CLINICAL STUDY PROTOCOL
GT-030

A Single-Center, Open-Label Phase 2a Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Patients with Moderate to Severe Plaque Psoriasis

Study GT-030

Sponsor:	Galectin Therapeutics Inc. 4960 Peachtree Industrial Blvd., Suite 240 Norcross, GA 30071
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Protocol Contributor	Peter G. Traber, MD Chief Medical Officer Galectin Therapeutics 4960 Peachtree Industrial Blvd., Suite 240 Norcross, GA 30071
Version of Protocol:	Protocol Version 5.0
Date of Protocol:	Original: March 26, 2015 Amendment 1: July 16, 2015 Amendment 2: August 20, 2015 Amendment 3: September 18, 2015 Amendment 4: March 14, 2016

CONFIDENTIAL

The study will be conducted according to the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Single-Center, Open-Label Phase 2a Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Patients with Moderate to Severe Plaque Psoriasis
Protocol Number	GT-030
Protocol Date	March 14, 2016

Protocol accepted and approved by:

Chief Medical Officer

Peter G. Traber, MD

4960 Peachtree Industrial Blvd, Suite 240
Norcross, GA 30071

Signature

14 MAR 2016
Date

Protocol Approval – Principal/Coordinating Investigator

Study Title A Single-Center, Open-Label Phase 2a Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Patients with Moderate to Severe Plaque Psoriasis

Protocol Number GT-030

Protocol Date March 14, 2016

Protocol accepted and approved by:

Principal/Coordinating Investigator

Dr. Simon Ritchie

Brooke Army Medical Center, Fort Sam Houston, TX

Ritchie, Simon, Maj, USAF, MC
Staff Dermatologist 1922257146
San Antonio Military Health System

Signature

22 Mar 16

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Single-Center, Open-Label Phase 2a Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Patients with Moderate to Severe Plaque Psoriasis" and the accompanying investigator's brochure, version 4.0, dated 31 August 2015.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 5.0, dated March 14, 2016, the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Galectin Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Galectin Therapeutics.

Ritchie, Simon, Maj, USAF, MC
Staff Dermatologist 1922257146
San Antonio Military Health System

Signature of Principal Investigator

22 Mar 16

Date

Simon Ritchie, MD

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	GT-030
Title:	A Single-Center, Open-Label Phase 2a Clinical Trial to Evaluate the Safety and Efficacy of GR-MD-02 for the Treatment of Patients with Moderate to Severe Plaque Psoriasis
Sponsor:	Galectin Therapeutics Inc. 4960 Peachtree Industrial Blvd., Suite 240 Norcross, GA 30071
Study Phase:	Phase 2
Study Sites:	Single study site at Brooke Army Medical Center, Fort Sam Houston, TX
Indication:	Moderate to Severe Plaque Psoriasis
Rationale:	The overall objective of this exploratory Phase 2 study is to establish the safety and efficacy of GR-MD-02 in subjects with moderate to severe plaque psoriasis. The rationale for this objective is the observation that a subject who received GR-MD-02 at a dose of 4 mg/kg for four doses over a 6-week period in a Phase 1 clinical trial in patients with NASH with advanced fibrosis, reported a complete response of her plaque psoriasis that was durable for at least 11 months.

Objectives:

The overall objective is to establish the safety and efficacy of GR-MD-02 in patients with moderate to severe plaque psoriasis.

Primary objective:

The objective is to evaluate the number of patients with moderate to severe plaque psoriasis who have 75% improvement in Psoriasis Activity Severity Index (PASI-75) following the first 12 weeks of therapy with GR-MD-02

Secondary objectives:

- To determine the PASI-50 and PASI-100 scores in patients with moderate to severe plaque psoriasis following the first 12 weeks of therapy with GR-MD-02
- To determine the PASI-50, PASI-75, and PASI-100 scores in patients with moderate to severe plaque psoriasis following an additional 12 weeks of therapy (total 24 weeks) with GR-MD-02
- To determine the durability of response to therapy in responders over a six-month period following the end of therapy
- To determine whether there is any change in disease status of patients who also have psoriatic arthritis
- To determine the incidence of adverse events and vital sign and laboratory abnormalities during study treatment

Subject Population:

Main Inclusion Criteria: Subjects will be entered into the study if they have biopsy proven psoriasis and active moderate to severe plaque psoriasis with PASI $\geq$ 12 and at least 10% of body area affected.

Additional Inclusion and Exclusion Criteria are outlined in the main protocol.

Study Design:

Study GT-030 is a phase 2a, single-center, open-label study of subjects with moderate to severe plaque psoriasis. All subjects are required to have signed Institutional Review Board (IRB) or Ethics Committee (EC)-approved informed consent prior to undergoing any study specific procedures.

After screening of the subject by the principal investigator for inclusion and exclusion criteria, the patient will have a skin punch biopsy to confirm the diagnosis of plaque psoriasis, unless one has been done previously. Ten (10) subjects who have a PASI (Psoriasis Activity and Severity Index) of ≥ 12 and at least 10% of skin affected will be enrolled in the trial.

Subjects will be administered GR-MD-02 intravenously in a dose of 8 mg/kg lean body weight every other week over 6 months for a total of 13 doses. During the treatment phase of the trial, all subjects in the study will attend study visits according to a schedule of visits for study administration and monitoring. Study assessments performed prior to each drug infusion will include vital signs, limited physical examination, and assessment of adverse events and concomitant medications. Additionally, body weight will be assessed at the first infusion, an ECG will be performed at the third infusion, clinical laboratory tests and urinalysis will be performed at the fourth, seventh, and tenth infusions, and a urine pregnancy test will be performed monthly. Patients will be called one week following each infusion to assess for adverse events. Prior to the first infusion (at baseline visit), before the 4^{th}, 7^{th}, and 10^{th} infusions, before the final infusion, and 30 days following the final infusion, PASI will be evaluated in the patient and full body integument photos will be taken by the Principal Investigator or his co-investigator.

All subjects are to attend a final study visit 30 days after the last dose (or at the time of early discontinuation) to evaluate safety. During this visit, in addition to PASI and integument photography, a final complete physical exam, ECG, clinical laboratory tests, urinalysis, and urine pregnancy test will be performed, vital signs and weight will be measured, and adverse events, if applicable, evaluated. Subjects will have follow up visits at 9 and 12 months after their initial infusion to evaluate disease activity and PASI.

Estimated Study Duration:

Subjects will remain on study therapy for a total of twenty-four (24) weeks and receive 13 total drug doses unless intolerable side effects develop, or the subject is withdrawn from study participation. Subjects may be discontinued at the discretion of the investigator.

Efficacy Assessments:

The primary endpoint will be PASI-75, or a 75% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at the day 84 (week 12) visit.

The secondary endpoints that will be evaluated include:

- PASI-75, or a 75% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 126, day 168, and 30 day follow up visits.
- PASI-50, or a 50% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 84, day 126, day 168, and 30 day follow up visits.
- PASI-100, or a 100% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 84, day 126, day 168, and 30 day follow up visits.
- Durability of response as assessed by PASI-50, 75 and 100 at 9 and 12 months after the initial infusion.

Safety Assessments:

Safety Endpoints:

- Incidence of adverse events during study treatment
- Emergent physical examination abnormalities
- Laboratory parameter abnormalities

Study Drug, Dosage, and Route of Administration:	GR-MD-02 (galactoarabino-rhamnogalacturonate) is provided as an aqueous solution and is dissolved at a concentration of 30 mg/ml in 7 mM phosphate buffered saline, pH 6.5, and provided in single use 10 mL vials. Subjects will receive GR-MD-02 in a dose of 8 mg/kg lean body weight (up to a maximum of 800 mg total). The study drug will be diluted in 100 ml of normal saline and infused intravenously over 30 min. The study drug will be administered every other week for 24 weeks for a total of 13 doses. No dose modification for GR-MD-02 is allowed. Phase I data from another trial using GR-MD-02 at the same dose as in this protocol has been submitted to the FDA which demonstrated no clinically meaningful adverse effects from the infusion of this medicine. Lean body mass (LBM) will be used for dosing because GR MD 02 is distributed primarily in the blood compartment. LBM will be estimated from height and weight measurements using formulas (Janmahasatian, et al. Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44: 1051-1065): • Males: LBM = 9270 X TBW / (6680 + 216 X BMI) • Females: LBM = 9270 X TBW / (8780 + 244 X BMI) Where TBW (total body weight) is in kg and BMI is mass (kg)/height (m)2.
Sample Size:	10 subjects will be enrolled in this exploratory study.
Statistical Methods:	Formal statistical analysis was not used to evaluate sample size in this study. A positive study will be considered a PASI-75 in ≥ 5 out of the 10 patients.
Date of Protocol:	March 14, 2016

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AP	alkaline phosphatase
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration-time curve from zero up to an infinite time
$AUC_{0\text{-}t}$	area under the concentration-time curve from zero up to a definite time
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	observed maximum plasma or serum concentration after administration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CV	curriculum vitae
ECG	Electrocardiogram
eCRF	electronic case report form
FAS	full-analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyltransferase
GI	Gastrointestinal
HBsAg	hepatitis B surface antigen
Hct	Hematocrit
Hgb	Hemoglobin
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
ITT	intent to treat

Abbreviation	Definition
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PASI	Psoriasis Activity and Severity Index
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	per protocol
PPS	per-protocol set
PSA	prostate-specific antigen
RBC	red blood cell
SAE	serious adverse event
TDD	total daily dose
TEAE	treatment-emergent adverse event
T_{max}	time to reach the observed maximum (peak) concentration
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell

1 Introduction

This clinical trial includes subjects with moderate to advanced plaque psoriasis. The reason for this focus is an observed clinical effect on psoriasis found in a phase 1 clinical trial for another indication, as will be described below.

GR-MD-02 is a complex carbohydrate drug that is delivered by intravenous infusion, which binds to galectin molecules, predominantly galectin-3, and inhibits their function. Galectin-3 is a galactose binding protein that has functions in the regulation of both adaptive and innate immunity as well as in tissue repair/fibrosis, and angiogenesis (1). In experimental models, galectin-3, as well as other galectin proteins, appear to have roles in a number of inflammatory, fibrotic, and neoplastic diseases. Experiments performed in animal models has shown that GR-MD-02 is able to reduce the inflammation in steatohepatitis (2) and to reduce and reverse liver fibrosis in both steatohepatitis and in a toxic model of liver fibrosis (3).

As a result of these preclinical findings in steatohepatitis and liver fibrosis, a Phase 1 clinical trial was conducted to characterize the safety, tolerability and dose-limiting toxicities (DLTs) for GR-MD-02 when administered intravenously to subjects with biopsy-proven NASH and advanced liver fibrosis. This trial was designed as an ascending dose cohort study which showed that doses of GR-MD-02 of 2 mg/kg, 4 mg/kg, and 8 mg/kg lean body weight given as single and multiple infusions (four total) over 6 weeks was safe and well tolerated. Results and pharmacokinetics are described in the Investigator brochure.

Thirty (30) patients total, 20 receiving active drug and 10 receiving placebo, completed the Phase 1 clinical trial. Of these patients, 4 were found to have a previous diagnosis of psoriasis and all four of these were in the active group as shown in the table below.

Subject #	Randomization #	GR-MD-02 dose	Psoriasis	Onset of Pso
1152-005	201	4 mg/kg	Yes	2010
1143-001	108	2 mg/kg	Yes	2010
1143-003	205	4 mg/kg	Yes	1991
1151-006	203	4 mg/kg	Yes	2014

Subject #1152-005 was found by the Principle Investigator to have a marked improvement in her psoriasis and she was further questioned about her response by the Principal Investigator of this proposed study, Dr. Simon Ritchie, a board-certified dermatologist. The subject was a 46 year old woman who reported 4-6 years of psoriasis that affected the front and back of

both arms, completely involving her elbows. She described that her elbows looked like "elephant knees" with thick, grey and scaling skin. In addition, she reported raised, "angry looking", erythematous skin associated with pain and pruritus. The rough skin caught on her clothes and she only wore long sleeves because of embarrassment. From the time of its first appearance, the psoriasis severity waxed and waned but was always present. The only therapy she used was topical steroid preparations. During the Phase 1 clinical trial, she began to see improvements after the third infusion, and following the fourth infusion she reported that her psoriasis was "completely gone" and her skin was "normal". Her skin remained normal 11 months after the final infusion of study drug. She is convinced that the improvement in her psoriasis is related to study drug.

After hearing about this incident case, information was gathered on the other three patients in the trial with psoriasis. Patient #1143-001 had a history of relatively mild psoriasis with infrequent flares that was well-controlled with a clobetasol topical preparation. She notes that there was probably was some improvement after receiving study drug because she has now no longer requires the steroid preparation. Subject 1143-003 had moderate to severe psoriasis and had no improvement on study drug, but represents a complicated case. Immediately prior to being enrolled in the Phase 1 study, Stelara (a biologic for psoriasis) had been discontinued and he had a flare of his psoriasis. Subject #1152-005 did not have a definitive diagnosis of psoriasis and his only symptom was dandruff which was not changed by therapy.

These serendipitous findings in a subject with psoriasis in the Phase 1 clinical trial led to this proposed exploratory phase 2 trial. Psoriasis is a common, chronic, relapsing/remitting, immune-mediated skin disease characterized by red, scaly patches, papules, and plaques, which usually itch. The disease affects 2–4% of the general population and may vary in severity from minor localized patches to complete body coverage. There are multiple therapies available for psoriasis including topical corticosteroid preparations, phototherapy, non-biological systemic treatments (methotrexate, cyclosporine, and retinoids), and biologics that interrupt the immune process involved in psoriasis, but are also associated with a small increase in the risk for infection. In addition to the currently marketed biologics (etanercept, adalimumab, infliximab, and ustekinumab), there are novel products in development such as Eli Lilly's ixekizumab, Amgen's brodalumab, Novartis' secukinumab, Merck's MK-3222, Pfizer's Xeljanz (tofacitinib), Celgene's apremilast, and Biocon's Alzumab (itolizumab).

While dermatologists agree that the current biologics have revolutionized the psoriasis landscape, there is a need for therapies that can provide long-lasting effects, without side effects or an increased risk of comorbidities. It is in this regard that we wish to explore the

use of GR-MD-02. This anti-galectin agent could add to the therapeutic armamentarium if the following conditions are met: 1) Efficacy as good or better at improving disease as current biologics; 2) Potential for remission of disease would be desirable since other biologicals do not induce long term remission; 3) Minimal adverse effects including infection; and 4) Lower cost than current biologicals.

In addition to the observation of improvement in a patient in the Phase 1 clinical trial, there are other biological reasons why GR-MD-02 might be effective in psoriasis. A number of galectin proteins are expressed in skin and are involved in cutaneous immunity and a number of skin disorders including atopic dermatitis, contact dermatitis, and psoriasis (4). While it appears there may be different, and sometimes opposite effects, of various galectin proteins, galectin-3 is markedly up-regulated in the capillary epithelia of psoriatic dermis (4, 5). This finding has led to the suggestion that galectin-3 may be involved in capillary changes in the psoriatic dermis and inflammatory cell recruitment (5).

What about testing in animal models of psoriasis? While animal models may provide some insight into various mechanisms of cutaneous inflammation, no models appear to recapitulate the complex nature of the human disease state (6). Therefore, because of the scientific data that suggests galectin-3 may have a role in psoriasis, the anti-inflammatory effect of GR-MD-02 in other pre-clinical models, and the marked effect in one patient in the Phase 1 trial, we feel that it is most relevant to perform a small, open label exploratory study in subjects with moderate to severe plaque psoriasis.

GR-MD-02 (galactoarabino-rhamnogalacturonate) represents a new class of drug that acts through binding to galectin proteins. GR-MD-02 is a complex carbohydrate molecule derived from a natural plant compound which has an average molecular weight of 54.8 KDa. Galectin-3 protein binds to terminal galactose residues on glycoproteins, thereby acting to modulate the function of those glycoproteins in various cellular processes including signaling, cell-cell interactions, and cell-matrix interactions. Single and multiple dose toxicology studies for up to 3 months in rats and monkeys and the safety results of the Phase 1 clinical trial (GT-020) do not predict significant clinical adverse events, as summarized in the Investigator Brochure. There are no known adverse class effects of galectin inhibitors. The route of administration is intravenous infusion and the dose chosen is the top dose from Phase 1 clinical trial given once every other week over three months for a total of 7 doses.

2 Study Objectives

2.1 Primary Objective(s)

The primary objective of this study is to evaluate the number of patients with moderate to severe plaque psoriasis who have 75% improvement in Psoriasis Activity Severity Index (PASI-75) following the first 12 weeks of therapy with GR-MD-02.

2.2 Secondary Objective(s)

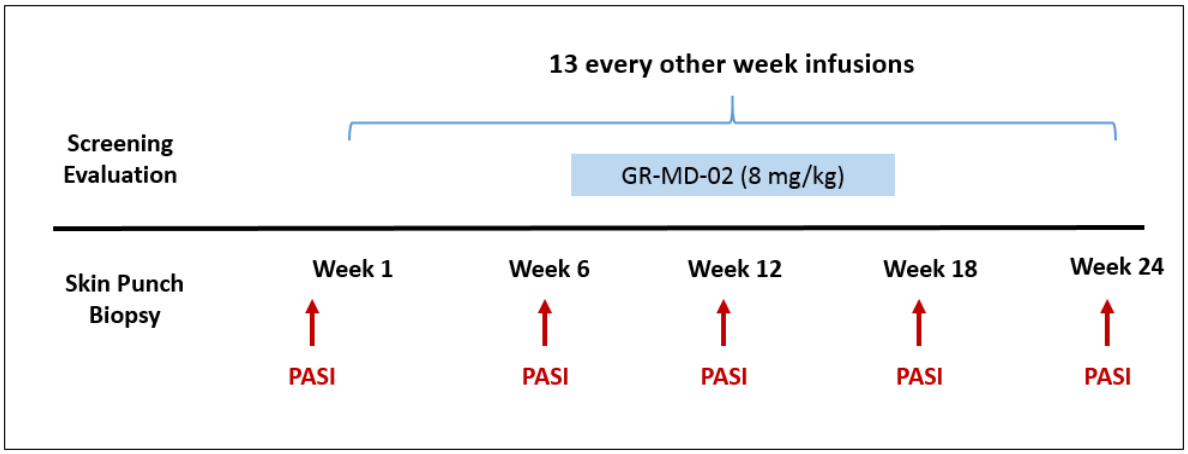
The secondary objectives of this study are:

- To determine the PASI-50 and PASI-100 scores in patients with moderate to severe plaque psoriasis following the first 12 weeks of therapy with GR-MD-02
- To determine the PASI-50, PASI-75, and PASI-100 scores in patients with moderate to severe plaque psoriasis following an additional 12 weeks of therapy (total 24 weeks) with GR-MD-02
- To determine the durability of response to therapy in responders over a six-month period following the end of therapy
- To determine the incidence of adverse events and vital sign and laboratory abnormalities during study treatment

3 Investigational Plan

3.1 Study Design

Study GT-030 is a phase 2a, single center, single group, non-controlled, non-blinded, open label study of subjects with moderate to severe plaque psoriasis. Below is a graphical representation of the study design. All subjects are required to have signed Institutional Review Board (IRB) or Ethics Committee (EC)-approved informed consent prior to undergoing any study specific procedures.



After screening of the subject by the principal investigator for inclusion and exclusion criteria, the patient will have a skin punch biopsy to confirm the diagnosis of plaque psoriasis, unless one has been done previously. Ten (10) subjects who have a PASI (Psoriasis Activity and Severity Index) of ≥ 12 or at least 10% of skin affected will be enrolled in the trial.

Subjects will be administered GR-MD-02 intravenously in a dose of 8 mg/kg lean body weight every other week over 6 months for a total of 13 doses. During the treatment phase of the trial, all subjects in the study will attend study visits according to a schedule of visits for study administration and monitoring (see Section 6.1). Study assessments performed prior to each drug infusion will include vital signs, limited physical examination, and assessment of adverse events and concomitant medications. Additionally, body weight will be assessed at the first infusion, an ECG will be performed at the third infusion, clinical laboratory tests and urinalysis will be performed at the fourth, seventh, and tenth infusions, and a urine pregnancy test will be performed monthly. Patients will be called one week following each infusion to assess for adverse events.

Prior to the first infusion (at baseline), before the 4th, 7th, and 10th infusions, before the final infusion, and 30 days following the final infusion, PASI will be evaluated in the patient and full body integument photos will be taken by the Principal Investigator or his co-investigator.

All subjects are to attend a final study visit 30 days after the last dose (or at the time of early discontinuation) to evaluate safety. During this visit, in addition to PASI and integument photography, a final complete physical exam, ECG, clinical laboratory tests, urinalysis, and urine pregnancy test will be performed, vital signs and weight will be measured, and adverse events, if applicable, evaluated. Subjects will have follow up visits 9 and 12 months after their initial infusion to evaluate disease activity and PASI.

3.1.1 Rationale of Study Design

The overall objective of this exploratory Phase 2 study is to establish the safety and efficacy of GR-MD-02 in subjects with moderate to severe plaque psoriasis. The design is a straightforward, exploratory phase 2a study to evaluate drug effect in an open-label design.

The rationale for this objective is the observation that a subject who received GR-MD-02 at a dose of 4 mg/kg for four doses over a 6-week period in a Phase 1 clinical trial in patients with NASH with advanced fibrosis, reported a complete response of her plaque psoriasis that was durable for at least 11 months. The design is appropriate to determine whether to progress this treatment to a larger, dose ranging phase 2 clinical trial.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 10 subjects will be enrolled at 1 site in the United States, Brooke Army Medical Center, Fort Sam Houston, TX. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Is capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements.
2. Is between the ages of 18 and 75 years.
3. Has biopsy proven psoriasis and active moderate to severe plaque psoriasis with a PASI of ≥ 12 and at least 10% of involved body surface area.
4. The patient is not pregnant and must have a negative pregnancy test prior to start of the study. Post-menopausal women must have been amenorrheic for at least 12 months to be considered of non-child-bearing potential.
5. Sexually active men or women of childbearing potential must agree to use effective means of contraception throughout their participation in this study and for 90 days after discontinuation of study medication.
6. Lactating females must agree to discontinue nursing before the start of study treatment and refrain from nursing until 90 days after discontinuation of study medication.
7. Male subjects must refrain from sperm donation throughout the study period and for a period of 90 days following the last dose of study drug.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Any medical illness that is not stable on therapy

2. Use of any biologic medication for psoriasis within 6 months

3. Use of non-biological systemic therapy to include: methotrexate, oral retinoids, phototherapy/PUVA, cyclosporine, or any other cytotoxic or immunosuppressive medication within 4 weeks of start of study

4. Topical treatment that is likely to impact signs and symptoms of psoriasis, *in the opinion of the Principal Investigator*, within 2 weeks of the start of study

5. Prior exposure to GR-MD-02

6. Known positivity for Human Immunodeficiency Virus (HIV) infection

7. Any patient who had major surgery within 8 weeks of Day 1, significant traumatic injury, or anticipation of need for major surgical procedure during the study.

8. Has a history of alcohol/drug abuse.

9. Any patient who has clinically significant and uncontrolled cardiovascular disease (e.g., uncontrolled hypertension, myocardial infarction, unstable angina), New York Heart Association (NYHA) Grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or Grade II or greater peripheral vascular disease within 12 months prior to Day 1.

10. Any patient with concurrent infection including diagnoses of fever of unknown origin (FUO) (subjects must be afebrile at the start of therapy).

11. History of malignant disease with a recurrence of that disease within 5 years of follow-up except for those that have been curatively treated including basal or squamous cell carcinoma of the skin and in situ carcinoma of the cervix

12. Participation in an investigational new drug (IND) trial in the 30 days before randomization.

13. Clinically significant medical or psychiatric condition considered a high risk for participation in an investigational study.

14. Has donated or lost a significant volume (>450 mL) of blood or plasma within 30 days of the study.

15. Failure to give informed consent

16. Subjects with known allergies to the study drug or any of its excipients.

17. Is an employee or family member of the investigator or study site personnel.

4.2 Withdrawal of Subjects From the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the last follow-up visit at 12 months from their initial infusion.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The reasons for subjects not completing the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

1. Does not meet the protocol inclusion or exclusion criteria.
2. Noncompliance with the protocol.
3. A serious or intolerable adverse event(s) (AE[s]) that in the investigator's opinion requires withdrawal from the study.
4. Laboratory safety assessments that reveal clinically significant hematological or biochemical changes from the baseline values.
5. Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal.
6. Lost to follow-up.
7. Other (e.g., pregnancy, development of contraindications of use of study drug).
8. The subject withdraws consent or the investigator or sponsor decide to discontinue the subject's participation in the study.

The investigator will also withdraw a subject if Galectin Therapeutics terminates the study by withdrawal of study drug. Upon occurrence of a serious or intolerable AE, the investigator will confer with Galectin Therapeutics. If a subject is discontinued because of an AE, the event will be followed until it is resolved. Any subject may withdraw his or her consent at any time.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the case report form (CRF). Whenever possible, all subjects who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-study assessments. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. This contact will consist of 2 documented phone calls followed by 1 registered letter.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

4.2.3 Replacements

If subjects discontinue the study before completion of the 24 week treatment phase, they may be replaced by new subjects.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

This is a single-group, unblended, open-label study.

5.2 Treatments Administered

GR-MD-02 for Injection is supplied in a sterile aqueous solution of phosphate buffered saline at a concentration of 30 mg/ml GR-MD-02 and should be diluted to the target dose in normal saline and administered intravenously over a period of 60 minutes. The product is expected to be stable at pH 4.0 to pH 7.5.

Phase I data from another trial using GR-MD-02 at the same dose as in this protocol has been submitted to the FDA which demonstrated no clinically meaningful adverse effects from the infusion of this medicine.

GR-MD-02 solution will be supplied in 10 mL vials with the following composition to the clinical study site (Table 1).

Table 1 Composition of GR-MD-02 Concentrate

Ingredient	Concentration
GR-MD-02	300 mg
USP Sodium Chloride	82 mg
USP Disodium Phosphate Heptahydrate	14.4 mg
USP Monosodium Phosphate Monohydrate	2.4 mg
USP Sterile Water for Injection	to 10 mL

The 10 mL vials of GR-MD-02 for Injection (30 mg/mL) are to be stored under refrigerated conditions at 2°C to 8°C until preparation of the drug infusion solution. To prepare the final infusion solution for administration, the GR-MD-02 can be diluted in sterile normal saline as required to achieve the target dose. Instructions on dosing preparation are provided in the pharmacy manual.

Once the infusion solutions are prepared, they may be stored at controlled room temperature and should be administered within 24 hours of preparation. Infusions should be administered

intravenously over a period of 60 minutes. Frequency of administration should be once every 2 weeks (bi-weekly).

5.3 Identity of Investigational Product

GR-MD-02 (galactoarabino-rhamnogalaturonate) is a soluble and physiologically compatible polysaccharide composed of alternating α-(1,2)-L-rhamnosyl-α-(1,4)-D-galacturonosyl backbone with side branches composed of mainly galactose and arabinose oligosaccharides. GR-MD-02 will be administered as an intravenous (IV) infusion through a peripheral vein over a period of 60 minutes.

GR-MD-02 solution for injection is a clear, light yellow-tan solution, and will be supplied in 10 mL sterile vials at a concentration of 30 mg/mL of phosphate buffered saline.

Detailed instructions for the preparation and administration of the GR-MD-02 by slow IV drip over a period of 60 minutes will be provided in the Pharmacy Manual. The pharmacist will be unblinded to treatment assignment and will prepare the GR-MD-02.

Lean body mass (LBM) will be used for dosing because it is anticipated that many subjects will be obese and GR-MD-02 is distributed primarily in the blood compartment. Lean body mass will be estimated from height and weight measurements using formulas that have been well-validated in obese individuals:

- Males: LBM = 9270 X TBW (total body weight) / (6680 + 216 X BMI)
- Females: LBM = 9270 X TBW / (8780 + 244 X BMI)

Where TBW is in kg and BMI is mass (kg)/height $(m)^2$. Tables of LBM values for a range of heights and weights will be provided to the pharmacies participating in the study as a check on calculations.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Galectin Therapeutics Inc. will provide IMP to the sites. The following drug supplies will be used in the study:

- GR-MD-02, supplied as 10 mL sterile vials

GR-MD-02 for Injection (30 mg/mL) in 10 mL vials are manufactured by Catalent Pharma Solutions, Woodstock, Illinois, and packaged and labeled for the clinical study by Catalent Pharma Solutions, Philadelphia, Pennsylvania.

The GR-MD-02 for Injection (30 mg/mL) vials are to be stored under refrigerated conditions at 2°C to 8°C until preparation of the drug infusion solution. To prepare the final infusion solution for administration, the GR-MD-02 can be diluted in sterile normal saline as required to achieve the target dose. Instructions on dosing preparation are provided in the pharmacy manual.

Once the infusion solutions are prepared, they may be stored at controlled room temperature and should be administered within 24 hours of preparation. Infusions should be administered intravenously over a period of 60 minutes. Frequency of administration should be once every 2 weeks (bi-weekly).

All medication provided to the study site will be prepared, packaged, and labeled by the Sponsor according to Standard Operating Procedures (SOPs), Good Manufacturing Practice guidelines, International Conference on Harmonization Good Clinical Practice guidelines (ICH GCP), and applicable local laws/regulations.

5.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

Current ICH GCP Guidelines require the Investigator to ensure that study drug deliveries from the Sponsor are received by a responsible person (e.g., pharmacist), and:

- That such deliveries are recorded.
- That study drug is handled and stored safely and properly.
- That study drug is only dispensed to study subjects in accordance with the protocol.
- That any unused, including expired, study drug is returned to the Sponsor or designee.

Drug inventory and accountability records for the study drugs will be kept by the Investigator/ pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

The Investigator agrees not to supply study drugs to any persons except the subjects in this study.

The Investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense these test drugs.

A study drug inventory will be maintained by the Investigator/pharmacist. The inventory will include details of material received and a clear record of when they were dispensed and to which subject. At the conclusion or termination of this study, the Investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.

Used and unused study drug must be returned to the Sponsor designated drug destruction facility after drug accountability has been conducted by the Sponsor or representative. With prior approval from the Sponsor and only if required by site operating procedures, used study may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted by the Sponsor or representative. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused study drug must be returned to the Sponsor or designee at the end of the study or upon expiration.

5.4.3 Other Supplies

Intravenous tubing with a filter will be supplied to the site for drug administration.

5.5 Overdose Management

There are no known or expected overdose signs or symptoms associated with GR-MD-02. An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to Galectin Therapeutics Inc. Chief Medical Officer. Overdoses without

signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant CRF.

5.5.1 Treatment of Overdose

There are no specific treatments for overdose. Patient should have a plasma sample drawn for drug levels and observed for 24 hours.

5.5.2 Medication Errors

If there is a medication error in route of administration, such as oral, there are no medical consequences. This should be reported to Galectin Therapeutics Inc.

5.5.3 Treatment of Medication Errors

No specific treatments are indicated.

5.6 Misuse for Illegal Purposes

There are no CNS effects of GR-MD-02 and no abuse potential.

5.7 Treatment Compliance

Subject compliance will be determined by observation of drug infusion in clinic.

5.8 Prior and Concomitant Therapy

Use of all concomitant medications will be recorded in the subject's CRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications. Any changes in concomitant medications also will be recorded in the subject's CRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the CRF.

5.8.1 Prohibited Concomitant Medication (Drugs and Therapies)

Topical treatments likely to impact signs and symptoms of psoriasis or biological or non-biological systemic therapy including acitretin, methotrexate, cyclosporine, phototherapy, or any other cytotoxic or immunosuppressive medication.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an informed consent form (ICF). Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator will also sign the ICF.

6.1 Schedule of Events

The overall schedule of events is outlined in Table 6-1, below.

Table 6–1 Schedule of Events

Procedure	Base line	Day 1	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84	Day 98	Day 112	Day 126	Day 140	Day 154	Day 168	30 day Follow-up	Month 9[4]	Month 12[4]
Visit Window (days)	**–28**	**+1**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**± 7**	**± 7**
Informed consent	X																
Medical history	X														X	X	X
12-lead electrocardiogram	X			X											X		
Serum pregnancy test	X																
Skin punch biopsy[1]	X																
Urine pregnancy test		X		X		X		X		X		X		X	X		
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests[3]	X				X			X			X				X		
Urinalysis	X				X			X			X				X		
Drug administration		X	X	X	X	X	X	X	X	X	X	X	X	X			
PASI	X				X			X			X			X	X	X	X
Integument Photography	X				X			X			X			X	X	X	X
Monitor AEs & Con Meds		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Call patient for AE check one week after infusion		X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: PASI (psoriasis activity and severity index); AE (Adverse Event); Con Med (Concomitant Medications); PE (Physical Examination)

[1] Perform skin punch biopsy to confirm the diagnosis of plaque psoriasis, unless one has been done previously.

[2] Complete PE at Baseline, at 1st and last infusion visits, and 30-day follow-up visits; limited PE at each interim infusion visit.

[3] Clinical laboratory tests include chemistry panel, CBC, platelet count, reticulocyte count, prothrombin time and partial thromboplastin time.

[4] Following the *first* infusion (i.e., Day 1)

6.2 Efficacy Assessments

Efficacy will be primarily assessed using the Psoriasis Area and Severity Index (PASI) as described in the table below.

Table 1 Elements of the Psoriasis Area and Severity Index (PASI)*

		Head	Upper extremities	Trunk	Lower extremities
1	Redness†				
2	Thickness†				
3	Scale†				
4	Sum of rows 1, 2, and 3				
5	Area score‡				
6	Score of row 4×row 5×the area multiplier	row 4×row 5×0.1	row 4×row 5×0.2	row 4×row 5×0.3	row 4×row 5×0.4
7	**Sum row 6 for each column for PASI score**				

**Steps in generating PASI score*
(*a*) Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
(*b*) Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0 = clear; 1–4 = increasing severity)†.
(*c*) Sum scores of erythema, thickness, and scale for each area.
(*d*) Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale (0 = 0%; 1 = <10%; 2 = 10–<30%; 3 = 30–<50%; 4 = 50–<70%; 5 = 70–<90%; 6 = 90–100%).
(*e*) Multiply score of item (*c*) above times item (*d*) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.
(*f*) Add these scores to get the PASI score.
†Erythema, induration and scale are measured on a 0–4 scale (none, slight, mild, moderate, severe)
‡*Area scoring criteria* (score: % involvement)
0: 0 (clear)
1: <10%
2: 10–<30%
3: 30–<50%
4: 50–<70%
5: 70–<90%
6: 90–<100%

6.3 Safety [Tolerability] Assessments

Safety will be determined using evaluation of vital signs and laboratory test as well as documenting AEs during the course of the trial.

6.3.1 Adverse Events

6.3.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or 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, or the development of drug dependency or drug abuse.

6.3.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to 30 days after the last dose of study drug.

Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, electrocardiogram [ECG] changes) or identified from review of other documents (e.g., subject diaries) that are relevant to subject safety.

6.3.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the CRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that meets SAE criteria (Section 6.3.1.1) must be reported to Galectin Therapeutics Inc. immediately (i.e., within 24 hours) after the time site personnel first learn about the event. The following contact information is to be used for SAE reporting:

Office of the Chief Medical Officer, Dr. Peter G. Traber
Galectin Therapeutics Inc., 4960 Peachtree Industrial Blvd, Suite 240, Norcross, GA 30071
SAE Hotline: 713 540-9776
SAE Fax line: 770 864-1327

6.3.1.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild: These events require minimal or no treatment and do not interfere with the subject's daily activities.

Moderate: These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.

Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.1.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.3.1.6 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the CRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.4 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that

occurs during study participation must be reported. To ensure subject safety, each pregnancy must be reported to Galectin Therapeutics Inc. within 2 weeks of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to Galectin Therapeutics Inc.

6.5 Laboratory Analyses

Safety laboratory tests will include hematology (CBC with differential, platelet count, and reticulocyte count), clinical chemistry panel, coagulation tests (PT and PTT), and urinalysis. Any abnormal laboratory test results or other safety assessments (e.g., vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

6.6 Sample Collections

Sample collections for safety labs as indicated in table 6-1 will be analyzed at the Brooke Army Medical Center under prevailing protocols.

7 Statistical and Analytical Plan

7.1 Primary Efficacy Endpoints

The primary endpoint will be PASI-75, or a 75% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at the day 84 (week 12) visit.

7.2 Secondary Efficacy Endpoints

The secondary endpoints that will be evaluated include:

- PASI-75, or a 75% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 126, day 168, and 30 day follow up visits.
- PASI-50, or a 50% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 84, day 126, day 168, and 30 day follow up visits.
- PASI-100, or a 100% improvement from baseline (day 1, prior to first infusion) in PASI score as assessed at protocol day 42, day 84, day 126, day 168, and 30 day follow up visits.
- Durability of response as assessed by PASI-50, 75 and 100 at 9 and 12 months from initial infusion.

7.3 [Other or Exploratory] Efficacy Endpoints

Principal investigator assessment of psoriatic arthritis, if present.

7.4 Sample Size Calculations

Formal sample size calculations were not done for this exploratory study. A total of 10 subjects (male or female) will be enrolled in the study. This number was chosen to determine whether ≥ 50% of subjects would achieve the primary endpoint which would make the therapy in a similar range as other biological therapies for moderate to severe plaque psoriasis.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full-analysis set (FAS): The FAS will consist of all participants who were assigned to receive study drug. The FAS can also be called the intent-to-treat [ITT] set.

Per-protocol set (PPS): The PPS will consist of all FAS participants who fulfill all inclusion/exclusion criteria, have at least 75% compliance with study treatment, have not

taken any prohibited medication and have no significant protocol deviations. All analyses using the PPS will group participants according to treatment actually received.

Safety set: The safety set will consist of all participants who received any study drug. All analyses using the safety set will group participants according to treatment actually received.

The PPS set will be used as the primary efficacy analysis set.

7.6 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

7.7 Statistical Analysis Methodology

No formal significance testing will be performed.

7.7.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint will be considered reached if ≥ 50% of subjects meet the primary endpoint.

7.7.2 Analysis of Secondary Efficacy Endpoint

The secondary efficacy endpoints will be considered reached if ≥ 50% of subjects meet the secondary endpoint.

7.7.3 Analyses of [Other or Exploratory] Efficacy Endpoint

No statistical analysis.

7.7.4 Safety Analyses

Clinical AEs will be displayed by SOC in the data listings for each subject, with summary tabulations by SOC for each treatment group, using MedDRA coding. Absolute laboratory values, changes in laboratory values from Baseline, and graded laboratory abnormalities will be displayed for each subject and treatment group.

The proportions of active-dosed subjects experiencing clinical AEs and laboratory abnormalities (overall, and of given types) will be tabulated. The group displays and comparisons for safety results will utilize descriptive statistics. Vital sign data will be

similarly displayed by treatment, using descriptive statistics, and any post-Screen changes in physical examination findings will be summarized in tabular form, by subject and by Data Quality Assurance.

Patient compliance will be assured by records of infusion dates and times.

7.7.5 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate CRFs and source documentation as part of the case histories.

The study site will supply the CRF. All CRFs should be completed legibly in black ink or typed. The CRFs may not be completed in pencil.

All CRF information is to be filled in. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed. A correction should be made by striking through the incorrect entry with a single line and the corrected information should be entered adjacent to the deleted item. The correction must be initialed and dated by the person making the correction.

Each completed CRF must be reviewed, signed, and dated by the investigator in a timely manner. The completed CRF will be collected by clinical monitors as soon as practical after completion. One copy will remain at the site in the investigator’s files.

8 Ethics

8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice, and all applicable regulations.

8.3 Subject Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject or legal guardian.

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/ IEC but will not result in protocol amendments.

9 Investigator's Obligations

9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the Food and Drug Administration (FDA), or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol

- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572

- Curriculum vitae (CV) for the investigator and each subinvestigator listed on Form FDA 1572

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject or legal guardian, and

- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

9.6 Adverse Events and Study Report Requirements

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the Galectin Therapeutics Inc. to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

10 Study Management

10.1 Monitoring

10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (e.g., FDA or other regulatory agency) access to all study records.

The investigator should promptly notify the sponsor and Galectin Therapeutics Inc. of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor and Galectin Therapeutics Inc. Amendments to the protocol must be submitted in writing to the investigator’s IRB/IEC for approval before subjects can be enrolled into an amended protocol.

10.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the subject without prior sponsor approval, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

Although Dr. Simon Ritchie has every intention of completing the study, Dr. Richie reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided

reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

11 Reference List

1. Yang RY, Rabinovich GA, Liu FT. Galectins: structure, function and therapeutic potential. Expert Rev Mol Med 2008;10:e17.

2. Traber PG, Zomer E. Therapy of experimental NASH and fibrosis with galectin inhibitors. PLoS One 2013;8(12):e83481.

3. Traber PG, Chou H, Zomer E, Hong F, Klyosov A, Fiel MI, et al. Regression of fibrosis and reversal of cirrhosis in rats by galectin inhibitors in thioacetamide-induced liver disease. PLoS One 2013;8(10):e75361.

4. Chen HY, Lo C-H, Li C-S, Hsu DK, Liu FT. Galectins and cutaneous immunity. Dermatologica Sinica 2012;30:121-127.

5. Lacina L, Plzakova Z, Smetana K, Jr., Stork J, Kaltner H, Andre S. Glycophenotype of psoriatic skin. Folia Biol (Praha) 2006;52(1-2):10-15.

6. Schon MP. Animal models of psoriasis: a critical appraisal. Exp Dermatol 2008 Aug;17(8):703-712.

12 Protocol Amendments

This section provides a summary of significant changes implemented via protocol amendment to the previous version of the protocol. Minor changes that do not affect the material substance or intent of the original protocol, such as correction of grammatical/typographical errors, minor wording/editorial revisions, date revisions, format changes, etc. are not described in the Description of Changes Table.

12.1 Amendment 1

Location of Change	Description of Change and Rationale (if needed)
• Cover Page	Changed Project Manager from Rex Horton to Adam Allgood
• Protocol Synopsis • 4.1.1. Inclusion Criteria	BSA ≥ 5% and PASI ≥6 increased to BSA ≥ 10% and PASI ≥12. **Rationale:** FDA recommended that Inclusion Criteria be revised to define a moderate to severe population suitable for treatment with a systemic investigational agent.
• Protocol Synopsis • 5.2 Treatments Administered	Added the following sentence: *"Phase I data from another trial using GR-MD-02 at the same dose as in this protocol has been submitted to the FDA which demonstrated no clinically meaningful adverse effects from the infusion of this medicine."* **Rationale:** IRB requested additional wording to the protocol reflecting upon the safety of dosing and justification of dosing/schedule.
• Protocol Synopsis • 3.1 Study Design • 6.1 Schedule of Events	Added ECG to day 28 visit and 30-day follow-up visit. **Rationale:** FDA requested additional ECGs at early steady state (agreed at 1 month) and at the end of the trial.
• 3.1 Study Design • 6.1 Schedule of Events	Added phone call to patient one week following each infusion to assess for adverse events. **Rationale:** FDA request.
• 4.1.2 Exclusion Criteria • 5.8.1. Prohibited Concomitant Medication	Removed exclusion of drugs with a narrow therapeutic window metabolized by CYP3A4, including fast acting opioids (alfentanil and fentanyl), immunosuppressive drugs (cyclosporine, sirolimus, and tacrolimus), some cardiovascular agents (ergotamine, quinidine and dihydroergotamine), and select psychotropic agents (pimozide). **Rationale:** Results of GT-029 Drug-Drug Interaction Study performed to evaluate CYP3A4 enzyme activity utilizing

Location of Change	Description of Change and Rationale (if needed)
	midazolam confirmed that there were no drug-drug interactions and no serious adverse events or drug-related adverse events. As agreed with FDA, upon successful completion of this study, the exclusion of drugs with a narrow therapeutic index metabolized by CYP3A4 can be removed from the protocol.
• 5.8.1. Prohibited Concomitant Medication	Added biological or non-biological systemic therapy including acitretin, methotrexate, cyclosporine, phototherapy, or any other cytotoxic or immunosuppressive medication. **Rationale:** To be consistent with the Exclusion Criteria whereby these therapies/medications are excluded within 6 months of the start of the study. If taken concomitantly during the study, these therapies/medications may also confound the study outcome measures.
• Protocol Synopsis • 3.1 Study Design • 6.1 Schedule of Events	Added urine pregnancy test to the Day 28, 56, 82, and 30-day follow-up visits. **Rationale:** In addition to the baseline serum pregnancy test, FDA requested that a pregnancy test be added monthly during treatment.
• 6.1 Schedule of Events	Revised table (including adding a footnote) to clarify that *complete* Physical Exams will be performed at Baseline, Day 1, Day 82 and at 30-day follow-up visits and *limited* Physical Exams will be performed at the other visits.
• 6.6. Sample Collections	Removed requirement that samples be drawn after an 8 hour fast. **Rationale:** Fasting not required, per Principal Investigator.

12.2 Amendment 2

Location of Change	Description of Change and Rationale (if needed)
• 4.1.2 Exclusion Criteria	Reduced the washout period for the use of non-biological systemic therapy from 6 months to 4 weeks. Added exclusion criterion for topical treatment that is likely to impact signs and symptoms of psoriasis, *in the opinion of the Principal Investigator*, within 2 weeks of the start of study. Added criterion to exclude patients with prior exposure to GR-MD-02. **Rationale:** Principal Investigator request.
• 5.8.1 Prohibited Concomitant Medication	Added topical treatments likely to impact signs and symptoms of psoriasis. **Rationale:** To be consistent with the Exclusion Criteria whereby these therapies/medications are excluded within 2 weeks of the start of the study. If taken concomitantly during the study, these therapies/medications may also confound the study outcome measures.

12.3 Amendment 3

Location of Change	Description of Change and Rationale (if needed)
• 6.1 Schedule of Events	Removed baseline chest X-ray. **Rationale:** IRB request.

12.4 Amendment 4

The purpose of this amendment is to extend the original 12 week treatment period for an additional 12 weeks. Open-label results from the first 3 subjects at 6 weeks show an apparent pharmacodynamic effect. The rationale for extending the treatment period in this exploratory study is to give the study drug more time to maximize its therapeutic effect to better inform potential future phase 2 studies, where it will be important to know *a priori* how long to treat.

Location of Change	Description of Change and Rationale (if needed)
• Protocol Synopsis (Objectives) • Study Objectives (Section 2)	Revised the Primary objective statement to reflect that the primary objective will be evaluation of the number of patients who have achieved PASI-75 following *the first 12 weeks of therapy*. Revised the first Secondary objective statement to reflect that the PASI-50 and PASI-100 scores will be determined following *the first 12 weeks of therapy*. Added a secondary objective to determine the PASI-50, 75, and 100 scores following the *additional 12 weeks of therapy*.
• Protocol Synopsis (Efficacy Assessments) • Statistical and Analytical Plan (Section 7)	Revised the Primary Efficacy endpoint to reflect that PASI-75 will be assessed at the *day 84 (week 12) visit*. Revised the Secondary Objectives to reflect that PASI-50, 75, and 100 will also be assessed during the additional 12 weeks of therapy, i.e., at *day 126 and day 168*.
• Protocol Synopsis • Study Design (Section 3.1)	Increased study drug administration period from over a 3 month period to *over a 6 month period*, resulting in an increase in total doses from 7 to *13*. Included urinalysis, clinical laboratory, full body integument photography, and PASI assessments during the additional 12 weeks of therapy, i.e., at the 7^{th} and 10^{th} infusion visits. Revised the study design pictorial schematic to reflect the additional 12 weeks of therapy.
• Schedule of Events (Section 6.1)	Revised the Schedule of Events table to reflect the additional 12 weeks of therapy and associated assessments.