adult. This dose corresponds to the maximum dose that can be administered using the injection method proposed for the initial cohort of subjects (four 20-µL injections around the perimeter of a sutured 6-mm excisional wound). The initial dosing regimen will include 6 doses administered over 2 weeks analogous to the regimen used in the completed Phase 1 clinical trial in normal healthy volunteers, in which subjects received doses as high as 14 mg MRG-201 (sodium salt form), equivalent to 13 mg active moiety or 0.22 mg/kg in a 60 kg adult using the 2-week dosing regimen. The highest dose per linear centimeter of incision in the Phase 1 study and the highest dose per linear centimeter of sutured excision in this protocol are equivalent (8.7 mg active moiety/cm incision vs. 8.8 mg active moiety/cm sutured excision). The results of nonclinical and clinical studies indicate that this dose and dosing regimen should be safe, well-tolerated and potentially efficacious in the prevention of keloid scar formation.

The sponsor may enroll up to 5 additional cohorts of approximately 12 subjects each to assess alternate doses and regimens. The dose may be decreased by reducing the dose volume or by dilution of the drug product solution. A longer duration of dosing, up to the 4-week duration used in GLP toxicology studies, may also be evaluated in subsequent cohorts at the 5.3 mg or lower dose levels. Any cohort treated for longer than two weeks in the initial treatment cycle will not be eligible for retreatment to avoid exceeding the maximum duration of dosing in GLP toxicology studies. The total exposure for any subject during the study will not exceed 12 doses of 5.3 mg MRG-201.

2.3 Potential Risks and Benefits

The potential risks and benefit of MRG-201 treatment are provided in the Investigator's Brochure.

2.3.1 Known Potential Risks

The majority of published information regarding the observed nonclinical and clinical toxicity of oligonucleotide drugs relates to single-stranded phosphorothioate oligonucleotides. Most of the observed side effects are believed to be hybridization-independent and related to the physical and chemical characteristics of this class of agents, including their relatively long plasma and tissue residence times. MRG-201 includes two phosphorothioate linkages. Its tissue and plasma clearance rates are significantly more rapid than that of many single-stranded phosphorothioate

oligonucleotides. In GLP toxicology studies in rats and rabbits and in a Phase 1 clinical trial in humans, MRG-201 was not associated with some of the more common toxicological effects of this class (e.g., kidney and liver toxicity).

Clinically, the most commonly observed side effects after systemic administration of phosphorothioate oligonucleotides are: 1) dermatological reactions at subcutaneous injection sites, 2) constitutional symptoms such as fever, chills, and myalgia primarily associated with initial doses, and 3) prolongation of activated partial thromboplastin time (aPTT) (when the drugs are given intravenously but not when administered subcutaneously). In general, these effects are mild and transient, and resolve spontaneously.

In the completed Phase 1 study in normal healthy volunteers (Study MRG201-30-001), AEs associated with the injection procedure, including reactions at the injection site (edema, erythema, paresthesia, warmth, bruising, pain, pruritus) have been observed, with other common AEs including nasopharyngitis and headache. Intradermal injection of MRG-201 was associated with mild or moderate injection site edema or erythema in approximately one-third of subjects. These study drug-related adverse events occurred with a similar incidence following single or multiple injections of MRG-201. All these injection site reactions resolved without sequela, were of short duration, and did not recur or worsen in subjects that received multiple doses of MRG-201. There did not appear to be direct relationship between dose strength and incidence of TEAEs.

Safety monitoring in clinical studies with MRG-201 includes assessments for typical class-related toxicities, including local tolerability at the injection site and systemic inflammation.

2.3.2 Known Potential Benefits

The completed Phase 1 study in normal healthy volunteers was designed primarily to evaluate safety and local tolerability, with efficacy collected as an exploratory endpoint. Preliminary evidence of PD activity as measured by gene expression changes and a reduction of fibroplasia following MRG-201 treatment has been observed and warrants further investigation.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Safety Objective

Investigate the safety and tolerability of multiple intradermal administrations of MRG-201 in subjects with a history of keloids.

3.1.2 Pharmacodynamic Objective

Investigate the activity of MRG-201 in prevention or reduction of keloid formation, in subjects with a history of keloids.

3.1.3 Other Objectives

- Evaluate additional pharmacodynamic endpoints of MRG-201 in subjects with a history of keloids.
- Evaluate Patient Reported Outcomes.
- Characterize the pharmacokinetics of MRG-201 in subjects with a history of keloids.

3.2 Endpoints

3.2.1 Safety Endpoints

- The safety and tolerability of MRG-201 will be assessed by determining the incidence and severity of clinically significant adverse events (including Grade 3 and 4 AEs, treatment-related AEs, SAEs, and AEs requiring discontinuation of MRG-201), and physical examination findings, changes in vital signs, electrocardiograms (ECGs), and laboratory parameters.
- AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

3.2.2 Pharmacodynamic Endpoint

The formation of a keloid will be defined as a persistent scar that exhibits a score of at least 3 on the mVSS (Fearmonti et al 2010, see Appendix D), with a score of at least 1 in the height sub-domain. For the purposes of this study, scars that form at one or both of the blinded wound sites following the initial treatment will be considered unconfirmed keloid(s) if they exhibit a

score of 3 to 5 on the mVSS, with a score of at least 1 in the height sub-domain. Unconfirmed keloid(s) with a score of 3 to 5 on the mVSS will be re-evaluated at the subsequent monthly visits for up to 12 weeks. Keloid(s) that persist after this 12-week observation period and/or progress to an mVSS score of ≥ 6 at any time (with a score of at least 1 in the height sub-domain) will be considered confirmed keloid(s). At the time of keloid confirmation, the investigator, in consultation with the subject, may elect to attempt local treatment of the keloid with triamcinolone as a standard of care therapy after consultation with the sponsor.

- Proportion of confirmed keloid formation at 24 weeks across subjects for treated vs. untreated lesions.
- Proportion of subjects with improvement, which is defined as no confirmed keloid formation in the treated lesion vs. confirmed keloid formation in the untreated lesion.
- Proportion of subjects forming confirmed keloids with MRG-201 treatment vs. placebo treatment at 12 weeks, 36 weeks, 52 weeks, and at the time of study withdrawal (if subjects do not complete the study).

3.2.3 Other Pharmacodynamic Endpoints

- Proportion of subjects forming confirmed keloids regardless of treatment application.
- Time to keloid formation.
- Volume of keloid at 24 weeks, 52 weeks and at time of triamcinolone injection (if applicable).

3.2.4 Exploratory Endpoints

- Modified Vancouver Scar Scale (mVSS; Fearmonti et al 2010, see Appendix D) score at visits occurring every 4 weeks from Day 29 to Day 365 after excisional wound creation.
- Patient and Observer Scar Assessment Scale (POSAS; Appendix E) scores at visits occurring every 4 weeks from Day 29 to Day 365 after excisional wound creation.
- Keloid volume and keloid severity (per mVSS in Appendix D and POSAS in Appendix E) at visits occurring every 4 weeks following a second cycle of dosing with MRG-201 or placebo in subjects exhibiting evidence that a keloid may be forming at one or both biopsy sites within 12 weeks after initiation of the first cycle of study dosing.

3.2.5 Pharmacokinetic Endpoints

- Plasma concentration of MRG-201 will be assessed at multiple time points on Day 1 and Day 12 (or Day 26 for cohorts dosing for 4 weeks), and at single time points on Day 2 and Day 13 (or Day 27 for cohorts dosing for 4 weeks). Voided urine samples for PK analyses will also be collected on Day 1 and 12 (or Day 26 for cohorts dosing for 4 weeks) predose and 3 hours postdose, and Day 2 and Day 13 (or day 27 for cohorts dosing for 4 weeks).

4 STUDY DESIGN

This is a double-blind, placebo-controlled, multi-center, outpatient exploratory efficacy study in subjects with a high likelihood of keloid formation (i.e., history of ≥ 10 keloids or history of large keloids, ≥ 4 cm), with MRG-201 and placebo administered by intradermal injection around the site of two separate punch biopsies.

A minimum of 12 subjects are anticipated for enrollment in the first cohort of the study to attain at least 10 subjects who complete study participation through 24 weeks after excisional wound creation. Subjects who drop out for reasons other than safety or study treatment tolerability may be replaced with sponsor approval (up to 16 total including replacements). The sponsor may enroll up to 5 additional cohorts of 12 to 16 subjects each (up to 80 total additional subjects) to assess lower doses and/or regimens.

Subjects in the initial cohort will undergo a screening period lasting up to 28 days, followed by a double-blind, 12-day active treatment period (first cycle of study dosing) conducted in the outpatient setting, a possible second 12-day cycle of study dosing as outlined in Section 4.2, and a follow-up period of up to 52 weeks (± 7 days) after initiation of the first cycle of study dosing. Subjects in additional cohorts may receive lower doses or an extended 26-day active treatment period without the option to receive a second cycle of treatment. Follow-up periods for those additional cohorts will remain unchanged.

Subjects will be continuously monitored for safety through evaluations of AEs, vital signs, physical examination findings, clinical laboratory measurements, and ECG monitoring.

Samples will be collected for plasma PK on Days 1, 2, 12, and 13 (or Days 1, 2, 26, and 27 for subjects receiving an initial 26-day treatment cycle).

The punch biopsy wound sites will be evaluated for keloid formation, photographic assessment, and clinical response during the active treatment and follow-up periods of the study. Biopsy

samples will be saved for future protein and/or nucleic acid analysis to assess MRG-201 effects in subjects who form keloids.

4.1 Punch Biopsies

On Day 1 of the study, subjects will be seen at the clinic in the morning to confirm study eligibility and for their baseline assessments, punch biopsy procedures, baseline photography of the biopsy sites, and administration of study treatments. Subjects will undergo two 6-mm punch biopsies bilaterally in the upper back/shoulder region in areas that can be covered with clothing and are likely to form keloids. The locations for the biopsies must be at least 10 cm from each other and far enough away from existing keloids that new keloid formation may be assessed. The punch biopsy excisional wound sites will be closed with sutures.

4.2 Treatments Administered

Following completion of the punch biopsies on Day 1, one punch biopsy wound site will be treated with MRG-201 and the other wound site will be treated with placebo. The treatment for each wound site will be randomized (left versus right) and blinded but consistent throughout dosing. MRG-201 and placebo will each be administered as four 20-µL injections around one wound site, with subjects receiving approximately 5.3 mg of the MRG-201 active moiety on each dosing day (approximately 1.3 mg per 20-µL injection). After all Day 1 assessments and procedures are complete, subjects will be discharged to home.

Subjects will return to the clinic on Days 3, 5, 8, 10, and 12 to receive repeat injections with the same blinded study treatment that was administered at each wound site on Day 1. Subjects will return to the clinic on Day 19 for additional assessments and safety monitoring, and the Principal Investigator (PI) will determine whether any tolerability concerns are present and warrant consultation and safety data review with the sponsor's Medical Monitor. If at any point clinically significant safety or tolerability issues are observed by the investigator and are thought to be possibly related or related to MRG-201, the subject will not receive further administration of MRG-201 pending follow-up with the Medical Monitor. In this event, the investigator must notify the sponsor's Medical Monitor by email or phone within 24 hours, and a meeting with the sponsor Medical Monitor may be convened.

On Day 8, Day 12, Day 19, Day 29 (4 weeks ± 3 days after completion of the punch biopsies) and then every 4 weeks for 1 year (Days 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337, 365, each ± 7 days), excisional wound sites will be assessed for keloid formation, photographic evaluations, and other study assessments.

For subjects receiving 6 doses of MRG-201 in the initial treatment cycle, if there is evidence that a keloid may be forming (defined as meeting a score of 1 or 2 on the mVSS and having an appearance consistent with an area likely to form a keloid according to investigator judgement) within 12 weeks after initiation of the first cycle of study dosing, and following the initial 29-day treatment and assessment period, subjects will undergo a second cycle of study dosing in one or both biopsy sites (depending on keloid formation). Subjects will be treated with MRG-201 or placebo according to the original treatment assignments (blinding will be maintained during the second treatment regimen). The treatment regimen for the second cycle of study dosing will be the same as for the first cycle, i.e., an initial dose followed by additional doses 2, 4, 7, 9, and 11 days after the initial dose, with follow-up visits at Days 19 and 29 after the re-start of dosing. Following the visit that occurs 29 days after the start of the second cycle of study dosing, re-treated biopsy sites will be followed according to the first cycle visit schedule. If the wound site scar(s) progress to an mVSS score of 3 to 5 (with a score of at least 1 in the height sub-domain) after the 12-week observation period and/or to an mVSS score of ≥ 6 at any time (with a score of at least 1 in the height sub-domain), the scar(s) will be considered confirmed keloid(s). At the time of keloid confirmation, the investigator, in consultation with the subject, may elect to attempt local treatment of the keloid with triamcinolone as a standard of care therapy after consultation with the sponsor.

Additional cohorts may be enrolled to test lower doses or an extended dosing schedule. Study procedures for the extended dosing cohorts will be identical to the cohort described above, with the following exceptions: 1) subjects in these cohorts may receive a total of 12 intradermal doses of MRG-201 and placebo on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26; 2) subjects will not undergo a second cycle of treatment if the 4-week dosing schedule is used; and 3) pharmacokinetic assessments will be performed on study Day 1, 2, 26, and 27 for subjects receiving an initial 26-day treatment cycle.

5 ENROLLMENT, DISCONTINUATION AND WITHDRAWAL OF STUDY PARTICIPANTS

5.1 Inclusion Criteria

Individuals must meet *all* of the following inclusion criteria to be eligible for participation in this study.

1. Must provide written informed consent (signed and dated), and any authorizations required by law, and be able to comply with all study requirements.

2. Males or females, ≥ 18 years of age at the time of informed consent.
3. Females must have a negative serum pregnancy test at screening and a negative urine pregnancy test on their first dosing day.
4. Females must not be or planning to be pregnant or lactating during the study. Females must be post-menopausal (confirmed by follicle-stimulating hormone [FSH] test for subjects whose last menstrual cycle was within the last 2 years before screening), abstinent, in a monogamous same sex relationship, surgically sterile or, if of child bearing potential, must use two acceptable methods of contraception with at least one being a barrier method throughout their study participation and for at least 6 months following the last dose of study treatment. Acceptable methods of contraception include oral, injectable or implantable hormonal contraception, intrauterine device, or medically-confirmed vasectomized partner.
5. Males must be surgically sterile, abstinent, or if engaged in sexual relations with a female of child-bearing potential, must be using two acceptable methods of contraception with at least one being a barrier method for at least 6 months following the last dose of study treatment. Contraception for male subjects could include a condom and a highly effective second method during and for at least 6 months after the last dose of study treatment.
6. Investigator feels that the subject is likely to form keloids in the upper back/shoulder area after punch biopsy based on a history of a high frequency of keloid formation (history of ≥ 10 keloids), or a history of large keloids (≥ 4 cm).
7. Must have bilateral 2 cm × 2 cm areas, where skin punch biopsy may be performed in the upper back/shoulder region and can be covered by clothing, that are free of keloids, acne, striae or other skin pathologies or complications (e.g., tattoos, excessive hair) that may obstruct the ability to evaluate the biopsy sites.
8. Subject is currently clinically stable and is likely to remain clinically stable for a minimum of 14 months from screening.
9. Subject is not anticipated to require systemic corticosteroids during participation in the study.
10. Must be able to communicate effectively with study personnel.

5.2 Exclusion Criteria

Individuals who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1. Recent history of alcoholism (within the past 1 year).

2. History of drug abuse or use of illicit drugs (such as cocaine, methamphetamines, or heroin) within 1 year prior to screening. Subjects must also agree to refrain from illegal drug use during the study.
3. Systemic use of steroids within 4 weeks of Day 1, or local use of steroids within 1 week of Day 1.
4. An active or uncontrolled infection at screening or Day 1.
5. Positive at the time of screening for human immunodeficiency virus (HIV), Hepatitis B (surface antigen), or Hepatitis C.
6. Liver dysfunction, as defined by alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or alkaline phosphatase > 1.5 × upper limit of normal (ULN) at screening or Day 1.
7. Renal dysfunction defined as serum creatinine > 2 mg/dL at screening or Day 1.
8. Clinically significant anemia, neutropenia, or thrombocytopenia at screening or Day 1.
9. History of bleeding diathesis or coagulopathy.
10. Genetic disorders that predispose to keloids. These include, among others, Ehlers-Danlos syndrome, Ullrich congenital muscular dystrophy, and Rubenstein-Taybi syndrome.
11. Prior malignancies within the past 3 years (allowing squamous cell and basal cell carcinomas with free margins at excision, or other malignancies considered cured by surgical resection).
12. Presence on ECG of QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec or > 480 msec if concomitant bundle branch block, at screening or Day 1.
13. Use of an investigational small molecule drug during the 30 days prior to screening or use of an investigational oligonucleotide or biologic drug during the prior 90 days.
14. History of allergy or severe adverse reaction to an oligonucleotide.
15. Unwillingness to comply with study procedures, including follow-up, as specified by this protocol, or unwillingness to cooperate fully with the Investigator.
16. Clinically significant abnormalities in medical history, physical examination, or laboratory values that, in the opinion of the Investigator, would make the subject unsuitable for inclusion in the study.

5.3 Participant Discontinuation or Withdrawal

5.3.1 Reasons for Participant Discontinuation or Withdrawal

Subjects may withdraw their consent to participate in the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. If a subject withdraws consent, the date and stated reason for consent withdrawal should be documented.

Subjects meeting any of the following criteria should discontinue study treatment:

- Unacceptable AE(s) or failure to tolerate study treatment;
- Changes in the subject's condition or development of an intercurrent illness that renders the subject unsuitable for further study treatment in the judgment of the Investigator;
- Withdrawal of consent;
- Pregnancy (treatment will be discontinued but study observations may continue);
- Subject is lost to follow-up;
- Discretion of the Investigator;
- Termination of the study by the Sponsor.

5.3.2 Procedures for Participant Discontinuation or Withdrawal

Wherever possible, the tests and evaluations listed for the post-treatment evaluation period should be carried out and an effort should be made to continue follow-up. The Sponsor should be notified of all study withdrawals through the designated electronic case report forms (eCRFs) in a timely manner.

Additional subjects may be enrolled in a given cohort (up to a total of 16 subjects in a cohort), if fewer than 10 subjects complete study participation through 24 weeks for reasons other than the safety or tolerability of study treatment, or if dosing is not completed per protocol for an individual subject for reasons other than the safety or tolerability of study treatment.

6 STUDY PRODUCTS

6.1 Study Product(s) Management

6.1.1 Acquisition

MRG-201 will be supplied by the Sponsor and sent to clinical study sites. The study sites will provide placebo comparator (0.9% sodium chloride injection, United States Pharmacopeia [USP]).

6.1.2 Formulation, Appearance, Packaging, and Labeling

The MRG-201 Drug Product is manufactured according to current Good Manufacturing Practice (cGMP) regulations for use in clinical trials.

The MRG-201 Drug Product is supplied as a sterile solution for injection. The Drug Product is formulated in an isosmotic phosphate buffer, pH 7.4 ± 0.5, corresponding to 66 mg/mL of the active moiety. The Drug Product is packaged in single-use glass vials with a rubber closure and an aluminum flip-off overseal, each containing 0.3 mL of a clear to slightly yellow liquid formulation.

6.1.3 Storage and Stability

The MRG-201 Drug Product is stored at -20 ± 5°C, protected from light.

6.1.4 Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study treatment. All drug supplies and associated documentation will be reviewed and verified by the Clinical Research Associate (CRA). Unused material cannot be disposed of until approval is obtained from the CRA. The study site is responsible for the disposal and/or destruction of all unused study treatment supplies, according to the site's standard operating procedures. If the site cannot dispose of these materials, arrangements should be made between the site and Sponsor's representative for destruction or return of the unused study treatment supplies.

6.2 Dosage, Preparation and Administration of Study Products

6.2.1 Dose and Regimen

As outlined in Section 4.2, each subject will receive injections with MRG-201 and placebo around the site of two separate 6-mm punch biopsies. The treatment for each wound site will be

randomized (left versus right) and blinded but consistent throughout dosing. MRG-201 and placebo will each be administered as four 20-µL injections around one wound site, with subjects receiving approximately 5.3 mg of MRG-201 active moiety on each dosing day (approximately 1.3 mg per 20-µL injection).

Study treatment injections for subjects receiving 6 doses in their initial treatment cycle will be administered on Days 1, 3, 5, 8, 10, and 12 of the first cycle of study dosing. A second cycle of 6 study treatment injections will be administered for subjects who exhibit evidence of keloid formation (defined as meeting a score of 1 or 2 on the mVSS and having an appearance consistent with an area likely to form a keloid according to investigator judgement) within 12 weeks after initiation of the first cycle of study dosing and following the initial 29-day treatment and assessment period. The treatment regimen for the second cycle of study dosing will be the same as for the first cycle, i.e., an initial dose on Day 1 followed by additional doses on Days 3, 5, 8, 10, and 12, with follow-up visits at Days 19 and 29 after the re-start of dosing.

Subjects in additional optional cohorts may receive blinded study treatment injections on Days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, and 26 and will not be given a second cycle of dosing.

6.2.2 Method of Assignment to Treatment

Subjects will be enrolled sequentially, starting with the first study cohort. The treatment for each wound site will be randomized (left versus right), such that all subjects will receive both MRG-201 and placebo in a double-blinded fashion.

6.2.3 Dose Preparation and Administration

MRG-201 must be prepared in accordance with local pharmacy practices using aseptic technique. Complete details on the preparation and administration of study treatment are provided in a separate Pharmacy Manual.

6.2.4 Assessment of Treatment Adherence

All study treatments will be administered at the investigational site by qualified study personnel.

6.2.5 Dose Modifications or Delays

Allergic events and/or injection-related toxicities should be managed according to institutional guidelines. If institutional guidelines are not available, the following recommendations apply. Rash, pruritus, urticaria and wheezing may be treated with diphenhydramine hydrochloride and/or steroids as clinically appropriate. Anaphylaxis or anaphylactoid signs or symptoms may

be treated with steroids and/or epinephrine as clinically indicated. Subjects should be treated in a facility equipped for cardiopulmonary resuscitation. Injection-related reactions (fever, rigors) should be treated per institutional guidelines but may be treated with acetaminophen and diphenhydramine hydrochloride.

6.3 Prior and Concomitant Medications

All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) through the end of the study will be recorded on the eCRF, using generic names when possible.

Systemic use of steroids is not permitted within 4 weeks of Day 1, and local use of steroids is not permitted within 1 week of Day 1. Systemic or local corticosteroids are not permitted during the first 12 weeks of study conduct. If an adverse event requires corticosteroid use, the investigator must contact the Medical Monitor to discuss the intervention and plans for continued subject participation. After 12 weeks, corticosteroids may be allowed after discussion with the Medical Monitor.

7 STUDY PROCEDURES

The procedures and assessments that are outlined in this section will be performed at the time points specified by study visit in Section 8 and summarized in Appendix A (Schedule of Events, First Cycle of Study Dosing) and Appendix B (Schedule of Events, Second Cycle of Study Dosing).

Written informed consent must be provided by each subject prior to the initiation of any study procedure or assessment that is not part of standard of care.

7.1 Clinical Assessments

7.1.1 Medical History

Medical history will be recorded at screening. Any ongoing conditions and signs and symptoms observed prior to first dose of study treatment should be recorded as medical history.

7.1.2 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be measured at screening and at the time points indicated in Appendix A, Appendix B, and Appendix C.

7.1.3 Physical Examination

A complete physical examination will be performed by trained medical personnel at screening and on Day 1 of each cycle of study dosing. Brief symptom-directed physical examinations should be performed at the subsequent time points specified in Appendix A, Appendix B and Appendix C. Weight will be documented only at screening, on Days 12 and 85 of the first cycle of study dosing (Day 26 and 85 if receiving 12 doses of blinded study treatment) and Day 12 of the second cycle of study dosing (if applicable), and at the end of the study (Day 365).

7.1.4 Prior and Concomitant Medications

All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment through the end of the study will be recorded.

7.2 Safety Assessments

7.2.1 Adverse Events

AEs will be assessed at each study visit by direct observation and subject interviews. The severity of AEs will be evaluated using the NCI CTCAE, version 5.0. All AEs that occur from initiation of study treatment through 30 days after the last dose of study treatment must be recorded, regardless of causal assessment to study treatment.

7.2.2 Clinical Laboratory Assessments

Blood or urine samples will be collected for the following clinical laboratory measurements at screening to determine eligibility and predose at each time point indicated in Appendix A, Appendix B, and Appendix C. Clinical laboratory assessments do not need to be performed on Day 1 of the study if screening laboratory measurements were performed within 3 days prior to Day 1.

- Hematology
- Clinical chemistry
- Urinalysis (including microscopy)

In addition, screening for HIV, hepatitis B, and hepatitis C will be performed during screening. Female subjects who are not surgically sterile or have had last menstrual period > 2 years from screening date will also undergo FSH testing during screening to confirm menopause.

7.2.2.1 Pregnancy Test

Female subjects must have a negative serum pregnancy test at screening and negative urine pregnancy tests at the subsequent time points specified in Appendix A and Appendix B. A positive pregnancy test will result in immediate discontinuation of study treatment; however, study assessments will continue to evaluate study endpoints. All pregnancies will be followed through to outcome.

7.2.3 Electrocardiograms

Single 12-lead ECGs will be performed at screening and on Days 1 (predose), 2, and 12 (predose) of each cycle of study dosing (or Day 26, predose, in subjects receiving 12 doses of blinded study treatment in the first cycle), as specified in Appendix A, Appendix B and Appendix C. Electrocardiogram parameters to be evaluated include the RR, QT, QRS, and PR intervals. In addition, Fridericia's formula should be used to calculate the QT interval corrected for heart rate (QTcF). Abnormal ECG measurements will be recorded as AEs only if they are considered to be clinically significant by the investigator.

7.3 Pharmacokinetic Sampling

Plasma samples to measure MRG-201 concentrations will be collected on Days 1, 2, 12 and 13 (or Days 1, 2, 26, and 27 for subjects receiving an initial 26-day treatment cycle) of the first cycle of study dosing at the pre- and postdose time points specified in Appendix A and Appendix C. Voided urine samples for PK analyses will also be collected on Day 1 and Day 12 (or Day 26 for cohorts dosing for 4 weeks) predose and 3 hours postdose, and Day 2 and Day 13 (or day 27 for cohorts dosing for 4 weeks).

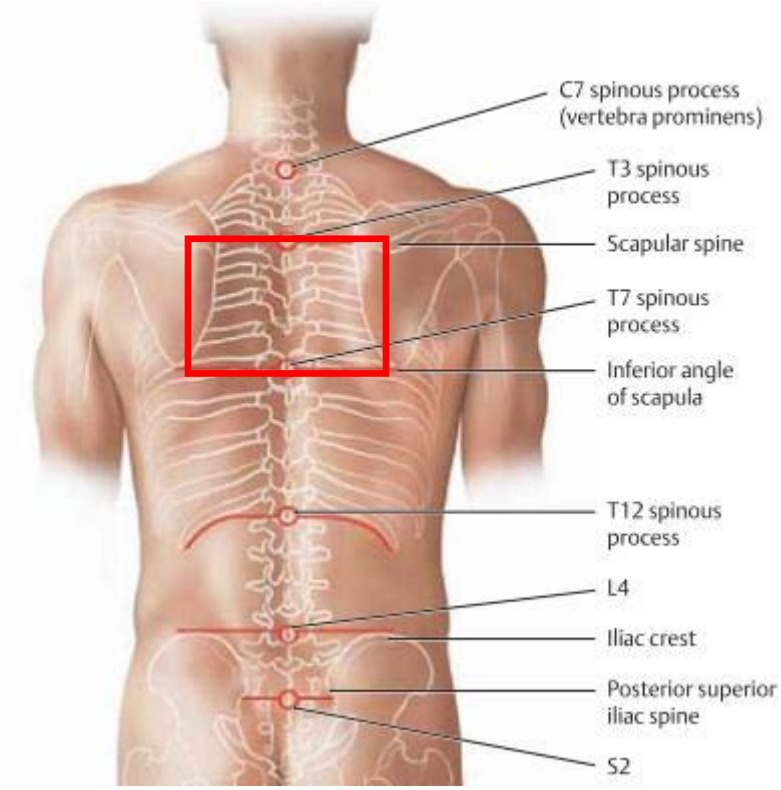
7.4 Pharmacodynamic Assessments

7.4.1 Punch Biopsies

On Day 1 of the first cycle of study dosing, subjects will undergo two 6-mm punch biopsies bilaterally in the upper back/shoulder region in areas that can be covered with clothing and are likely to form keloids. For the purposes of this protocol, the upper back/shoulder region is defined as the area from T3 to the inferior angle of the scapula and extending 10 cm from the midline of the back. The biopsy area is depicted in Figure 2. The locations for the biopsies must be at least 10 cm from each other and far enough away from existing keloids that new keloid formation may be assessed. The biopsies will be performed bilaterally in 2 cm × 2 cm areas

where there are no skin lesions or markings (e.g. tattoos) that could affect keloid assessment. The punch biopsy excisional wound sites will be closed with sutures. Detailed instructions for the punch biopsy will be provided in the Study Manual.

Figure 2: Pictorial Guide to Punch Biopsy Locations



7.4.2 Physician Assessment of Keloid Formation

Excisional wound sites will be evaluated by the investigator for keloid formation (predose on dosing days) at the time points outlined in Appendix A and Appendix B, utilizing the mVSS and POSAS scales.

The formation of a keloid will be defined as a persistent scar that exhibits a score of at least 3 on the mVSS (Fearmonti et al 2010, see Appendix D), with a score of at least 1 in the height sub-domain. For the purposes of this study, scars that form at one or both of the blinded wound sites following the initial treatment will be considered unconfirmed keloid(s) if they exhibit a score of 3 to 5 on the mVSS, with a score of at least 1 in the height sub-domain. Unconfirmed keloid(s) with a score of 3 to 5 on the mVSS will be re-evaluated at the subsequent monthly

visits for up to 12 weeks. Keloid(s) that persist after this 12-week observation period and/or progress to an mVSS score of ≥ 6 at any time (with a score of at least 1 in the height sub-domain) will be considered confirmed keloid(s). At the time of keloid confirmation, the investigator, in consultation with the subject, may elect to attempt local treatment of the keloid with triamcinolone as a standard of care therapy after consultation with the sponsor.

7.4.2.1 Modified Vancouver Scar Scale

The mVSS is a common tool for the assessment of keloid formation and will be used as the basis for defining keloid formation in this study. Scars observed at the biopsy wound sites will be evaluated and scored according to the mVSS (Fearmonti et al 2010, see Appendix D) at the time points outlined in Appendix A, Appendix B, and Appendix C.

7.4.2.2 The Patient and Observer Scar Assessment Scale

The POSAS v2.0 consists of two parts: a Patient Scale and an Observer Scale. Both scales contain six items that are scored numerically on a ten-step scale. Together they make up the 'Total Score' of the Patient and Observer Scale. Category boxes are available to score nominal parameters (e.g. type of color). Moreover, the patient and observer also score their 'Overall Opinion'. Scars observed at the biopsy wound sites will be evaluated and scored according to the Patient Scale and Observer Scales (Appendix E) of the POSAS, at the time points outlined in Appendix A, Appendix B, and Appendix C.

7.4.3 Patient Reported Outcome

The Dermatology Life Quality Index (DLQI) will be completed as an exploratory Patient Reported Outcome to evaluate how much keloid scar formation has affected the subject's quality of life. The DLQI will be assessed at baseline and at about 6 and 12 months after the start of treatment. Assessments will be completed at Day 1, Day 8, Day 169 (24 weeks), and Day 365 (52 weeks).

7.4.4 Biopsy Wound Site Photography

During the first cycle of study dosing, biopsy wound sites will be photographed after completion of the biopsy on Day 1 and predose, as applicable, at the time points outlined in Appendix A, as well as at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation. During the second cycle of study dosing (if applicable), biopsy wound sites will be photographed before study dosing on

Day 1 and subsequently as outlined in Appendix B. Detailed instructions for photography will be provided in the Study Manual.

7.5 Pharmacodynamic Biomarkers

Serum for anti-drug antibody analysis will be collected on Days 1, 12 (15 for 26-day dosing), 29, 85, and 169 of the first cycle of study dosing.

7.6 Specimen Preparation, Handling, and Shipping

Site-specific handling instructions for blood, tissue, and urine samples will be provided in a separate Laboratory Manual.

8 STUDY SCHEDULE

Before recruitment of subjects into the study, written Institutional Review Board (IRB) approval of the protocol, informed consent and any additional subject information must be obtained.

8.1 Screening Period (Day -28 to Day 0)

During screening, a unique number will be assigned to each subject who signs informed consent for the study. Once a subject is in screening or is enrolled in the study, s/he will only be identified by the assigned identification number.

The following procedures and assessments will be performed during the screening period, which may last up to 28 days from the time a subject signs the IRB-approved informed consent form (ICF).

- Obtain informed consent of potential participant verified by written signature on an ICF.
- Record medical history.
- Record prior and concomitant medications taken from 30 days prior to the first dose of study treatment.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination (including documentation of weight).
- Perform a single 12-lead ECG.
- Collect blood for the following:
    - Screening for HIV, hepatitis B, and hepatitis C;

- Confirmation of menopause by FSH (females who are not surgically sterile or last menstrual period is >2 years from screening date);
- Serum pregnancy test (females);
- Hematology;
- Clinical chemistry.

- Collect urine for urinalysis.
- Confirm eligibility of medical history and laboratory measurements according to inclusion/exclusion criteria.

8.2 First Cycle of Dosing with MRG-201 and Placebo with 6 Doses for Initial Treatment Cycle

Study assessments to be performed during the first cycle of study dosing are summarized in Appendix A.

8.2.1 Day 1 (First Day of Study Treatment Administration)

- Complete DLQI
- Verify inclusion/exclusion criteria.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination.
- Collect blood for the following:
  - Hematology (predose; only if screening measurement was performed > 3 days before Day 1);
  - Clinical chemistry (predose; only if screening measurement was performed > 3 days before Day 1);
  - Antibody analysis;
  - PK (1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] postdose).
- Collect urine (predose) for urinalysis (only if screening measurement was performed > 3 days before Day 1) and pregnancy test (females).
- Perform a single 12-lead ECG (predose).

- Obtain two 6-mm punch biopsies and suture the resulting excisional wounds.
- Photograph biopsy sites (post-biopsy and suture).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.

8.2.2 Day 2

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a single 12-lead ECG (approximately 24 hours after Day 1 dosing).
- Collect blood for the following:
  - PK (24 ± 4 hours after Day 1 dosing);
  - Hematology;
  - Clinical chemistry.
- Collect urine for urinalysis.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.3 Days 3 and 5

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.4 Day 8

- Complete DLQI.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).

- Perform a brief, symptom-directed physical examination.
- Collect blood (predose) for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine (predose) for urinalysis.
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.5 Day 10

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.6 Day 12

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Perform a single 12-lead ECG (predose).

- Collect blood (predose) for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis;
  - PK (1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] postdose).
- Collect urine for PK 3 hours after dose (± 1 hour).
- Collect urine (predose) for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.7 Day 13

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for PK (24 ± 4 hours after Day 12 dosing).
  - Collect urine for PK (24 ± 4 hours after Day 12 dosing).
- Review and record AEs and concomitant medications.

8.2.8 Day 19 (± 2 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry.

- Collect urine for urinalysis.
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.9 Day 29 (± 3 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.2.10 Days 57, 113, 141, 197, 225, 281, 309, 337 (± 7 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Review and record AEs and concomitant medications.

- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.2.11 Day 85 (± 7 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.2.12 Days 169 and 253 (± 7 Days)

- Complete DLQI (Day 169 only).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis (Day 169 only).
- Collect urine for urinalysis.
- Perform physician assessment of keloid formation and volume.

- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.3 Second Cycle of Dosing with MRG-201 and/or Placebo

For subjects receiving 6 doses of MRG-201 in the initial treatment cycle, if there is evidence that a keloid may be forming (defined as meeting a score of 1 or 2 on the mVSS and having an appearance consistent with an area likely to form a keloid according to investigator judgement) within 12 weeks after initiation of the first cycle of study dosing, and following the initial 29-day treatment and assessment period, subjects will undergo a second cycle of study dosing in one or both biopsy sites (depending on keloid formation). Subjects will complete the procedures that were planned at the scheduled visit (e.g., Day 85 visit procedures, if that is the current visit), as well as be treated with MRG-201 or placebo according to the originally assigned study treatments. The study assessments to be performed during the second cycle of study dosing are summarized in Appendix B.

8.3.1 Day 1

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology (predose);
  - Clinical chemistry (predose).
- Collect urine (predose) for urinalysis and pregnancy test (females).
- Perform a single 12-lead ECG (predose).
- Photograph biopsy sites (predose).
- Perform physician assessment of keloid formation.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatment(s).

- Review and record AEs and concomitant medications.

8.3.2 Day 2

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a single 12-lead ECG (approximately 24 hours after Day 1 dosing).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine for urinalysis.
- Perform physician assessment of keloid formation.
- Review and record AEs and concomitant medications.

8.3.3 Days 3 and 5

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform physician assessment of keloid formation (predose).
- Administer intradermal study treatment(s).
- Review and record AEs and concomitant medications.

8.3.4 Day 8

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood (predose) for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine (predose) for urinalysis.
- Perform physician assessment of keloid formation and volume (predose).
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).

- Administer intradermal study treatment(s).
- Review and record AEs and concomitant medications.

8.3.5 Day 10

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform physician assessment of keloid formation (predose).
- Administer intradermal study treatment(s).
- Review and record AEs and concomitant medications.

8.3.6 Day 12

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Perform a single 12-lead ECG (predose).
- Perform physician assessment of keloid formation and volume (predose).
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatment(s).
- Review and record AEs and concomitant medications.

8.3.7 Day 19 (± 2 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Review and record AEs and concomitant medications.

8.3.8 Day 29 (± 3 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).

- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.3.9 Subsequent Visits, Every 4 Weeks (± 7 Days)

Following the visit that occurs 29 days after the start of the second cycle of study dosing, re-treated biopsy sites will be followed according to the first cycle visit schedule (see Section 8.2.10 [Days 57, 113, 141, 197, 225, 281, 309, and 337], Section 8.2.11 [Day 85], and Section 8.2.12 [Days 169 and 253]).

8.4 Dosing with MRG-201 and Placebo with 12 Doses for a Single Treatment Cycle

Study assessments to be performed during the single 26-day cycle of study dosing are summarized in Appendix C.

8.4.1 Day 1 (First Day of Study Treatment Administration)

- Complete DLQI.
- Verify inclusion/exclusion criteria.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a complete physical examination.
- Perform a single 12-lead ECG (predose).

- Collect blood for the following:
  - Hematology (predose; only if screening measurement was performed > 3 days before Day 1);
  - Clinical chemistry (predose; only if screening measurement was performed > 3 days before Day 1);
  - Antibody analysis;
  - PK (1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] postdose).
- Collect urine (predose) for urinalysis (only if screening measurement was performed > 3 days before Day 1) and pregnancy test (females).
- Obtain two 6-mm punch biopsies. Suture.
- Photograph biopsy sites (post-biopsy).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.

8.4.2 Day 2

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a single 12-lead ECG (approximately 24 hours after Day 1 dosing).
- Collect blood for the following:
  - PK (24 ± 4 hours after Day 1 dosing);
  - Hematology;
  - Clinical chemistry.
- Collect urine for urinalysis and PK (24 ± 4 hours after Day 1 dosing).
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.3 Days 3, 5, 10, 12, 17, 19 and 24

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.4 Day 8

- Complete DLQI.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood (predose) for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine (predose) for urinalysis.
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.5 Days 15 and 22

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.

- Collect blood (predose) for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis.
- Collect urine (predose) for urinalysis (Day 15 only).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.6 Day 26

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Administer intradermal study treatments.
- Review and record AEs and concomitant medications.
- Collect blood (predose) for PK (1 hour [± 10 minutes], 2 hours [± 15 minutes], and 3 hours [± 15 minutes] postdose).
- Collect urine for PK 3 hours after dose (± 1 hour).
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.7 Day 27

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Collect blood for PK (24 ± 4 hours after Day 26 dosing).
- Collect urine for PK (24 ± 4 hours after Day 26 dosing).

- Review and record AEs and concomitant medications.

8.4.8 Day 29 (± 1 Day)

- Obtain vital signs and weight (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Perform a single 12-lead ECG.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.9 Day 36 (± 2 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Review and record AEs and concomitant medications.

8.4.10 Days 57, 113, 141, 197, 225, 281, 309, 337 (± 7 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform physician assessment of keloid formation and volume.

- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Review and record AEs and concomitant medications.
- Note: Biopsy wound sites are to be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation.

8.4.11 Day 85 (± 7 Days)

- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;
  - Antibody analysis.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.4.12 Days 169 and 253 (± 7 Days)

- Complete DLQI (Day 169 only).
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination.
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry;

  - Antibody analysis (Day 169 only).
- Collect urine for urinalysis.
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

8.5 End of Study Visit (Day 365 ± 7 Days)

The end of study assessments will be performed on Day 365 (± 7 days). For subjects who discontinue treatment early, the end of study assessments should be performed at the final study visit (assuming the subject has not withdrawn consent).

- Complete DLQI.
- Obtain vital signs (blood pressure, heart rate, respiratory rate, and body temperature).
- Perform a brief, symptom-directed physical examination (including documentation of weight).
- Collect blood for the following:
  - Hematology;
  - Clinical chemistry.
- Collect urine for urinalysis and pregnancy test (females).
- Perform physician assessment of keloid formation and volume.
- Assign mVSS and POSAS scoring (Fearmonti et al 2010, see Appendix D and Appendix E).
- Photograph biopsy sites.
- Review and record AEs and concomitant medications.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

Safety will be evaluated through continuous monitoring of AEs, vital signs, physical examinations, clinical laboratory measurements, and ECGs.

9.2 Definition of Adverse Events

9.2.1 Adverse Event

An AE is any untoward medical occurrence whether or not considered drug related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

9.2.2 Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

9.2.3 Life-Threatening AE or Life-Threatening Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

9.2.4 Serious AE or Serious Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE (see Section 9.2.3).
- Requires prolongation of existing hospitalization.

- A persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.5 Unexpected AE or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the Reference Safety Information in the Investigator’s Brochure or is not listed at the specificity or severity that has been previously observed.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator’s Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator’s Brochure listed only cerebral vascular accidents.

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator’s Brochure 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.

9.3 Adverse Event Classification

9.3.1 Relationship to Investigational Product

The Investigator’s assessment of causality must be provided for all adverse events (serious and non-serious). An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE.

- Not related: The AE is clearly not related or is unlikely to be related to the study therapy. The temporal relationship of the onset of the AE relative to administration of the product is not reasonable, or the AE can be explained by another cause such as an underlying

medical condition or other concomitant medication, or the adverse event has no plausible relationship to study therapy.

- Related: The AE is related to the study therapy. The temporal relationship of the AE to administration of the product is reasonable and there is no other cause to explain the event. AEs should be classified as related if the investigator feels there is evidence to suggest a causal relationship between the drug and the adverse event.

9.3.2 Severity

All adverse events entered into the eCRF will be graded for severity using the NCI CTCAE, version 5.0. If an adverse event is not listed in the CTCAE version 5.0, then the Investigator will use the terms: Mild, Moderate, Severe, Life-threatening, or Death to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

Severity	Definition
Grade 0	No change from Normal or Reference Range
Grade 1 (Mild)	No limitation of usual activities.
Grade 2 (Moderate)	Some limitation of usual activities.
Grade 3 (Severe)	Inability to carry out usual activities.
Grade 4 (Life-threatening)	Immediate risk of death.
Grade 5 (Death)	Resulting in death.

9.4 Collection and Reporting of Adverse Events

9.4.1 Initial Reporting of Adverse Events

Subjects will be evaluated and questioned generally to identify adverse events during the course of the study. Any events occurring prior to administration of the first dose of study treatment will be recorded on the Medical History eCRF. Events occurring after administration of the first dose of study treatment or those that increase in severity or frequency will be recorded as treatment-emergent AEs on the Adverse Event eCRF. Adverse events that occur up to and including 30 days after administration of the last dose of study treatment must be reported.

All AEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings, as assessed by the Investigator, is considered an AE and

must be recorded on the Adverse Event eCRF. In addition, an abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinically significant symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including additional concomitant drug treatment or other therapy. Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study treatment dosing or discontinuation of subject participation in the clinical research study.
- The test finding is considered an AE by the Investigator.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not associated with a documented disease or syndrome, the sign or symptom should be recorded as a separate AE. Laboratory data are to be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus rather than hyperglycemia).

9.4.2 Follow-up of Adverse Events

All AEs considered to be related to study treatment will be followed until resolution or stabilization.

9.5 Collection and Reporting of Serious Adverse Events

9.5.1 Initial Serious Adverse Event Reports

All SAEs that occur up to and including 30 days after administration of the last dose of study treatment must be reported by the Investigator to the Sponsor or Sponsor's designee within 24 hours of awareness of the event by submission of a SAE Notification Form. Investigators must report to the Sponsor any SAE, whether or not considered drug related, including those listed in the protocol or Investigator's Brochure. The initial report must contain at a minimum a subject identifier code, an event term, and an assessment of causality. The SAE Notification Form should be e-mailed to:

If the Investigator is unable to complete and send the SAE Notification Form within the timeframe required, the SAE must be reported via phone call to:

Primary Contact

Back-up Contacts

An Investigator may be requested by the Sponsor to obtain specific follow-up information in an expedited fashion. This information may be more detailed than that captured on the Adverse Event eCRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or the Sponsor's designated representative.

9.5.2 Follow-up of Serious Adverse Events

All SAEs should be followed up until resolution or stabilization. The timelines and procedure for follow-up reports are the same as those for the initial report.

New information regarding an SAE that becomes available after the submission of the initial SAE Notification Form must be reported by the Investigator to the Sponsor by completion of a SAE Follow-up Report Form or through other written documentation (e.g., laboratory tests,

discharge summary, postmortem results). Follow-up reports and/or written documentation must be provided to the Sponsor within 24 hours of the Investigator's receipt of the information.

9.6 Post-Trial Adverse Events

Any AE that occurs outside of the protocol-specified observation period or after the end of the trial but is considered to be caused by the investigational product must be reported to the Sponsor.

9.7 Pregnancy Reporting and Follow-up

Pregnancy in a female clinical trial participant is not an SAE per se. Complications of such pregnancies, for example, spontaneous abortion, may qualify as an SAE and should be reported as an SAE even if they occur after the SAE reporting period has ended.

The Investigator must notify the Sponsor via telephone or e-mail within 24 hours of awareness of a pregnancy in a study participant and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The participant will not receive any further doses of their assigned study treatment. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended. Information regarding the course of the pregnancy, including perinatal and postnatal offspring outcome up to 8 weeks of age should be reported as follow-up information on the Pregnancy Notification Form. While treatment will be discontinued for pregnant subjects, study observations may continue to evaluate study endpoints.

Male study participants will be instructed to notify the Investigator if a female partner becomes pregnant during the study. The Investigator must notify the Sponsor within 24 hours via telephone or e-mail and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The Investigator should obtain informed consent from the subject's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the subject's partner provides informed consent, the Investigator should follow the pregnancy until outcome as described above for female study participants and report the follow-up information on the Pregnancy Notification Form.

9.8 Halting Rules

Safety data will be reviewed on an ongoing basis by the Sponsor's Medical Monitor. While no formal stopping rules will be implemented, the Sponsor may suspend enrollment or terminate the study at any time for safety concerns.

9.9 Emergency Sponsor Contact

In a medical emergency (i.e., an event that requires immediate attention regarding operation of the clinical study and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor or the designated Sponsor representative, as indicated in Section 1 of this protocol.

10 TRIAL-SPECIFIC COMMITTEES

No study-specific committees will be used for this trial.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical and Analytical Plans

Final statistical analysis will be completed after the last subject completes or discontinues the study and the study database has been cleaned, verified, and locked.

A statistical analysis plan (SAP) will be created prior to the unblinding or review of any data and prior to statistical analyses being performed. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures.

The results of the final analysis will be presented in the clinical study report appendices. Any deviations from planned statistical analyses will also be presented in the clinical study report.

11.2 Study Hypotheses

This early Phase 2 study is not designed to test any formal hypotheses.

11.3 Analysis Sets

Assignment of patients to analysis sets will be done prior to database lock. The following analysis sets will be defined: The Full Analysis Set (FAS), the Per Protocol Set (PPS), and the PK Analysis Set (PKAS).

11.3.1 Full Analyses Set (FAS)

The FAS will include all randomized patients who received any amount of study drug (MRG-201 or placebo). The treatment assignment for FAS will be as randomized for efficacy analyses and actual for safety analyses. The FAS will be used for all efficacy and safety analyses. All patient data listings will use the FAS.

11.3.2 Per Protocol Set (PPS)

The PPS will consist of all participants who enrolled and completed the study, received all planned doses of study treatment, and completed all assessments necessary for the evaluation of the pharmacodynamic endpoints. The PPS will be used for an additional analysis of efficacy endpoints.

11.3.3 PK Analysis Set (PKAS)

The PKAS will be those patients in the FAS who have plasma concentration data available.

11.4 Statistical Methods

11.4.1 General Approach

All descriptive statistical analyses will be performed using the most recently released and available SAS statistical software (version 9.3 or higher), unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be presented. For continuous variables, the sample size (n), mean, median, and standard deviation, as well as the minimum and maximum values, will be presented. Missing data will not be imputed unless otherwise stated.

11.4.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline disease characteristics will be summarized by variable type across all subjects.

11.4.3 Analysis of the Safety Endpoint: Safety and Tolerability

11.4.3.1 Adverse Events

The analysis of the safety endpoint will be based on AE incidence, physical examination findings, vital signs, ECG results and changes in clinical laboratory tests.

Adverse events will be coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA®) and summary tables for all AEs will be

generated for the FAS. Incidence rates and percentages will be summarized for each preferred term and system organ class. Additional summary tables will be generated for the following subsets: subjects with SAEs, subjects with related AEs, subjects with severe (Grade 3 or 4) AEs, and subjects who discontinue due to AEs. Depending on the doses achieved in this study, AEs may also be summarized by dose level. Severity, investigator-attributed relationship to study treatment, and action taken will also be recorded.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD; 01 September 2017 or later version). A dictionary listing of all unique concomitant medications used in the study will be provided.

11.4.3.2 Physical Examination

Clinically significant changes in vital signs and new findings on physical examination will be recorded as AEs. Incidences of subjects with changes from normal physical examination findings at baseline to abnormal during the study may be generated.

11.4.3.3 Laboratory Data

All hematology, blood chemistry, and urinalysis results will be listed by subject for each assessment and descriptive statistics may be tabulated for select criteria. Changes from baseline and normal-abnormal shift tables may be summarized.

11.4.3.4 Twelve-lead ECG

Information on ECGs will be presented in listings. The incidence of subjects with changes from normal ECG findings at baseline to abnormal during the study will be generated as appropriate. Summary of mean/median changes in ECG intervals may be generated on a data-driven basis.

11.4.4 Analysis of Pharmacodynamic Endpoints: Keloid Formation

Pharmacodynamic analyses of keloid formation, including incidence of keloid formation, time to keloid formation, keloid volume and keloid severity, mVSS and POSAS scores, exploratory Patient Reported Outcomes, and other study assessments (e.g., antibody analyses) will be performed on a data-driven basis.

Pharmacodynamic endpoints:

- Proportion of confirmed keloid formation at 24 weeks across subjects for treated vs. untreated lesions.

Other pharmacodynamic endpoints:

- Proportion of subjects with improved treated outcomes, which is defined as no confirmed keloid formation in the treated lesion vs. confirmed keloid formation in the untreated lesion, at 24 weeks over their untreated lesion.
- Proportion of subjects forming confirmed keloids with MRG-201 treatment vs. placebo treatment at 12 weeks, 36 weeks, 52 weeks, and at the time of study withdrawal (if subjects do not complete the study).
- Proportion of subjects with improved treated outcomes, which is defined as no confirmed keloid formation in the treated lesion vs. confirmed keloid formation in the untreated lesion, at 12 weeks, 36 weeks, 52 weeks, and at the time of study withdrawal (if subjects do not complete the study).
- Proportion of subjects forming confirmed keloids regardless of treatment application.
- Intra-patient and aggregated time from initial treatment on Day 1 to unconfirmed and confirmed keloid formation subjects in treated vs. untreated lesions.
- Intra-patient and aggregated keloid volume between treated and untreated lesions at 24 weeks, 52 weeks, and at the time of triamcinolone intervention (if applicable) for subjects in treated vs. untreated lesions.

Exploratory endpoints:

- Difference in mVSS and POSAS scores within subjects and across subjects for treated vs. untreated lesions.
- Other Patient Reported Outcomes.
- Other exploratory biomarker assessments.

A complete description of pharmacodynamic analyses will be included in the final clinical study report.

11.4.5 Analysis of Exploratory Endpoint: Pharmacokinetics

PK parameters (C_{max}, T_{max}, apparent half-life [$t_{1/2}$], apparent volume of distribution of the terminal phase [V_z/F], apparent clearance [Cl/F], and AUC extrapolated to infinity [$AUC_{0-\infty}$]) will be derived from plasma concentrations of MRG-201 using the actual sampling times. Concentration data and all PK parameters will be listed by subject and summarized descriptively per dose. Standard algorithms of the non-compartmental PK analysis program, WinNonLin software, will be used for these analyses.

Individual plasma concentration versus actual time profiles for each subject and treatment, as well as the mean (± standard deviation) plasma concentration versus scheduled time profiles for each dose level, will be presented graphically.

11.4.6 Planned Interim Analyses

Aggregated blinded interim analyses will be completed when at least 50% of the study subjects reach 12 weeks, 36 weeks and 52 weeks after study Day 1.

11.5 Sample Size Determination

Approximately 12 subjects are anticipated for enrollment in the first cohort to attain approximately 10 subjects who complete study participation through at least 24 weeks. A sample size of 10 subjects on active treatment is considered to be adequate for analysis of safety in this early Phase 2 study. Additional subjects may be enrolled, up to a total of 16, if fewer than 10 subjects complete study participation through 24 weeks for reasons other than the safety or tolerability of study treatment, or if dosing is not completed per protocol for an individual subject for reasons other than the safety or tolerability of study treatment.

The study is designed to start at an expected effective dose for a 2-week duration. The sponsor may enroll up to 5 additional cohorts of 12 to 16 subjects each (up to 80 total additional subjects) to assess the effect of a lower dose or the effect of an increased dosing duration. As with the first cohort, additional subjects may be enrolled in the additional cohorts, up to a total of 16 each, if fewer than 10 subjects in a given cohort complete the study through 24 weeks for reasons other than the safety or tolerability of study treatment, or if dosing is not completed per protocol for an individual subject for reasons other than the safety or tolerability of study treatment.

11.6 Measures to Minimize Bias

11.6.1 Randomization Procedures

Subjects will be enrolled sequentially, starting with the first study cohort. The treatment for each wound site will be randomized (left versus right), such that all subjects will receive both MRG-201 and placebo in a double-blinded fashion (Investigators and subjects will be blinded).

Subject treatment assignments across all sites will be randomized using a central Interactive Web Response System.

11.6.2 Evaluation of Success of Blinding

Not applicable

11.6.3 Breaking the Study Blind

The blind may be broken for individual subjects for medical reasons if knowledge of the type of study treatment administered is required to guide appropriate treatment decisions. If such unblinding is necessary, the Sponsor's Medical Monitor must be consulted when possible.

12 DATA HANDLING AND RECORD KEEPING

12.1 Study Files and Patient Source Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include the participant's clinical source documents and Investigator's Study Files.

Participant clinical source documents may include, but are not limited to, hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, radiograph, pathology and special assessment reports and consultant letters.

The investigator will ensure the Study Files are maintained, including the eCRFs and query forms, protocol/amendments, IRB and regulatory approvals with associated correspondence, signed ICFs, study treatment records, staff curriculum vitae and authorization forms, all correspondence and other appropriate documents. Such data shall be secured in order to prevent loss.

The investigator will allow personnel authorized by the Sponsor access to all study data at any time.

12.2 Data Collection Methods

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. An eCRF must be completed for each person who signs informed consent, regardless of the duration of their trial participation.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL. Documents (including laboratory reports, hospital records subsequent to SAEs, etc.) transmitted to the CRO or the Sponsor should

include the assigned subject identifier but should not include the subject's name in order to ensure confidentiality.

Electronic CRFs will be provided for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and maintained in the participant's official electronic study record. The Investigator should consult the eCRF Completion Guidelines for comprehensive instructions for completing the eCRF.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Medidata Rave, a 21 Code of Federal Regulations (CFR) Part 11-compliant data capture system provided by Medidata Solutions, Inc. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.3 Retention of Records

All clinical study documents must be retained by the investigator until at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may need to retain documents longer if required by applicable regulatory requirements or if requested by the Sponsor. The investigator must notify the Sponsor prior to destroying any clinical study records. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and miRagen to securely store the documents in an off-site storage location so that they can be returned to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for off-site storage.

12.4 Protocol Deviations

The investigator and the study site staff are responsible for ensuring the study is conducted in accordance with the schedule of procedures and assessments described in this protocol and in accordance with Good Clinical Practice (GCP). The site must use continuous vigilance to identify and report deviations within 24 hours of knowledge of their occurrence. miRagen standard operating procedures will be followed for the reporting of study deviations.

Intentional deviations from the protocol shall not be made without discussion with the Sponsor except in a medical emergency, when the intent is to reduce immediate risk to the subject. In such cases, the Sponsor, CRO, the IRB and regulatory authorities, as appropriate, should be notified, in accordance with local requirements. In all other cases, the nature of the deviation, the justification for the deviation, and prior written approval of the Sponsor must be documented.

Changes to the protocol may be made only when a written substantial protocol amendment has been approved by the Sponsor and submitted to the IRB and applicable regulatory agencies in accordance with local requirements. Appropriate approval(s) must be obtained before changes can be implemented.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control procedures will be implemented beginning with the data entry system, and data quality control checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

miRagen is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the eCRFs by assigning CRAs to each site. The CRA is responsible for reviewing the eCRFs at regular intervals throughout the study, verifying adherence to the protocol, assuring completeness, consistency and accuracy of the data, reviewing study files and drug accountability. The data will be verified against the original medical records and laboratory results as part of source document verification to ensure validity of the data. The investigator's responsibility is to ensure that any issues detected in the course of a monitoring visit are resolved.

To ensure compliance with GCP and all applicable regulatory requirements, a quality assurance audit may be conducted by the Sponsor or the Sponsor's designee. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to

allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

The investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies (see Section 12.3). In signing this protocol, the investigator understands and agrees to give access to the necessary documentation and files.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

This Section 14 of the Clinical Trial Protocol is subject to the terms of the Clinical Trial Agreement between miRagen Therapeutics, Inc. and the study centers. In the event of a discrepancy between the Clinical Trial Agreement and this Clinical Trial Protocol, the terms of the Clinical Trial Agreement shall control.

14.1 Ethical Conduct of the Study

This study will be conducted in compliance with the ICH GCP guidelines, United States regulations for the ethical conduct of clinical studies under 21 CFR Parts 50, 56 and 312, the Declaration of Helsinki, and with ICH guidelines regarding scientific integrity (E4, E8, E9 and E10). This study will also adhere to all Food and Drug Administration (FDA), state and local regulatory requirements, and requirements for data protection.

14.2 Institutional Review Board Review

Before trial initiation, the investigator and institution must have written and dated approval from an accredited IRB for the study protocol, written ICF, subject recruitment procedures (e.g., advertisements), and any written information to be provided to subjects. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Appropriate reports on the progress of the study will be made by the investigator to the IRB and the Sponsor in accordance with applicable regulations. All correspondence with the IRB should be retained in the investigator's Study File. Copies of IRB approvals should be forwarded to miRagen or its designee.

14.3 Informed Consent Process

An ICF template will be provided by the Sponsor to the investigator for submission to the IRB. Any site-specific changes to the ICF must be approved by the Sponsor prior to its submission to the IRB. The ICF must be approved by the IRB prior to being presented to potential study participants.

Individuals may agree to participate in the clinical trial only after the risks and possible benefits of their participation have been explained and extensively discussed. The investigator will explain the purposes, procedures, and potential risks of the research study in terms suited to their comprehension, as well as their rights as a research subject. Participants will have the opportunity to carefully review the written ICF, discuss the study with their surrogates, and ask questions prior to signing. Written informed consent must be obtained from each study participant or his/her legally acceptable representative prior to conducting any study-related procedures.

The investigator must use the most current IRB-approved ICF for documenting written consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally acceptable representative and by the person obtaining consent. The site must retain the original signed ICF and provide a copy to the subject.

14.4 Confidentiality of Information

Individual subject medical information obtained as a result of this study is considered confidential. The investigator and the study center will adhere to all applicable laws relating to the protection of subject information. To assure that subject confidentiality is maintained, subject data will be identified only by a study-assigned number on any Sponsor forms, reports, publications, or in any other disclosures, except where required by law.

All miRagen and delegated personnel will handle subject data in a confidential manner in accordance with applicable regulations governing clinical research. Subject records will be inspected only in connection with this research project. Information generated as a result of a subject's participation in this study may be disclosed to third parties for research, regulatory, and other purposes in any country as determined by miRagen Therapeutics, Inc. However, subjects will not be individually identified but will be referred to by the study-assigned number.

14.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at miRagen or a designated laboratory. After the study is completed, the de-identified, archived data will be transmitted to and stored at the miRagen or a delegated contract long-term storage vendor, for use by miRagen and its research collaborators. Permission to analyze data and the future use of laboratory specimens will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at miRagen or a designated vendor, and then a long-term storage vendor. These samples could be used for future research performed by miRagen or its collaborators.

15 PUBLICATION POLICY

Publication and/or disclosure of information or data related to this Clinical Trial Protocol is subject to and governed by the Clinical Trial Agreement between miRagen Therapeutics, Inc. and the study center to which the Principal Investigator is a signatory.

After conclusion of the study, investigators in this study may make oral presentations of study results or publish such results in scientific journals or other scholarly media without prior written approval from miRagen Therapeutics, Inc., only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of miRagen Therapeutics, Inc. in an abstract, manuscript or presentation forum;
- The investigator has complied with the terms of the Clinical Trial Agreement and all requests from miRagen Therapeutics, Inc. to delete any references to its confidential information (other than study results);
- The study has been completed at all study sites for at least 2 years.

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17 LIST OF APPENDICES

Appendix A. Schedule of Events for First Cycle of Dosing with MRG-201 and Placebo with 6 Doses at Initial Treatment Cycle

Study Procedure	Screening (up to 28-day window)	Day 1 [a]	Day 2	Days 3 and 5	Day 8	Day 10	Day 12	Day 13	Day 19 (±2 days)	Day 29 (±3 days)	Days 57, 113, 141, 197, 225, 281, 309, 337 (±7 days)	Day 85 (±7 days)	Days 169 and 253 (±7 days)	Day 365/ End of Study (± 7 days) [o]
Informed Consent	X													
Medical History	X													
Inclusion/Exclusion Criteria	X	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination [b]	X	X			X		X		X	X		X	X	X
Weight	X						X					X		X
HIV, Hepatitis B, Hepatitis C	X													
FSH [c]	X													
Pregnancy Test [d]	X	X					X			X		X		X
12-lead ECG [e]	X	X	X				X							
Laboratory Assessments [f]	X	X	X		X		X		X	X		X	X	X
Serum Collection for Antibody Analysis		X					X			X		X	X (Day 169 only)	
6-mm Punch Biopsies [g]		X												
Study Treatment Injections [h]		X		X	X	X	X							
Physician Assessments for Keloid Formation and Volume									X	X	X	X	X	X
Modified Vancouver Scar Scale and POSAS					X		X		X	X	X	X	X	X
DLQI		X			X								X (Day 169 only)	X
Adverse Events [i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sample Collection		X [k]	X [l]				X [k]	X [l]						
Urine Sample Collection for PK [m]		X	X				X	X						
Photography of Biopsy Sites [n]		X								X		X	X	X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic(s); PT = prothrombin time; SAE = serious adverse event

a) Day 1 refers to the first dosing day for the first double-blind active treatment period.
b) Complete physical examination at screening and Day 1; brief physical examination at all other time points.
c) Only for women who are not surgically sterile as confirmation of menopause.
d) Serum pregnancy test at screening and urine pregnancy tests on Days 1, 12, 29, 85 and at the end of the study for female subjects.
e) Performed at screening, predose on Day 1, on Day 2 (approximately 24 hours after Day 1 dosing), and predose on Day 12.
f) Hematology, clinical chemistry, and urinalysis (including microscopy) will be collected predose as indicated in the protocol. Laboratory assessments do not need to be performed on Day 1 if screening laboratory measurements were performed within 3 days prior to Day 1.
g) 6-mm punch biopsy to create two excisional wounds (one treated with MRG-201 and one treated with placebo on Day 1) as described in the Study Manual.
h) Subjects will receive intradermal injections of MRG-201 and intradermal injections of placebo at each time point. Refer to the Study Manual for detailed instructions on intradermal injections – Biopsy Site Selection, Injection, and Brief Photography Instructions.
i) All AEs, including SAEs, will be recorded from the time of administration of the first dose of study treatment on Day 1 until 30 days after the last dose of study treatment or the end of study visit, whichever occurs last. Treatment-related AEs ongoing at the follow-up visit should be followed to resolution or until the investigator considers them "chronic" or "stable."
j) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of study (Day 365) will be recorded on the eCRF.
k) On Day 1 and Day 12, plasma for PK will be drawn at 1 hour (± 10 minutes), 2 hours (± 15 minutes), and 3 hours (± 15 minutes) after injection.
l) On Day 2 and Day 13, plasma for PK will be drawn 24 (± 4) hours after Day 1/12 dosing.
m) A voided urine sample will be collected on Day 1 and 12 predose and 3 hours postdose, Day 2 and 13 (24 ± 4 hours after Day 1/12 dosing).
n) Photography of biopsy wound sites will be performed post-biopsy on Day 1. In addition to the indicated time points, wound sites will be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation (predose if coinciding with a dosing day). Refer to the Study Manual for detailed instructions.
o) End-of-study assessments will be performed on Day 365 or at the final visit for subjects who discontinue treatment early (if the subject has not withdrawn consent).

Appendix B. Schedule of Events for Second Cycle of Dosing with MRG-201 and/or Placebo (6 Doses after Initial Treatment Cycle)

Study Procedure	Monthly Visit for Keloid Identification	Day 1 [a]	Day 2	Days 3 and 5	Day 8	Day 10	Day 12	Day 19 (±2 days)	Day 29 (±3 days)	Subsequent Visits, Every 4 Weeks (±7 days) [k]	Day 365/ End of Study (± 7 days) [l]
Keloid Identification	X									See Appendix A for a complete list of time points and assessments to be performed	See Appendix A for a complete list of assessments to be performed
Vital Signs		X	X	X	X	X	X	X	X		
Physical Examination [b]		X			X		X	X	X		
Weight		X					X				
Pregnancy Test [c]		X							X		
12-lead ECG [d]		X	X				X				
Laboratory Assessments [e]		X	X		X				X		
Study Treatment Injections [f]		X		X	X	X	X				
Physician Assessments for Keloid Formation and Volume [g]		X	X	X	X	X	X	X	X		
Modified Vancouver Scar Scale and POSAS		X			X		X	X	X		
Adverse Events [h]		X	X	X	X	X	X	X	X		
Concomitant Medications [i]		X	X	X	X	X	X	X	X		
Photography of Biopsy Sites [j]		X							X		

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; eCRF = electronic case report form; INR = international normalized ratio; PT = prothrombin time; SAE = serious adverse event

a) Day 1 refers to the first dosing day for the second double-blind active treatment period. Procedures required for the regularly scheduled visit day must also be performed.

b) Complete physical examination on Day 1; brief physical examination at all other time points.

c) Urine pregnancy test on Days 1 and 29 and at the end of the study for female subjects.

d) Performed on Day 1 predose, on Day 2 (approximately 24 hours after Day 1 dosing), and predose on Day 12.

e) Hematology, clinical chemistry, and urinalysis (including microscopy) will be collected predose as indicated in the protocol.

f) Subjects will receive intradermal injections of MRG-201 and/or placebo at each time point, depending on the location of the suspected keloid. Refer to the Study Manual for detailed instructions on intradermal injections – Biopsy Site Selection, Injection, and Brief Photography Instructions.

g) Physician Assessments will be completed predose on dosing visit days.

h) All AEs, including SAEs, will be recorded from the time of administration of the first dose of study treatment on Day 1 until 30 days after the last dose of study treatment or the end of study visit, whichever occurs last. Treatment-related AEs ongoing at the follow-up visit should be followed to resolution or until the investigator considers them "chronic" or "stable."

i) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of study (Day 365) will be recorded on the eCRF.

j) Photography of biopsy sites will be performed predose on Day 1. Refer to the Study Manual for detailed instructions.

k) Following the visit that occurs 29 days after the start of the second cycle of study dosing, re-treated biopsy sites will be followed according to the first cycle visit schedule (Appendix A).

l) End-of-study assessments will be performed on Day 365 or at the final visit for subjects who discontinue treatment early (if the subject has not withdrawn consent).

Appendix C. Schedule of Events for Single Cycle of Dosing with MRG-201 and/or Placebo (12 Doses for Initial Treatment Cycle)

Study Procedure	Screening (up to 28-day window)	Day 1 [a]	Day 2	Days 3, 5, 10, 12, 17, 19, and 24	Day 8	Days 15 and 22	Day 26	Day 27	Day 29 (±1 day)	Day 36 (±2 days)	Days 57, 113, 141, 197, 225, 281, 309, 337 (±7 days)	Day 85 (±7 days)	Days 169 and 253 (±7 days)	Day 365/ End of Study (± 7 days) [o]
Informed Consent	X													
Medical History	X													
Inclusion/Exclusion Criteria	X	X												
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination [b]	X	X			X	X			X			X	X	X
Weight	X								X			X		X
HIV, Hepatitis B, Hepatitis C	X													
FSH [c]	X													
Pregnancy Test [d]	X	X							X			X		X
12-lead ECG [e]	X	X	X						X					
Laboratory Assessments [f]	X	X	X		X	X			X			X	X	X
Serum Collection for Antibody Analysis		X				X (Day 15 only)			X			X	X (Day 169 only)	
6-mm Punch Biopsies [g]		X												
Study Treatment Injection [h]		X		X	X	X	X							
Physician Assessments for Keloid Formation and Volume					X	X			X		X	X	X	X
Modified Vancouver Scar Scale and POSAS					X	X			X		X	X	X	X
DLQI		X			X								X (Day 169 only)	X
Adverse Events [i]		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Sample Collection		X [k]	X [l]				X [k]	X [l]						
Urine Sample Collection for PK [m]		X	X				X	X						

Photography of Biopsy Sites [n]		X							X			X	X	X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; ECG = electrocardiogram; eCRF = electronic case report form; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic(s); PT = prothrombin time; SAE = serious adverse event

a) Day 1 refers to the first dosing day for the first double-blind active treatment period.

b) Complete physical examination at screening and Day 1; brief physical examination at all other time points.

c) Only for women who are not surgically sterile as confirmation of menopause.

d) Serum pregnancy test at screening and urine pregnancy tests on Days 1 29, 85 and at the end of the study for female subjects.

e) Performed at screening, predose on Day 1, on Day 2 (approximately 24 hours after Day 1 dosing), and predose on Day 29.

f) Hematology, clinical chemistry, and urinalysis (including microscopy) will be collected predose as indicated in the protocol. Laboratory assessments do not need to be performed on Day 1 if screening laboratory measurements were performed within 3 days prior to Day 1.

g) 6-mm punch biopsy to create two excisional wounds (one treated with MRG-201 and one treated with placebo on Day 1) as described in the Study Manual.

h) Subjects will receive intradermal injections of MRG-201 and intradermal injections of placebo at each time point. Refer to the Study Manual for detailed instructions on intradermal injections – Biopsy Site Selection, Injection, and Brief Photography Instructions.

i) All AEs, including SAEs, will be recorded from the time of administration of the first dose of study treatment on Day 1 until 30 days after the last dose of study treatment or the end of study visit, whichever occurs last. Treatment-related AEs ongoing at the follow-up visit should be followed to resolution or until the investigator considers them "chronic" or "stable."

j) All medications (including over-the-counter medicines, herbal treatments, supplements, and vitamins) administered 30 days before the first administration of study treatment (Day 1) until the end of study (Day 365) will be recorded on the eCRF.

k) On Day 1 and Day 26, plasma for PK will be drawn at 1 hour (± 10 minutes), 2 hours (± 15 minutes), and 3 hours (± 15 minutes) after injection.

l) On Day 2 and Day 27, plasma for PK will be drawn 24 (± 4) hours after Day 1/Day 26 dosing.

m) A voided urine sample will be collected on Day 1 and 26 predose and 3 hours postdose, and Day 2 and 27 (24 ± 4 hours after Day 1/26 dosing).

n) Photography of biopsy wound sites will be performed post-biopsy on Day 1. In addition to the indicated time points, wound sites will be photographed at the time the investigator suspects a keloid may be forming, at the time of observation of an unconfirmed keloid, and at the time of keloid confirmation (predose if coinciding with a dosing day). Refer to the Study Manual for detailed instructions.

o) End-of-study assessments will be performed on Day 365 or at the final visit for subjects who discontinue treatment early (if the subject has not withdrawn consent).

Appendix D. Modified Vancouver Scar Scale

	Scar Characteristic	Score
Vascularity	Normal	0
	Pink	1
	Red	2
	Purple	3
Pliability	Normal	0
	Supple	1
	Yielding	2
	Firm	3
	Ropes	4
	Contracture	5
Height	Flat	0
	<2 mm	1
	2-5 mm	2
	>5 mm	3
	Total score	**11**

Derived from: Fearmonti R, Bond J, Erdmann D, Levinson H. (2010) A review of scar scales and scar measuring devices. Eplasty 10:e43.

Appendix E. The Patient and Observer Scar Assessment Scale (POSAS) v 2.0 EN

POSAS Observer scale

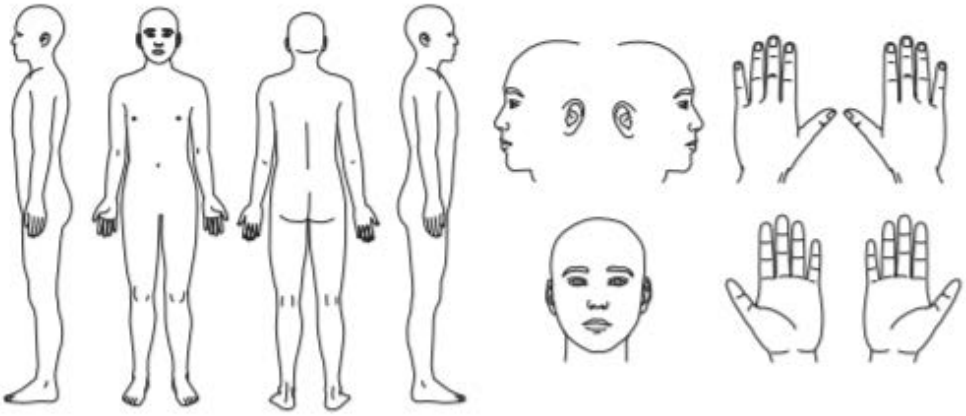
The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination: _____ **Name of patient:** _____

Observer: _____ _____

Location: _____ **Date of birth:** _____

Research / study: _____ **Identification number:** _____



PARAMETER	1 = normal skin	2	3	4	5	6	7	8	9	worst scar imaginable = 10	CATEGORY
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable').
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

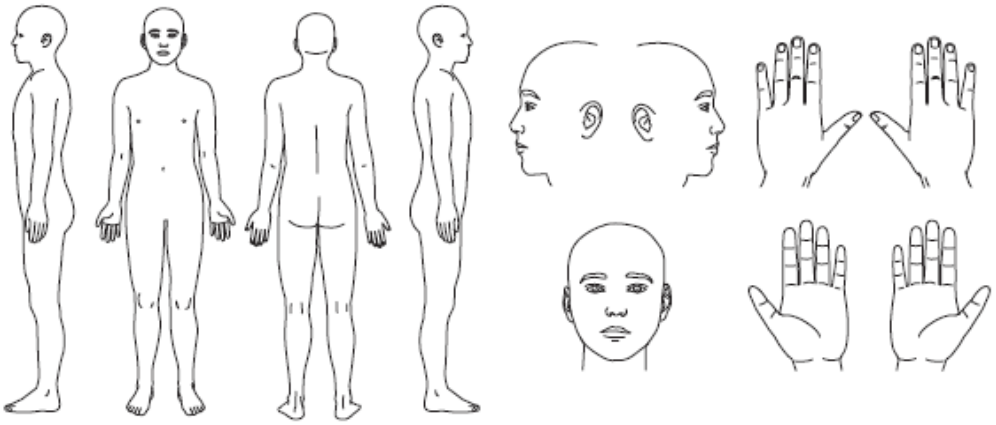
Explanatory notes on the items:

- VASCULARITY Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- PIGMENTATION Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- THICKNESS Average distance between the subcutical-dermal border and the epidermal surface of the scar
- RELIEF The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- PLIABILITY Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- SURFACE AREA Surface area of the scar in relation to the original wound area

POSAS Patient scale

The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination:	**Name of patient:**
Observer:	
Location:	**Date of birth:**
Research / study:	**Identification number:**



	1 = no, not at all … yes, very much = 10
HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?	1 2 3 4 5 6 7 8 9 10
HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?	1 2 3 4 5 6 7 8 9 10

	1 = no, as normal skin … yes, very different = 10
IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?	1 2 3 4 5 6 7 8 9 10
IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	1 2 3 4 5 6 7 8 9 10
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	1 2 3 4 5 6 7 8 9 10
IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?	1 2 3 4 5 6 7 8 9 10

	1 = as normal skin … very different = 10
WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?	1 2 3 4 5 6 7 8 9 10

Appendix F. The Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: ..... **Date:** .....

Name: ..... **Score:** .....

Address: ..... **Diagnosis:** .....

.....

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐		
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ☐ No ☐	Not relevant ☐	
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ☐ A little ☐ Not at all ☐		
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐	

Please check you have answered EVERY question. Thank you.

Appendix G. Estimated Blood Volumes for 6-dose Regimen at Initial Treatment Cycle

Study Day	Time Point	Test	Draw Amount (mL)
Screening (28-day window)		Hematology	4
		Chemistry	8.5
		Serum Pregnancy	(with chemistry)
		HIV, Hep B, Hep C	(with chemistry)
		Total Screening	**12.5**
Day 1		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		PK (1 hour)	5
		PK (2 hours)	5
		PK (3 hours)	5
		Total Day 1	**32.5**
Day 2	24 hours following Day 1 dose	Hematology	4
		Chemistry	8.5
		PK	5
		Total Day 2	**17.5**
Day 8		Hematology	4
		Chemistry	8.5
		Total Day 8	**12.5**
Day 12		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		PK (1 hour)	5
		PK (2 hours)	5
		PK (3 hours)	5
		Total Day 12	**32.5**
Day 19		Hematology	4
		Chemistry	8.5
		Total Day 5	**12.5**
Day 29		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 29	**17.5**
Day 85		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 85	**17.5**
Day 169		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 169	**17.5**

Study Day	Time Point	Test	Draw Amount (mL)
Day 253		Hematology	4
		Chemistry	8.5
	Total Day 253		**12.5**
Day 365 / EOS		Hematology	4
		Chemistry	8.5
	Total Day 365 / EOS		**12.5**
Study total (not including repeats or unscheduled samples)			**197.5***

- **Up to an additional 50 mL of blood will be drawn if a second cycle of dosing is required (6 doses after initial treatment cycle)**

Estimated Blood Volumes for 12-dose Regimen at Initial Treatment Cycle

Study Day	Time Point	Test	Draw Amount (mL)
Screening (28-day window)		Hematology	4
		Chemistry	8.5
		Serum Pregnancy	(with chemistry)
		HIV, Hep B, Hep C	(with chemistry)
	Total Screening		**12.5**
Day 1		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		PK (1 hour)	5
		PK (2 hours)	5
		PK (3 hours)	5
	Total Day 1		**32.5**
Day 2	24 hours following Day 1 dose	Hematology	4
		Chemistry	8.5
		PK	5
	Total Day 2		**17.5**
Day 8		Hematology	4
		Chemistry	8.5
	Total Day 8		**12.5**
Day 15		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
	Total Day 15		**17.5**
Day 22		Hematology	4
		Chemistry	8.5
	Total Day 22		**12.5**
Day 26		PK (1 hour)	5
		PK (2 hours)	5
		PK (3 hours)	5
	Total Day 26		**15**

Study Day	Time Point	Test	Draw Amount (mL)
Day 27	24 hours after Day 26 dose	PK	5
		Total Day 27	**5**
Day 29		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 29	**17.5**
Day 85		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 85	**17.5**
Day 169		Hematology	4
		Chemistry	8.5
		Antibody Serum Sample	5
		Total Day 169	**17.5**
Day 253		Hematology	4
		Chemistry	8.5
		Total Day 253	**12.5**
Day 365 / EOS		Hematology	4
		Chemistry	8.5
		Total Day 365 / EOS	**12.5**
Study total (not including repeats or unscheduled samples)			**202.5**