A PHASE 2B, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE -DOSE STUDY TO EVALUATE THE EFFICACY, SAFETY, AND TOLERABILITY OF NDI-034858 IN SUBJECTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

PROTOCOL 4858-201

FINAL

AMENDMENT 2

VERSION 3.0

04-Feb-2022

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PROTOCOL VERSION HISTORY

Version	Reason for amendment	Main changes to the protocol
1.0 / 21-May-2021	Initial version	N/A
2.0-Amendment 1/ 02-Sep-2021	To add clarity and implement minor corrections to text	Global: Minor administrative changes to the protocol for clarity and to correct typographical or minor errors were implemented.
	To update the list of secondary and exploratory efficacy endpoints for clarity of intended analysis	Section 1.1 and Section 3: The list of secondary and efficacy endpoints was updated.
	To clarify or add the photographic process for biopsies or the photographic process for medical photographs of full body.	Section 1.1; Section 1.3, Table 1; Section 4.1; Section 8.3.11; Section 8.3.11.1 (added section; and Section 8.3.11.2 (added section): Optional medical photographs were added to Week 4 visit. It was also clarified that for all subjects consenting to biopsy collection, the biopsied areas will be photographed and for a subset of subjects who consent to the procedure, photographs of the full body (front and back) will be performed.
	To clarify the list of highly effective methods of contraception.	Section 1.1 and Section 5.1, Inclusion Criterion 7: It was clarified that bilateral tubal ligation or occlusion are both considered as highly effective methods of contraception.
	To clarify which systemic corticosteroid treatments are exclusionary, prohibited, and/or trigger discontinuation of study treatment.	Section 1.1 and Section 5.2, Exclusion Criterion 21; Section 6.4.2, Table 4; and Section 7.1: It was clarified that oral, intravenous, intramuscular, and intralesional injections of corticosteroids are prohibited during the study. In addition, use of oral, intravenous, or intramuscular steroids will lead to subject permanent discontinuation from study treatment.
	To clarify that non-live -attenuated vaccines for COVID-19 are allowed during the study.	Section 1.1 and Section 5.2, Exclusion Criterion 24; Section 6.4.2, Table 4; and Section 7.1: It was clarified that non-live -attenuated vaccines for COVID-19 are allowed during the study.

Version	Reason for amendment	Main changes to the protocol
	To exclude subjects enrolled in previous studies of NDI-034858 to minimize bias.	Section 1.1 and Section 5.2, Exclusion Criterion 27: exclusion criteria added.
	To update or add unscheduled visits, virtual visits, direct-to-subject shipping of study product, and local lab use processes as appropriate, including for COVID-19 mitigation.	Section 1.3; Section 4.2; Section 8.3.4.1 (added section): Unscheduled visits, virtual visits, direct-to-subject shipping of study product processes, as well as process for use of local laboratories were added.
	To update the criteria for mandatory, permanent discontinuation from study treatment from cytopenia of Grade ≥2 to cytopenia of Grade ≥3.	Section 2.2.1, Table 2; Section 7.1; Section 8.3.4; and Section 8.4.7: The reason for permanent discontinuation from study treatment due to cytopenia was updated from cytopenia of Grade ≥2 to cytopenia of Grade ≥3.
	To include a definition of noncompliance pertaining to missed doses.	Section 6.3.2: The number of doses missed to clearly state the definition of noncompliance pertaining to missed doses was added.
	To clarify the process to follow if a subject starts prohibited medication or procedure.	Section 6.4.2: The process to follow if a subject starts prohibited medication or procedure was clarified.
	To clarify the potential reasons for permanent discontinuation from study treatment.	Section 7.1: Potential reasons for subject permanent discontinuation from study treatment were updated.
	To clarify that subjects who discontinue before Day 1 dosing could be replaced.	Section 7.2: It was clarified that subjects who discontinue after Day 1 dosing will not be replaced.
	To clarify the potential reasons for discontinuation from study.	Section 7.2: Potential reasons for subject permanent discontinuation from study were updated
	To clarify that an indeterminate QuantiFERON-TB test result obtained at screening can be repeated once.	Section 8.3.4: It was clarified that a QuantiFERON-TB test can only be repeated once if the result is indeterminate; tests with positive or negative results will not be repeated.
	To update the process for reporting of serious adverse events (SAEs), adverse events of	Section 8.4.6; Section 8.4.7.1 (added section); and Section 8.4.9: The reporting process for SAEs. AESIs, and pregnancies was updated.

Version	Reason for amendment	Main changes to the protocol
	special interest (AESIs), and pregnancies.	
	To incorporate into AESI an extended list of events characteristic of inhibitors targeting other JAK family kinases.	Section 8.4.7: Additional AESIs were included according to the known adverse effects of JAK inhibitors, including major cardiovascular events, thromboembolic events, gastrointestinal perforation, malignancies, infections, and AEs of abnormal liver function tests, and renal dysfunction.
	To clarify the sample size determination.	Section 9.1: The sample size was calculated using two different methods in the original protocol, only the appropriate method was kept in this section.
3.0-Amendment 2/ 04-Feb-2022	To add clarity and implement minor corrections to text	Global: Minor administrative changes to the protocol for clarity and to correct typographical or minor errors were implemented
	To further clarify Inclusion Criterion 7	Section 1.1 and Section 5.1 were updated.
	To correct a typo in Inclusion Criterion 9	Section 1.1 and Section 5.1 were updated.
	To clarify the Schedule of Events	Section 1.3, Table 1: Week 16 column edited to clarify assessments and procedures done only at early termination visits that occur before Week 12.
	To clarify process/timing of eligibility assessment prior to randomization	Section 1.3, Table 1: Footnote a was modified to reflect the clarification. Section 6.3 was updated accordingly.
	To update the criteria for temporary or permanent discontinuation of study drug in case of cytopenia CTCAE Grade ≥2.	Section 2.2.1, Table 2; Section 7.1; Section 8.3.4; and Section 8.4.7 were updated.
	To clarify reporting of adverse events and clinically significant laboratory abnormalities	Section 1.3, Table 1, Footnote r; Section 8.3.1; Section 8.3.2; Section 8.3.3, Section 8.3.4; Section 8.4.4; Section 8.4.6;

Version	Reason for amendment	Main changes to the protocol
		Section 8.4.7 and Section 8.4.9 were updated.
	To update the BMI range indicated in the inclusion criteria	Section 1.1 and Section 5.1: Inclusion criterion 10 was updated.
	To update the laboratory tests allowed for TB screening	Section 1.1; Section 1.3, Foootnote c; Section 5.2, Exclusion Criterion 17; Section 8.3.4, and Section 8.3.4.1 were updated.
	To clarify that intraarticular and intrathecal corticosteroid injections are prohibited	Section 1.1; Section 5.1, Exclusion Criterion 21; Section 6.4.2 (Table 4), and Section 7.1 were updated.
	To clarify that non-live-attenuated boosters for COVID-19 are allowed	Section 1.1; Section 5.2, Exclusion Criterion 24; Section 6.4.2, Table 4; and Section 7.1 were updated.
	To clarify statistical analyses and align with the statistical analysis plan.	Section 1.1;Section 9.2 and Section 9.3.1 were updated.

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/REB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB before the changes are implemented to the study. All changes to the consent form will be IRB/REB approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this study will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and date (DD-MMM-YYYY)
[redacted], MD	[redacted], Early Clinical Development Nimbus Lakshmi, Inc.	[redacted] 07-Feb-2022
[redacted], BSc	[redacted], Scientific and Regulatory Affairs Innovaderm Research Inc.	DocuSigned by: [redacted] 08-Feb-2022 | 11:25:06 EST
[redacted], MSc	[redacted], Biometrics Innovaderm Research Inc.	DocuSigned by: [redacted] 08-Feb-2022 | 11:48:03 EST

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____

(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	adverse event
ADL	activities of daily living
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-HBc	antibody to hepatitis B core antigen
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC%	percentage of the area under the concentration versus time curve
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve from time 0 to infinity
$AUC_{0\text{-}last}$	area under the plasma concentration versus time curve from time 0 to the time of last measurable concentration
$AUC_{0\text{-}tau}$	area under the plasma concentration versus time curve from time 0 to the end of the dosing period
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
C_{avg}	average concentration over the dosing interval
CLr	renal clearance
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CV	coefficient of variation

Abbreviation or Specialist Term	Explanation
CYP3A	cytochrome P450 3A
DDI	drug drug interaction
DILI	drug induced liver injury
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ET	early termination
F%	oral bioavailability
FDA	Food and Drug Administration
FE%	fraction of the dose excreted in urine
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
hADME	human absorption, distribution, metabolism, and excretion
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator Brochure
IC30	30% inhibitory concentration
IC50	half maximal inhibitory concentration
IC50	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation or Specialist Term	Explanation
IL	interleukin
IND	Investigational New Drug
IFNγ	interferon gamma
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
LOCF	last observation carried forward
LMW	low molecular weight
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed effect model repeated measures method
MPV	mean platelet volume
mRNA	messenger ribonucleic acid
N/A	not applicable
NCI	National Cancer Institute
NMSC	nonmelanoma skin cancer
NOAEL	no observable adverse effect level
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI-100	100% improvement from baseline in Psoriasis Area and Severity Index
PASI-50	50% improvement from baseline in Psoriasis Area and Severity Index

Abbreviation or Specialist Term	Explanation
PASI-75	75% improvement from baseline in Psoriasis Area and Severity Index
PASI-90	90% improvement from baseline in Psoriasis Area and Severity Index
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	pharmacodynamic
PDE4	phosphodiesterase Type 4
PGA	Physician's Global Assessment
PK	pharmacokinetic
PLT	platelets
PP	per-protocol
PT	prothrombin time
PUVA	Psoralen and ultraviolet A
QC	quality control
QD	once daily
RBC	red blood cell (count)
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	spray dried dispersion
SOC	system organ class
sPGA	static Physician's Global Assessment
STAT	signal transducers and activators of transcription
$t_{1/2}$	terminal half-life
TB	tuberculosis
TBT	T-Spot.TB test
TEAE	treatment-emergent adverse event
Th	T helper

Abbreviation or Specialist Term	Explanation
T_{max}	time to maximum observed concentration
TNF	tumor necrosis factor
TPGS	d-α-tocopheryl polyethylene glycol 1000 succinate
TYK2	tyrosine kinase 2
UV	ultraviolet
WBC	white blood cell (count)
WHO-DD	World Health Organization - Drug Dictionary
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	Name of Investigational Product: NDI-034858	Name of Active Ingredient: NDI-034858

Title of Study:

A Phase 2b, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Multiple -Dose Study to Evaluate the Efficacy, Safety, and Tolerability of NDI-034858 in Subjects with Moderate to Severe Plaque Psoriasis

Phase of Development:

Phase 2b

Study Sites:

Approximately 60 study sites located in Canada and the United States will participate in this study.

Number of Subjects (planned):

Approximately 250 subjects will be randomized in this study (approximately 50 subjects/arm).

Duration of Study:

The maximum study duration per subject is approximately 20 weeks, including up to 30 days for the screening period, a 12-week treatment period, and a 4-week safety follow-up period.

Investigational Products, Dosage, and Mode of Administration:

NDI-034858 at doses of 2 mg, 5 mg, 15 mg, or 30 mg, or placebo will be orally administered once daily (QD) for 12 weeks. NDI-034858 will be available in 2 mg, 5 mg, and 15 mg strength capsules. Matching placebo will be identical to NDI-034858 but will not contain the active ingredient.

Subjects will be randomized in a 1:1:1:1:1 ratio.

Objectives:

The primary objective is:

- To assess the efficacy of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg for 12 weeks in subjects with moderate to severe plaque psoriasis

The secondary objectives are:

- To assess the safety and tolerability of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg for 12 weeks in subjects with moderate to severe plaque psoriasis
- To evaluate the plasma concentration of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg in subjects with moderate to severe plaque psoriasis

The exploratory objectives are:

- To assess the effects of NDI-034858 on joint pain in subjects with moderate to severe plaque psoriasis and concomitant psoriatic arthritis
- To evaluate the effects of NDI-034858 on histology and messenger ribonucleic acid (mRNA) biomarkers in psoriatic skin plaques (optional skin biopsies and optional tape strips) in subjects with moderate to severe plaque psoriasis

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- To evaluate the effects of NDI-034858 on cytokines and other inflammatory biomarkers in blood in subjects with moderate to severe plaque psoriasis

Endpoints:

Primary efficacy endpoint:

- Proportion of subjects achieving at least a 75% improvement from baseline in Psoriasis Area and Severity Index (PASI-75) at Week 12

Secondary efficacy endpoints:

- Proportion of subjects achieving a Physician Global Assessment (PGA) of clear (0) or almost clear (1) at Week 12
- Proportion of subjects achieving at least a 90% improvement from baseline in Psoriasis Area and Severity Index (PASI-90) at Week 12
- Proportion of subjects achieving a 100% improvement from baseline in Psoriasis Area and Severity Index (PASI-100) at Week 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Week 12

Exploratory efficacy endpoints:

- Proportion of subjects achieving at least a 50% improvement from baseline in Psoriasis Area and Severity Index (PASI-50) at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving PASI-75 at Weeks 2, 4, and 8
- Proportion of subjects achieving PASI-90 at Weeks 2, 4, and 8
- Proportion of subjects achieving PASI-100 at Weeks 2, 4, and 8
- Change from baseline in Psoriasis Area and Severity Index (PASI) at Weeks 2, 4, 8, and 12
- Percent change from baseline in PASI at Weeks 2, 4, 8, and 12
- Change from baseline in PGA at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Weeks 2, 4, and 8
- Proportion of subjects with at least a 2-grade decrease from baseline in PGA at Weeks 2, 4, 8, and 12
- Change from baseline in body surface area (BSA) at Weeks 2, 4, 8, and 12
- Change from baseline in pruritus numeric rating scale (NRS) at Weeks 2, 4, 8, and 12
- Proportion of subjects with a baseline pruritus NRS of 4 or greater achieving at least a 4-point decrease from baseline in pruritus NRS at Weeks 2, 4, 8, and 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 4 and 8
- Change from baseline in pain NRS at Weeks 2, 4, 8, and 12 for subjects with concomitant psoriatic arthritis

Secondary safety endpoints:

- Incidence of adverse events (AEs)

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- Changes in vital signs, clinical laboratory parameters, and electrocardiograms (ECGs)

Secondary pharmacokinetic (PK) endpoint:

- Measurement of plasma concentrations of NDI-034858 in subjects receiving active treatment

Exploratory pharmacodynamic (PD) endpoints:

- Quantification of skin biomarkers (immune cell infiltration and mRNA expression levels) in lesional and non-lesional skin
- Quantification of circulating cytokines and other inflammatory biomarkers

Study Design

This is a Phase 2b, randomized, multicenter, double-blind, placebo-controlled, multiple dose study designed to evaluate the efficacy, safety, and tolerability of NDI-034858 in subjects with moderate to severe plaque psoriasis. This study will also evaluate the plasma concentrations of NDI-034858 and explore the immune response (in blood and skin) to NDI034858 in subjects with moderate to severe plaque psoriasis.

Approximately 250 male and female subjects, aged 18 to 70 years (inclusive), with moderate to severe plaque psoriasis will be randomized in this study. To be eligible for the study, the subjects will need to have a history of plaque psoriasis for at least 6 months prior to the screening visit. In addition, the subjects will need to have the following characteristics at screening and on Day 1: PASI score ≥ 12, PGA score ≥ 3, and BSA involved with plaque psoriasis ≥ 10%.

All subjects will read and sign an informed consent form (ICF) prior to any screening procedures being performed. Subjects who fulfill all inclusion criteria and none of the exclusion criteria will be included into the study. During a screening period of no longer than Day -30 to Day -1, subjects will be randomized (on Day -7) to receive either one of the four doses of NDI-034858 (2 mg, 5 mg, 15 mg, or 30 mg), or placebo on Day 1. The goal is to have approximately 50 subjects randomized per treatment group (1:1:1:1:1 ratio) on Day 1. During the treatment period, NDI-034858 (2 mg, 5 mg, 15 mg, or 30 mg) or placebo will be orally administered QD for 12 weeks. The 12-week treatment period will be followed by a 4-week safety follow-up period.

For scheduled study visits, subjects will come to the study site on 8 occasions: screening, Day 1, and Weeks 1, 2, 4, 8, 12 (end of treatment [EOT]), and 16 (end of study [EOS] / early termination visit [ET]).

Efficacy will be assessed using PASI, PGA, BSA involved with plaque psoriasis, pruritus NRS, and pain NRS for subjects with concomitant psoriatic arthritis. Quality of life will be evaluated using DLQI.

Safety will be assessed by collecting AEs, recording vital signs, performing physical examinations, and evaluating clinical laboratory and ECGs results.

Blood samples will be collected to measure plasma levels of NDI-034858 as follows:

- On Day 1 prior to dosing and 1 hour (± 5 min) post-dosing;
- At Week 4 prior to dosing, 1 hour (± 5 min) postdosing, and 4 hours (± 10 min) post-dosing;
- At Week 8 prior to dosing;

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- At Week 12 anytime (no study treatment administration at this visit).
- At ET visit anytime (if ET visit is planned before Week 12 visit).

Urine samples will be collected on Day 1, and at Weeks 4, 12, and 16 and may be used to evaluate the effect of NDI-034858 on exploratory biomarkers.

Blood samples will be collected on Day 1, and at Weeks 4 and 12 to evaluate the effect of NDI-034858 on circulating inflammatory biomarkers.

In a subset of subjects who consent to the procedure, the effect of NDI034858 on skin biomarkers will be evaluated by collecting three or four optional skin biopsies. Two 5-mm punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected on Day 1, and one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar, even if the lesion has cleared) at Week 12. In addition, one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies. Photographs of biopsied areas will be performed.

In a subset of subjects who consent to the procedure, the effect of NDI034858 on skin biomarkers will be evaluated by collecting tape strips. Skin tape strips will be collected from lesional skin and from adjacent non-lesional skin on Day 1, and from same lesional skin at Week 12.

At certain study sites, in a subset of subjects who consent, optional medical photographs of full body, front and back, will be taken to illustrate the outcome of the study.

No interim analysis is planned in this study.

Inclusion/Exclusion Criteria:

Inclusion criteria:

In order to be eligible to participate in this study, a subject must meet all following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Male or female subject aged 18 to 70 years, inclusive, at the time of consent.
2. Subject has a history of plaque psoriasis for at least 6 months prior to the screening visit.
3. Subject had no significant flare in psoriasis for at least 3 months before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has moderate to severe plaque psoriasis as defined by a PASI score ≥ 12 and a PGA score ≥ 3 at screening and Day 1.
5. Subject has plaque psoriasis covering ≥ 10% of his or her total BSA at screening and Day 1.
6. Subject must be a candidate for phototherapy or systemic therapy.
7. For female subjects of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided vasectomy was performed ≥ 4 months prior to

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screening), bilateral tubal ligation or occlusion, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

Note: Subjects must have been on a stable dose of combined hormonal contraceptives for at least 4 weeks before Day 1.

Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study, and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods) is not acceptable.

Note: A female subject of nonchildbearing potential is defined as follows:

- Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy);
- Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

8. Female subjects of childbearing potential have had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
9. For male subjects involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 7, from Day 1 until at least 12 weeks after the last study product administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 12 weeks after the last study product administration.

   Note: Male subjects must refrain from donating sperm from Day 1 until at least 12 weeks after the last study product administration.

   Note: No restrictions are required for a male subject who underwent a vasectomy at least 4 months prior to screening and the procedure is documented. If vasectomy procedure is not documented or was performed less than 4 months prior to screening, male subjects must follow the same contraception and sperm donation requirements as for nonvasectomized subjects.
10. Subject has a body mass index (BMI) within the range of 18 to 42 kg/m^2, inclusive (BMI = weight [kg]/[height (m)]^2), and total body weight >50 kg (110 lb).
11. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
12. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

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1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or -drug induced psoriasis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has immune-mediated conditions commonly associated with psoriasis, such as psoriatic arthritis, uveitis, inflammatory bowel disease, that require systemic treatment (including corticosteroids, immunosuppressants, or biologics).

   Note: Subjects with immune-mediated conditions that do not require systemic treatment may be included in the study. Certain therapies such as NSAIDs may be permitted but should be discussed with the Medical Monitor prior to determination of subject eligibility.
5. Subject has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, or local active infection/infectious illness), psychiatric condition, or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
6. Subject had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
7. Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
8. Subject has been hospitalized in the past 3 months for asthma, has ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or has required more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within 6 months prior to Day 1.
9. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
10. Subject has a history of fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection within 4 weeks prior to Day 1.
11. Subject has an active bacterial, viral, fungal, mycobacterial infection, or other infection (including TB or atypical mycobacterial disease), or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 12 weeks prior to Day 1, or oral antibiotics within 4 weeks prior to Day 1.
12. Subject has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection, recurrent urinary tract infection, fungal infection (except for superficial fungal infection of the nailbed), or infected skin wounds or ulcers.

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13. Subject has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis if that prosthesis has not been removed or replaced.
14. Subject has active herpes infection, including herpes simplex 1 and 2 and herpes zoster (demonstrated on physical examination and/or medical history) within 8 weeks prior to Day 1.
15. Subject has a history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status in the opinion of the investigator (eg, history of splenectomy, primary immunodeficiency).
16. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).
17. Subject has clinical or laboratory evidence of active or latent tuberculosis (TB) infection at screening.

    Note: Subjects with a history of active or latent TB will not be included in the study, unless documentation of prior and complete anti-TB treatment, appropriate in duration and type according to current local country guidelines, can be provided.

    Note: Subject will be evaluated at screening for latent TB infection with a QuantiFERON-TB Gold (QFT) test. Latent TB is defined as a positive QFT test or two successive indeterminate QFT tests at screening.

    Note: The T-Spot.TB test (TBT) is an acceptable alternative to the QFT test in regions where the TBT is standard practice for tuberculosis screening. The medical monitor should be informed prior to using the TBT in place of the QFT test. A negative TBT is required if the QFT test is not performed.
18. Subject with any of the following laboratory values at the screening visit:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 3 times the upper limit of normal (ULN);
    b. Hemoglobin < 11.0 g/dL (< 110.0 g/L);
    c. White blood cell count < 3.5 x 10^9/L (< 3500/mm^3);
    d. Absolute neutrophil count of < 1.8 x 10^9/L (< 1800/mm^3);
    e. Absolute lymphocyte count of < 1.0 x 10^9/L (< 1000/mm^3);
    f. Platelet count < 100 x 10^9/L (< 100,000/mm^3);
    g. Total bilirubin > 2 times the ULN.
19. Subjects who have given > 50 ml of blood or plasma within 30 days of screening or > 500 mL of blood or plasma within 56 days of screening (during a clinical study or at a blood bank donation).
20. Subject has used any topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar) within 2 weeks prior to Day 1.
21. Subject has used any systemic treatment that could affect psoriasis (including oral, intravenous, intramuscular, intraarticular, intrathecal, or intralesional corticosteroids; oral retinoids;

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immunosuppressive/immunomodulating medication; methotrexate; cyclosporine; oral JAK inhibitors; or apremilast) within 4 weeks prior to Day 1.

Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

22. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
23. Subject has had psoralen and ultraviolet A (PUVA) treatment within 4 weeks prior to Day 1.
24. Subject has received any live-attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live-attenuated vaccine during the study and up to 4 weeks or 5 half-lives of the study product, whichever is longer, after the last study product administration.

    Note: Non-live-attenuated vaccines or boosters for Coronavirus Disease 2019 (COVID-19) (eg, RNA-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines) are allowed during the study. The study site should follow local guidelines related to COVID-19.
25. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
26. Subject has received any marketed or investigational biological agent within 12 weeks or 5 -half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criterion 27 and 28 that are to be excluded for 6 months).
27. Subject was previously enrolled in any study with NDI-034858.
28. Subject has a history of lack of response to any therapeutic agent targeting interleukin (IL)-12, IL-17, and/or IL-23 (eg, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab) at approved doses after at least 12 weeks of therapy, and/or received one of these therapies within 6 months prior to Day 1.
29. Subject has received rituximab or other immune cell depleting therapy within 6 months.
30. Subject is currently being treated with strong or moderate cytochrome P450 3A (CYP3A4) inhibitors (such as itraconazole) or has received moderate or strong CYP3A4 inhibitors within 4 weeks prior to Day 1.
31. Subject is currently being treated with terbinafine or has received terbinafine within 4 weeks prior to Day 1.
32. Subject has consumed grapefruit within 1 week prior to Day 1.

    Note: Consumption of grapefruit must be avoided during the treatment period and for at least 1 week after last dose administration.
33. Subject has used tanning booths within 4 weeks prior to Day 1, has had excessive sun exposure, or is not willing to minimize natural and artificial sunlight exposure during the study.

    Note: Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

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34. Subject has a known or suspected allergy to NDI-034858 or any component of the investigational product, or any other significant drug allergy (such as anaphylaxis or hepatotoxicity).
35. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
36. For subjects consenting to biopsy collection only:
    - Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    - Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    - Subject has taken anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, or antiplatelet agents (except low-dose aspirin ≤ 81 mg which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal-anti-inflammatory drugs will not be considered antiplatelet agents and will be allowed.

Statistical methods:

Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

Further details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values (if applicable) will be detailed in a separate statistical analysis plan (SAP) that will be prepared before the database is locked and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final Clinical Study Report, as appropriate.

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified in the SAP. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group and ending with the lowest dose group (30-mg NDI-034858, 15-mg NDI-034858, 5-mg NDI-034858, and 2-mg NDI-034858, in order). No adjustment to alpha will be made to account for multiple testing between treatment groups for the secondary and exploratory efficacy endpoints.

Efficacy Analyses:

The primary endpoint can be translated as a responder analysis, where a subject will be classified as responder if he or she achieves PASI-75 at Week 12. The comparison between groups for the primary endpoint will be done using a Cochran-Mantel-Haenszel (CMH), with prior treatment with biologics included as a stratification factor. The primary efficacy analysis will be performed on the modified intent-to-treat (mITT) analysis set, while the per-protocol (PP) analysis set will be used as a sensitivity analysis.

The secondary endpoints involving proportions of subjects will be analyzed using the same approach (CMH test) as described for the primary efficacy analysis, at each time point and based on the mITT analysis.

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The continuous secondary endpoints involving absolute change from baseline will be analyzed using a mixed effect model repeated measures method (MMRM) based on the mITT analysis set only. The model will include treatment, visit, treatment by-visit interaction, and prior treatment with biologics as fixed effects, and baseline score as a covariate.

Safety Analyses:

All safety analyses will be conducted using the safety analysis set. No inferential statistics will be performed on safety variables.

Adverse events and serious adverse events (SAEs) will be presented and tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) classification by treatment group. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, action taken with respect to the study product, and the outcome.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by system organ class, preferred term, reported verbatim severity, seriousness, and investigator's assessment of the relationship to study product. For the summary of AEs by severity, each subject will be counted only once within a system organ class or a preferred term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a system organ class or a preferred term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a system organ class or a preferred term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by treatment group, subject, detailing verbatim, system organ class, preferred term, start date, stop date, intensity, outcome, action taken with respect to study product, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. Serious adverse events will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing. Similar listings will be provided for the SAEs and AEs leading to the discontinuation from the study.

Results from vital signs, laboratory analyses, and ECGs will be tabulated by treatment group and visit using descriptive statistics. The observed value at each visit, as well as the change from baseline will be presented. Shift tables describing shifts to out-of-normal range will be provided for clinical laboratory results, and normal to abnormal shift tables may be provided for vital signs.

Concomitant medications will be coded with the World Health Organization – Drug Dictionary (WHO-DD) and listed by subject. Summary of medications will also be tabulated.

Pharmacokinetic Analyses:

Concentration data will be listed per subject and summarized descriptively per dose.

Pharmacodynamic Analyses:

Analyses of urine, blood, and skin biomarker levels will be described in a separate analysis plan.

Other Analyses:

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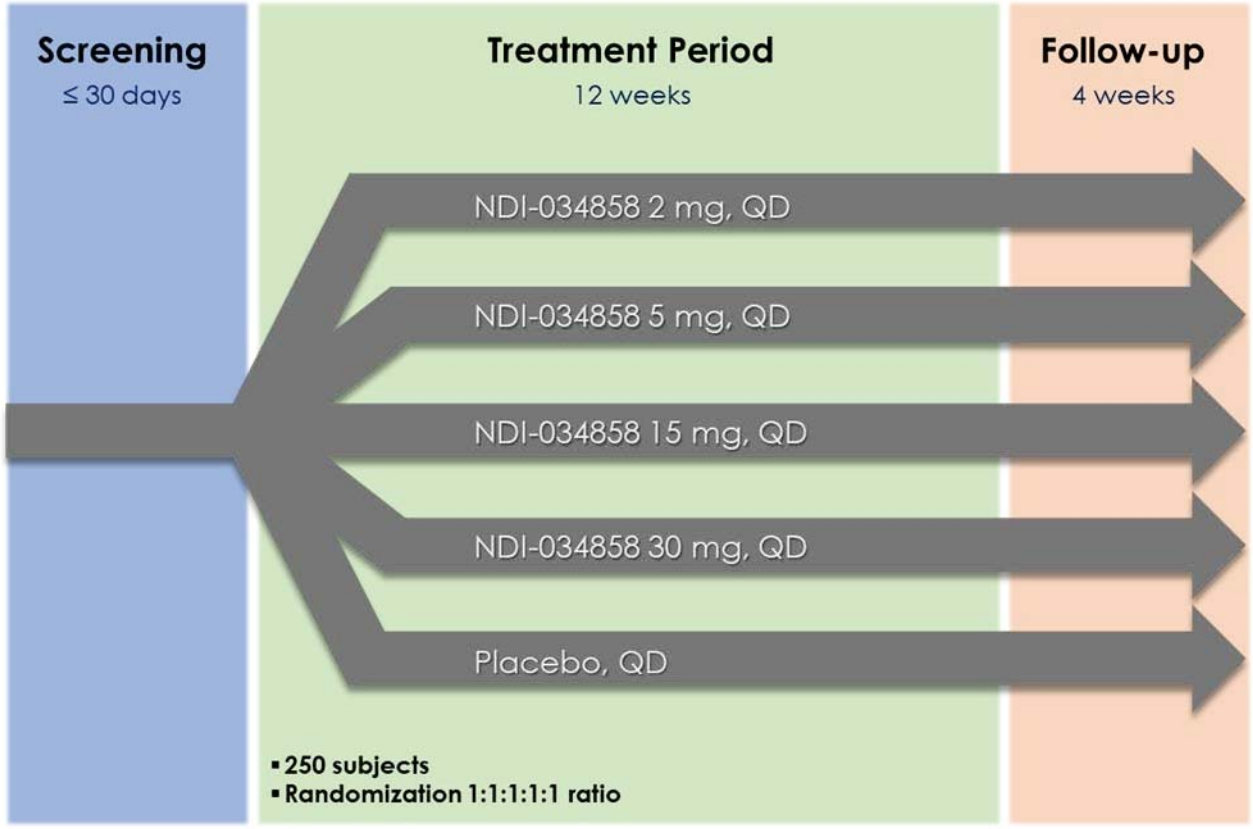
Descriptive summaries of subject disposition and baseline characteristics (including demographic data and prior concomitant therapy) will be presented by treatment group. In addition, a list of subjects who discontinued from the study along with discontinuation reason will be provided. Protocol deviations will be summarized by treatment and category.		
Sample Size Consideration: The sample size determination is based on testing equality of two independent response rates using a 2-sided test with significance level of alpha = 0.05 and power 85%. The formula used for the calculation is the same as used in the nQuery® (ie, normal approximation with Fleiss' formula and continuity correction). Assuming the placebo response rate at end of Week 12 is 10% (proportion of subjects achieving PASI-75), at least one of the NDI-034858 dose treatment groups will have a response rate at least 40%, and after adjustment of 15% dropout rate, a total of 250 subjects (50 per treatment group) will be randomized in the study. Fifty subjects per treatment group, with 1-sided, 2-sample Fisher's exact test at significant level 0.05, will provide at least approximately 90% power to detect at least 30% difference in the response rate in PASI-75 between any two treatment groups.		

1.2. Study Diagram

Figure 1: Study Diagram



Abbreviation: QD, once daily.

1.3. Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF. No treatment or study-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

Unless specified otherwise, the study assessments scheduled during the treatment period must be performed before study product administration, if applicable (no drug administration the day of Week 12 visit).

Quality of life assessment (DLQI), pruritus NRS, and pain NRS (for subjects with concomitant psoriatic arthritis) must be completed prior to other efficacy assessments (PASI, PGA, and BSA involved with plaque psoriasis).

The COVID-19 pandemic may impact the ability to adhere to the study procedures described in Table 1 due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines. Please refer to Section 4.2 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

Every attempt should be made to adhere to the visit schedule. If an unscheduled visit (eg, an additional visit not specified in Table 1) is unavoidable or necessary, the investigator may allow it at his or her discretion. All study-specific unscheduled visits should be documented in the subjects record and the appropriate clinical data should be entered into the Electronic Data Capture (EDC).

Table 1: Schedule of Events

Study Visits	Screening Period		Treatment Period						Follow-up or Early Termination
	Screening Visit	Day -7[a]	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12/End of Treatment	Week 16
Windows (days)	-30 to -8	(±1)		(±2)	(±2)	(±2)	(±3)	(±3)	(±4)
Informed consent	X								
Demographics	X								
Medical and surgical history	X		X						
Inclusion and exclusion criteria	X[a]		X						
Pregnancy test[b]	X		X	X	X	X	X	X	X
Serology (HIV, HBV [HbsAg, anti-HBc], HCV)	X								
QuantiFERON-TB Gold test[c]	X								
Vital signs[d]	X		X	X	X	X	X	X	X
Complete physical examination	X							X	
Targeted physical examination			X			X	X		X
Clinical laboratory tests (hematology, chemistry, urinalysis, FSH[e])	X		X	X	X	X	X	X	X
Urine sample for biomarkers evaluation[f]			X			X		X	X
Fasting lipid panel			X					X	
Electrocardiogram[g]	X		X	X	X	X	X	X	
PASI	X		X		X	X	X	X	X[h]
PGA	X		X		X	X	X	X	X[h]
BSA	X		X		X	X	X	X	X[h]
Pruritus NRS			X		X	X	X	X	X[h]
DLQI Questionnaire			X			X	X	X	X[h]
Pain NRS			X		X	X	X	X	X[h]
Randomization		X							
On-site study product administration[i]			X	X	X	X	X		
Dispense of study product			X	X	X	X	X		
Collection of study product				X	X	X	X	X	X[h]
Subject dosing diary distribution/collection/ review			X	X	X	X	X	X	X[h]
Blood samples for NDI-034858 concentration			X[j]			X[k]	X[l]	X[m]	X[h]

Study Visits	Screening Period		Treatment Period						Follow-up or Early Termination
	Screening Visit	Day -7[a]	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12/End of Treatment	Week 16
Windows (days)	-30 to -8	(±1)		(±2)	(±2)	(±2)	(±3)	(±3)	(±4)
Blood samples for biomarkers evaluation			X			X		X	
Skin biopsies (optional)[n]			X			X[o]		X	
Tape strips (optional)[p]			X					X	
Medical photographs (optional)[q]			X			X		X	
Concomitant medication	X		X	X	X	X	X	X	X
Adverse events evaluation			X[r]	X	X	X	X	X	X

Abbreviations: anti-HBc, antibody to hepatitis B core antigen; BSA, body surface area; DLQI, Dermatology Life Quality Index;; FSH, Follicle-Stimulating Hormone; HbsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; QD, once daily.

[a] Day -7 is not a subject visit and is only planned for randomization. Before Day -7, available eligibility information will be reviewed and Subject Eligibility Form will be submitted for approval. Subject will then be randomized.

[b] For female subjects of childbearing potential only, serum pregnancy test at screening, and urine pregnancy test at the other visits.

[c] A T-Spot.TB test may be used as an alternative to the QuantiFERON-TB Gold test as per Exclusion Criterion 17.

[d] Including height and weight. Height will be measured only at screening.

[e] FSH to be performed at screening only, for females who has had a cessation of menses for ≥ 12 months prior to the screening visit without an alternative medical cause.

[f] Urine collected for urinalysis will be split on Day 1, Week 4, Week 12, and Week 16, and processed for both urinalysis and urine biomarkers evaluation as directed in the laboratory manual.

[g] In addition to the time points specified in the schedule of events, ECGs may be performed at any time during the study if in the opinion of the investigator it is clinically warranted.

[h] Only performed at ET visit if ET visit is planned before Week 12 visit.

[i] Study products will be taken at home QD for 12 weeks, except on visit days, when the study products will be administered on-site. No drug administration the day of Week 12 visit.

[j] Samples to be taken predose and 1 hour (± 5 min) postdose on Day 1.

[k] Samples to be taken predose, 1 hour (± 5 min) postdose, and 4 hours (± 10 min) postdose at Week 4.

[l] Samples to be taken predose at Week 8.

[m] Samples to be taken anytime at Week 12 (no study treatment administration at this visit).

[n] Optional, only for subjects who consent to the procedure: two 5-mm skin biopsies on Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one 5-mm punch biopsy at Week 12 (from same lesional skin; outside the scar of the previous biopsy, at least 1 cm away from the previous scar, even if the lesion has cleared). Biopsied areas will be photographed.

[o] An additional 5-mm skin biopsy (from same lesional skin; outside the scar of the previous biopsy, at least 1 cm away from the previous scar) will be collected at Week 4 for subjects who consent to four biopsies. Biopsied areas will be photographed

Study Visits	Screening Period		Treatment Period						Follow-up or Early Termination
	Screening Visit	Day -7[a]	Day 1	Week 1	Week 2	Week 4	Week 8	Week 12/End of Treatment	Week 16
Windows (days)	-30 to -8	(±1)		(±2)	(±2)	(±2)	(±3)	(±3)	(±4)

[p] Optional, only for a subset of subjects who consent to the procedure: skin tape strips will be collected from lesional skin and from adjacent nonlesional skin on Day 1, and from same lesional skin at Week 12.
[q] At certain study sites, in a subset of subjects who consent, optional medical photographs of full body, front and back, will be taken.
[r] Adverse events evaluation begins after dosing on Day 1.
Note: Unscheduled visits are described in Section 1.3.

2. INTRODUCTION

2.1. Background

2.1.1. Plaque Psoriasis

Plaque psoriasis is a chronic inflammatory skin disorder characterized by thickened and inflamed areas of skin. These plaque regions exhibit a confluent parakeratotic scale, loss of the granular cell layer, increased number of epidermal cell layers, and prominent lymphocyte infiltration.[1] Markers of inflammation and specific immune cell subsets are highly elevated in psoriatic plaques. This includes elevated mRNA and protein levels of IL-23 / T helper (Th) 17 activity (such as IL-23, IL-17A, IL-17F, and IL-22), elevated markers of keratinocyte activation and proliferation, and markers of infiltrating immune cells.[2]

Plaque psoriasis is a prevalent disease worldwide, with 1-2% of people affected, and its severity is generally categorized based on PASI, total BSA affected, and PGA.[3,4] The primary goal of psoriasis therapies is clearance of psoriatic plaques, and the benchmark level of treatment response in most current clinical studies is PASI-75 at Week 12 or 16. This benchmark is readily achieved by the majority of patients treated with biologic therapies targeting tumor necrosis factor (TNF)-α, IL-12/23, IL-23, and IL-17.[5]

While there are multiple biologic agents approved for the treatment of moderate to severe plaque psoriasis, there are a very limited number of oral small molecule therapies available to patients. Some patients can be treated with oral immunosuppressive drugs; however these treatments generally exhibit limited efficacy.[6] The only other approved oral agent for the treatment of plaque psoriasis is a phosphodiesterase Type 4 (PDE4) inhibitor (apremilast), which is generally safe but exhibits significantly lower efficacy than most biologic therapies and has recognized tolerability liabilities including severe diarrhea, nausea, and vomiting in some patients.[5,7,8]

2.1.2. NDI-034858

NDI-034858 is a small molecule allosteric inhibitor that binds to the JH2 pseudokinase domain of tyrosine kinase 2 (TYK2), leading to inhibition of the TYK2 catalytic JH1 kinase domain and subsequent downstream signaling events. The allosteric interaction of NDI-034858 with the TYK2 JH2 domain results in highly selective inhibition of TYK2 kinase activity compared to the other homologous proteins in the Janus kinase (JAK) family of nonreceptor tyrosine kinases (JAK1, JAK2, and JAK3).

Tyrosine kinase 2 (TYK2) catalyzes the phosphorylation of signal transducers and activators of transcription (STAT) proteins downstream of several cytokine receptors, including the IL-23 receptor, as well as the Type I interferon receptor and the IL-12 receptor.[9] The activation of TYK2 dependent receptors by their cytokine ligands results in the activation of STAT---dependent transcription and cellular functional responses specific for the receptors and cell types they are expressed on.[10] The cytokine signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders. Most relevant for psoriasis pathogenesis, the

cytokine IL-23 is central for the expansion and survival of Th17 cells and innate lymphoid cells, both of which have been shown to play key pathogenic roles in autoimmunity.[11] IL-23 stimulation drives the production of key proinflammatory cytokines by Th17 cells, including IL-17A, IL-17F, and IL-22, all of which are effector molecules in psoriatic skin.

2.1.3. Study Rationale

There are currently a very limited number of small oral molecule therapies available to patients with plaque psoriasis. A safe, well-tolerated, and highly efficacious oral therapy for plaque psoriasis would provide an appealing treatment option for both patients and physicians.

NDI-034858 has the potential to add value to the treatment algorithm of psoriasis, particularly considering the lack of highly efficacious oral agents. Inhibition of TYK2 by NDI-034858 is expected to impact psoriasis pathogenesis primarily through its effects on the IL-23/Th17/Th22 axis. In addition, safety and efficacy data in psoriasis presented to date for a TYK2 inhibitor (BMS-986165 or deucravacitinib),[12,13] which also inhibits TYK2 activity through allosteric binding of the JH2 domain, sets the clinical precedence for selectively targeting TYK2 activity in this disease. Specific inhibition of TYK2 is expected to be more efficacious than any current oral therapies and could be comparable to the efficacy observed for some biologic therapies currently in use.

2.1.4. Clinical Experience

2.1.4.1. Study 4858-101

Study 4858-101 was a randomized, single-center, double-blind, placebo-controlled, single, and multiple ascending dose study in healthy subjects 18 to 55 years of age. This study investigated single ascending doses (SAD) of 5 mg, 20 mg, 75 mg, 100 mg, and 200 mg, and multiple ascending doses (MAD) of 20 mg and 35 mg given QD for 14 days. An additional open-label cohort was also included to evaluate the comparative bioavailability of two drug product formulations, the original d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) formulation and a new spray dried dispersion (SDD) formulation, to assess the PK of single oral doses of the SDD formulation of NDI-034858 in healthy subjects under fed and fasted conditions. The SDD formulation is being used in the clinical studies of NDI-034858.

2.1.4.1.1. Safety Results in Study 4858-101

In Study 4858-101, 47 participants (healthy volunteers) were enrolled in single-dose cohorts (35 treated with NDI-034858 ranging from 5 mg to 200 mg, and 12 treated with placebo). Treatment with NDI-034858 was generally safe and well tolerated. A total of 14 of 35 (40%) participants treated with NDI-034858 experienced at least one TEAE, compared with 3 of 12 (25%) treated with placebo. The most common Aes associated with NDI-034858 treatment were acneiform dermatitis/papular rash and aphthous stomatitis; these events were mild and did not lead to treatment discontinuation. There were no deaths, serious or severe AEs, or AEs leading to discontinuation from study or study drug in either active- or placebo-treated participants. No adverse trends were noted in safety laboratory tests, ECGs, vital signs, or physical exam findings.

In Study 4858-101, 16 participants (healthy volunteers) were enrolled in multiple-dose cohorts (12 treated with either 20 mg or 35 mg of NDI-034858 daily for two weeks and 4 treated with placebo daily for two weeks). Treatment with NDI-034858 was generally safe and well tolerated. A total of 12 of 12 (100%) participants treated with NDI-034858 had at least one TEAE during the study period, compared with 2 of 4 (50%) who received placebo. The most common (≥ 2 subjects) TEAEs observed by preferred term were acneiform dermatitis, reported in 8 subjects treated with NDI-034858 (all 6 who received 20 mg and in 2 who received 35 mg daily for 2 weeks). Papular rash was reported in 3 subjects treated with 35 mg NDI034858. All events of acneiform dermatitis or papular- rash were deemed to be drug related. They were all mild in intensity and resolved within one to two weeks of onset without requiring treatment discontinuation. Aphthous ulcer occurred in 2 subjects in the 20 mg group and 1 in the 35 mg group, all of whom also experienced acneiform dermatitis. All events were considered drug -related. None of these events were observed in the placebo group. There were no deaths, serious or severe AEs, or AEs leading to discontinuation from the study. One participant in the 20 mg group discontinued treatment due to atrial fibrillation associated with hyperthyroidism but completed study follow-up. This event was deemed unrelated to study drug and was not serious. No adverse trends were noted in safety laboratory tests, ECGs, vital signs, or physical exam findings.

Of 6 subjects enrolled in the open-label cohort, only 1 TEAE of oral herpes was observed in 1 subject (16.7%) after receiving a single dose of 35 mg NDI-034858 (SDD formulation) under fasting conditions. This TEAE was mild in severity and was judged as unrelated to NDI-034858 by the investigator. This event was also a TEAE of special interest and was resolved before the end of study. No SAEs were observed and none of the subjects experienced TEAEs leading to dose discontinuation during the study period.

2.1.4.1.2. Pharmacokinetic Results in Study 4858-101

In the study, the absorption of NDI-034858 was generally rapid with the mean peak plasma concentrations observed at a median time to maximum observed concentration (T_{max}) of 3-5 hours postdose in the SAD Cohorts 1-6 and the MAD Cohorts 7 and 8. For the SAD Cohort 9, Periods 1 and 2, NDI-034858 (as a TPGS formulation and an SDD formulation, respectively) was administered to the fasted subjects and T_{max} was similar to the other SAD cohorts and was observed at a median time of 4-5 hours postdose. For the SAD Cohort 9, Period 3, NDI-034858 (as an SDD formulation) was administered to the fed subjects and T_{max} was observed at a median of 8 hours postdose and individual values ranged from 8-24 hours postdose.

For Cohorts 1-3 (doses of 5, 20, and 75 mg NDI-034858), the mean maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner (21.6 – 237.4 ng/mL, or an 11-fold increase in C_{max} over a 15-fold increase in dose) and inter-subject variability was moderate for C_{max} (coefficient of variation [CV] of 20-28%). For doses of 100, 150, and 200 mg (Cohorts 5, 4, and 6 respectively), the mean C_{max} increased in a less than dose proportional manner (232.5 – 250 mg/mL) and inter-subject variability was somewhat greater (CV 35-57%).

Similarly, for Cohorts 1-3 (doses of 5, 20, and 75 mg NDI-034858), the mean area under the plasma concentration versus time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) increased in an approximately dose-proportional manner (589.4 – 8369.8 hr*ng/mL, or a 14-fold increase in $AUC_{0\text{-}inf}$ over a 15-fold increase in dose). For doses of 100 and 150 mg (Cohorts 5 and 4), the mean $AUC_{0\text{-}inf}$ increased in a less than dose proportional manner (10744.9 and 12190.8 hr*ng/mL, respectively). The exposure in Cohort 6 (dose of 200 mg) did not increase further and the mean $AUC_{0\text{-}inf}$ was 9015 hr*ng/mL. For the single dose Cohorts 1-6, the percentage of the area under the concentration versus time curve (AUC%) extrapolated was moderate ranging from 9.9 – 30.9%.

Upon multiple dose administration for 14 days at a 20 or 35 mg daily dose (Cohorts 7 and 8, respectively), the accumulation ratio for C_{max} was 2.6 and 2.2, respectively and the area under the plasma concentration versus time curve from time 0 to the end of the dosing period ($AUC_{0\text{-}tau}$) was 2.9 and 2.4, respectively. After repeat dosing at 20 or 35 mg, on day 14, the minimum observed concentration (C_{min}) at 24 hours prior to the next daily dose was 82.7 and 169.9 ng/mL, respectively.

Across the single dose Cohorts 1-6 and the multiple dose Cohorts 7 and 8, the terminal half-life ($t_{1/2}$) was consistent across the dose levels tested and ranged from 17.1 to 37.4 hours.

Cohort 9 Periods 1 and 2 allowed the assessment of comparative bioavailability of the TPGS formulation (used to formulate NDI-034858 for dosing of Cohorts 1-8) to the SDD formulation at as a single dose of 35 mg to fasting subjects. Overall, exposure was similar after a single dose of NDI-034858 as TPGS or SDD formulation as assessed by C_{max} (112.3 ng/mL and 148 ng/mL, respectively) and $AUC_{0\text{-}inf}$ (3146.3 and 4027.5 hr*ng/mL, with relative oral bioavailability (F%) of the SDD formulation to the TPGS formulation calculated to be 128%). Cohort 9 Periods 2 (fasted, SDD formulation) and 3 (fed, SDD formulation) allowed assessment of the potential for food effect on exposure. Generally, exposure in the two periods was similar with the ratio of fed to fasted pharmacokinetic parameters all close to unity for C_{max} (0.91), $AUC_{0\text{-}inf}$ (1.07), area under the plasma concentration versus time curve from time 0 to the time of last measurable concentration ($AUC_{0\text{-}last}$; 1.02), and $t_{1/2}$ (0.95). Thus, no food effect was observed in this study.

Overall, renal elimination of the parent drug represented a low but measurable percentage of the total administered dose of NDI-034858 and the fraction of the dose excreted in urine (FE%) ranged between 0.37 – 1.89 % of dose. Thus, renal excretion may contribute to clearance of the parent drug but is expected to be a relatively minor route of clearance based on this study. Renal clearance (CLr) ranged from 0.06 – 0.30 L/hr.

2.1.4.1.3. Pharmacodynamic Results in Study 4858-101

The PD effect of treatment with NDI-034858 in Study 4858-101 was assessed using an ex-vivo immune-assay measuring the amount of TYK2-dependent interferon gamma (IFNγ) produced by whole blood samples that were stimulated with the cytokines IL-12 and IL-18 at baseline (predose) and following treatment. Increasing exposures to NDI-034858 led to greater reduction in IFNγ, confirming a robust effect of this compound on biological endpoints relevant to the pathogenesis of several autoimmune diseases (see Investigator Brochure [IB] for more details).

2.1.4.2. Study 4858-102

Study 4858-102 was a Phase 1, randomized, multicenter, double-blind, placebo-controlled multiple ascending dose study of NDI-034858 in subjects with moderate to severe plaque psoriasis. The study objective was to provide preliminary evidence of safety, tolerability, pharmacokinetics, pharmacodynamics, and early efficacy in a moderate to severe plaque psoriasis population.

The study enrolled a total of 26 subjects, who were randomized to daily treatment with either placebo (N=5) or 1 of 3 doses of NDI-034858 (N=21) for a total duration of 28 days. Dose levels were 5 mg (N=8), 10 mg (N=7), or 30 mg (N=6). The TPGS formulation was used for the 5 mg dose level, and the SDD formulation was used for the 10 mg and 30 mg dose levels. Food intake was not restricted except when performing study procedures during clinic visits.

2.1.4.2.1. Efficacy Results in Study 4858-102

Exploratory efficacy data in psoriasis (PASI, static PGA [sPGA]) were obtained in Study 4858-102. This study had a small sample size (25 subjects contributed to efficacy data) and treatment duration was limited to 28 days. A total of 25 subjects (N = 8 for 5 mg, N = 7 for 10 mg, N = 5 for 30 mg, and N = 5 for placebo) were included in the efficacy analysis set, which included subjects who had PASI and/or sPGA data at Day 1 and Day 28. Efficacy data were complete for these 25 subjects, and no imputation was needed for missing data.

- Treatment with NDI-034858 showed a dose-dependent trend in reduction of disease severity, with mean percent reduction from PASI score at Day 28 compared to Day 1 of 30% (mean PASI reduced from 15.4 on Day 1 to 10.9 on Day 28), 47% (mean PASI reduced from 18.2 on Day 1 to 9.6 on Day 28), and 48% (mean PASI reduced from 20.0 on Day 1 to 10.4 on Day 28), in the 5, 10, and 30 mg groups, respectively, compared with a 26% reduction (mean PASI reduced from 13.5 on Day 1 to 10.0 on Day 28) in the placebo group.
- PASI-50 was achieved in 13% (1/8), 57% (4/7), and 40% (2/5) in the 5, 10, and 30 mg groups, respectively, compared to 0% (0/5) in the placebo group.
- PASI-75 was achieved in 1 subject (1/5; 20%) in the 30 mg group but not achieved in the other groups. The same subject also achieved PASI 90.
- Treatment with NDI-034858 also improved the sPGA score compared to placebo, with one subject in the 30-mg cohort achieving an sPGA of 1 (minimal disease) at Day 28.

2.1.4.2.2. Safety Results in Study 4858-102

Treatment with NDI-034858 was generally safe and well tolerated. There were no deaths or serious Aes. TEAEs occurred in 38% (3/8), 57% (4/7), and 67% (4/6) of subjects receiving 5, 10, or 30 mg NDI-034858, compared with 20% (1/5) of subjects in the placebo group. All TEAEs were mild (Grade 1) or moderate (Grade 2) in intensity except for one severe (Grade 3) adverse event of neutropenia in a subject treated with 30 mg of NDI-034858 that led to discontinuation of treatment. This event was observed on Day 8 of treatment resulting in discontinuation of study drug on Day 12. The subject's neutrophil count was normal on Day 15, 3 days after treatment

was stopped. The Grade 3 neutropenia was the only adverse event constituting Grade 2 or higher hematologic toxicity observed in this study. It was deemed related to study drug but not serious. Further information on changes in safety laboratory tests, including cytopenia and blood creatine phosphokinase (CPK) elevation, is presented in Section 2.2.1. There were no events of acneiform dermatitis, papular rash, or aphthous ulcer reported in this study. There were no clinically significant changes in vital signs, physical exam, or ECG. One subject in the 30 mg cohort received only one dose of study drug and discontinued the study after Day 1 due to a positive TB test. This subject was included in the safety analysis set, but not in the efficacy analysis.

2.1.4.2.3. Pharmacokinetic Results in Study 4858-102

In Study 4858-102, absorption of NDI-034858 was generally rapid with mean peak plasma concentrations observed at a median of 3-4 hours postdose in Cohorts 1-3 (5 to 30 mg once daily). Between 5 and 30 mg doses, mean C_{max} generally increased in a slightly greater than dose-proportional manner under steady-state conditions (ie, on Day 28 of dosing), with an 8-fold increase in C_{max} over a 6-fold increase in dose. Similarly, the observed exposure over the dosing interval, $AUC_{0\text{-}tau,}$ increased in a greater than dose-proportional manner with a 11-fold increase in $AUC_{0\text{-}tau}$ over a 6-fold increase in dose. Owing to the small sample size, and the large inter-subject variability observed in the study (55-111% CV for C_{max} and 47-269% CV for $AUC_{0\text{-}tau}$), this lack of observed dose-proportionality may not be pharmacokinetically or pharmacologically relevant. The observed accumulation ratio, between Day 1 and Day 28, in this study was consistent with the value obtained in the previous study in healthy volunteers.

2.2. Risk/Benefit Assessment

2.2.1. Known Potential Risks

No important identified risks have emerged from Clinical Studies 4858-101 in healthy volunteers or 4858-102 in subjects with moderate to severe plaque psoriasis.

Potential risks based on preclinical findings (see IB for details), include tachycardia and increased serum bilirubin. To date, no clinically significant increases in heart rate or in serum bilirubin have been observed in Studies 4858-101 or 4858-102. Vital signs, ECG, and serum bilirubin will continue to be monitored per protocol in Study 4858-201.

Potential risks, based on observations from clinical studies 4858-101 and 4858-102, or modeling or drug interactions, are described in Table 2. An association between the safety findings considered potential risks and use of the study drug has not been established and requires further evaluation.

Table 2: Potential Risks of NDI-034858

Potential Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Cytopenia	One Grade 3 AE of neutropenia occurred in a subject treated with NDI-034858 30 mg daily in Study 4858-102, which resulted in discontinuation of study medication. The absolute neutrophil count for this subject	In Study 4858-201: Subjects with absolute neutrophil count of $< 1.8 \times 10^9$/L ($< 1800/mm^3$) are excluded from participation.

Potential Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
	returned to normal within three days of discontinuation of study medication. Overall, 3 subjects (3/21; 14%) treated with NDI-034858 and 1 subject (1/5; 20%) treated with placebo experienced neutropenia of Grade ≥ 2 in Study 4858-102. 2 subjects (2/21; 10%) treated with NDI-034858 and no subjects (0/5; 0%) treated with placebo experienced lymphopenia of Grade ≥ 2 in Study 4858-102. No cases of anemia or thrombocytopenia of Grade ≥ 2 were noted in Study 4858-102. No subjects treated with NDI-034858 in Study 4858-101 experienced any cytopenia of Grade ≥ 2, and there were no toxicology findings in 4-week or 13-week rat or monkey studies suggesting this risk.	Subjects with absolute lymphocyte count of < 1.0 x 10^9/L (< 1000/mm^3) are excluded from participation. White blood cell count and differentials will be monitored per protocol. Cytopenia ≥ Grade 2 is an AESI. If the subject experiences a CTCAE Grade ≥2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.4.7 , dosing must be held. The subject should be followed with periodic testing until the laboratory values return to normal range, at which time dosing may be resumed. If the same subject develops CTCAE Grade ≥2 cytopenia for a second time after dosing is resumed, then the subject will be permanently discontinued from treatment but may be continued in the trial and followed until resolution of the abnormality.
CPK elevation	Grade 2-3 elevations of CPK occurred in subjects on NDI-034858 and placebo in studies 4858-101 and 4858-102. No clinically significant increases in serum creatinine or abnormalities on urinalysis accompanied these elevations in CPK. There was no apparent temporal association with administration of study drug.	In Study 4858-201: CPK will be monitored per protocol. CPK elevation ≥ Grade 3 is an AESI. Subjects with a drug-related SAE or severe drug-related AE may be discontinued from study medication.
Drug interaction	A physiologically based pharmacokinetic model (PBPK modeling; Module 2.6.4) predicted a strong victim interaction with the strong CYP3A4 inhibitor itraconazole. Moderate victim interactions with moderate inhibitors are also predicted based on this model.	In Study 4858-201: Strong and moderate inhibitors of CYP3A4 are prohibited in Study 4858-201. Exclusion criteria in Study 4858-201 ensure adequate wash out of strong and moderate inhibitors of CYP3A4. Future planned studies: A clinical study to evaluate the DDI potential with itraconazole is planned in parallel with Study 4858-201. If a DDI is observed, then additional clinical DDI evaluations may be performed after completion of hADME study. The hADME study is planned prior to Phase 3 to help understand clearance

Potential Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
		mechanisms of the drug, and to refine magnitude of DDI risk.
Abbreviations: CPK, creatine phosphokinase; DDI, drug-drug Interaction; hADME, human absorption, distribution, metabolism, and excretion; PBPK, physiologically based pharmacokinetic.		

Inhibitors of other JAK family kinases have been associated with increased risk of serious infection, malignancy, thrombosis, and changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. Through allosteric inhibition of TYK2, NDI-034858 shows high selectivity for TYK2 compared to other members of the JAK family of kinases. To date, the safety profile for NDI-034858 continues to reflect selectivity for TYK2, with avoidance off-target inhibition of JAK1-3.

Mild events of acneiform dermatitis and similar events within the skin and subcutaneous tissue disorders system organ class (SOC) were commonly observed in subjects (healthy volunteers) treated with NDI-034858 in Study 4858-101. Similar findings were noted in Phase 1 studies of deucravacitinib.[14] No events of acneiform dermatitis or similar events within the skin and subcutaneous tissue disorders SOC were observed in subjects treated with NDI-034858 in Study 4858-102. Similarly, events of acneiform dermatitis were rare in psoriasis subjects treated with deucravacitinib, another allosteric TYK2 inhibitor, in Phase 2b and Phase 3 studies.[12,13]

2.2.2. Known Potential Benefits

NDI-034858 has potential to treat a variety of autoimmune and inflammatory disorders, including psoriasis. These diseases present serious, long-term health risks with significant unmet medical need. Exploratory efficacy data from Study 4858-102 in subjects with moderate to severe plaque psoriasis (Section 2.1.4.2.1) suggest that NDI-034858 may demonstrate efficacy in larger, randomized controlled studies including proposed Study 4858-201. Efficacy data from Phase 3 trials of the allosteric TYK2 inhibitor deucravacitinib demonstrate that deucravacitinib has superior efficacy to apremilast,[13] the only FDA-approved oral medication for moderate-to-severe plaque psoriasis. Thus, early clinical data from NDI-034858 and pivotal data from Phase 3 studies of deucravacitinib, another allosteric TYK2 inhibitor, support the potential for NDI-034858 to treat moderate to severe plaque psoriasis.

2.2.3. Assessment of Risks and Benefits

NDI-034858 has undergone nonclinical and clinical development as described in the latest version of the IB. The collective nonclinical safety profile and safety results of the completed Phase 1 studies 4858-101 and 4858-102 have not resulted in identification of safety signals and suggest that NDI-034858 is generally safe and well tolerated. The potential risks associated with NDI-034858 can be monitored and mitigated, as outlined, by inclusion/exclusion criteria, monitoring of clinical laboratory tests and vital signs, treatment discontinuation criteria, and by exclusion of concomitant medications that may have clinically significant interaction with NDI-034848.

Efficacy data from the Phase 1 Study 4858-102 suggest the therapeutic potential of NDI-034858 in moderate to severe plaque psoriasis. This is supported by Phase 2b and Phase 3 studies from deucravacitinib which validated blockade of TYK2 as a therapeutic approach for treatment of moderate to severe plaque psoriasis.

In summary, the collective preclinical and clinical evidence supporting the inhibition of TYK2 as a therapeutic approach in psoriasis and the safety profile of NDI-034858 established to date in healthy volunteers and psoriasis subjects provide a strong scientific and clinical rationale for pursuing development of NDI-034858 in subjects with moderate to severe plaque psoriasis. The benefit/risk for further development of NDI-034858 in psoriasis is therefore warranted.

3. OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary Objective	
To assess the efficacy of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg for 12 weeks in subjects with moderate to severe plaque psoriasis	**Primary Efficacy Endpoint** • Proportion of subjects achieving PASI-75 at Week 12 **Secondary Efficacy Endpoints** • Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Week 12 • Proportion of subjects achieving at least PASI-90 at Week 12 • Proportion of subjects achieving at least PASI-100 at Week 12 • Change from baseline in DLQI at Week 12 **Exploratory Efficacy Endpoints** • Proportion of subjects achieving PASI-50 at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving PASI-75 at Weeks 2, 4, and 8 • Proportion of subjects achieving PASI-90 at Weeks 2, 4, and 8 • Proportion of subjects achieving PASI-100 at Weeks 2, 4, and 8 • Change from baseline in PASI at Weeks 2, 4, 8, and 12 • Percent change from baseline in PASI at Weeks 2, 4, 8, and 12 • Change from baseline in PGA at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Weeks 2, 4, and 8 • Proportion of subjects with at least a 2-grade decrease from baseline in PGA at Weeks 2, 4, 8, and 12 • Change from baseline in BSA at Weeks 2, 4, 8, and 12 • Change from baseline in pruritus NRS at Weeks 2, 4, 8, and 12 • Proportion of subjects with a baseline pruritus NRS of 4 or greater achieving at least a 4-point decrease from baseline in pruritus NRS at Weeks 2, 4, 8, and 12 • Change from baseline in DLQI at Weeks 4 and 8

OBJECTIVES	ENDPOINTS
Secondary Objectives	
To assess the safety and tolerability of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg for 12 weeks in subjects with moderate to severe plaque psoriasis	**Secondary Safety Endpoints** • Incidence of AEs • Changes in vital signs, clinical laboratory parameters, and ECGs
To evaluate the plasma concentration of NDI-034858 orally administered QD at 2 mg, 5 mg, 15 mg, or 30 mg in subjects with moderate to severe plaque psoriasis	**Secondary Pharmacokinetic Endpoint** • Measurement of plasma concentrations of NDI-034858 in subjects receiving active treatment
Exploratory Objectives	
To assess the effects of NDI-034858 on joint pain in subjects with moderate to severe plaque psoriasis and concomitant psoriatic arthritis	**Exploratory Efficacy Endpoints** • Change from baseline in pain NRS at Weeks 2, 4, 8, and 12 for subjects with concomitant psoriatic arthritis
To evaluate the effects of NDI-034858 on histology and mRNA biomarkers in psoriatic skin plaques (optional skin biopsies and optional tape strips) in subjects with moderate to severe plaque psoriasis	**Exploratory Pharmacodynamic Endpoints** • Quantification of skin biomarkers (immune cell infiltration and mRNA expression levels) in lesional and non-lesional skin
To evaluate the effects of NDI-034858 on cytokines and other inflammatory biomarkers in blood in subjects with moderate to severe plaque psoriasis	• Quantification of circulating cytokines and other inflammatory biomarkers
Abbreviations: AE, adverse event; BSA, body surface area; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; mRNA, messenger ribonucleic acid; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PASI-100, 100% improvement from baseline in PASI; PASI-50, 50% improvement from baseline in PASI; PASI-75, 75% improvement from baseline in PASI; PASI-90, 90% improvement from baseline in PASI; PGA, Physician's Global Assessment; QD, once daily.	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, multicenter, double-blind, placebo-controlled, multiple dose- study designed to evaluate the efficacy, safety, and tolerability of NDI-034858 in subjects with moderate to severe plaque psoriasis. This study will also evaluate the plasma concentrations of NDI-034858 and explore the immune response (in blood and skin) to NDI-034858 in subjects with moderate to severe plaque psoriasis.

Approximately 250 male and female subjects, aged 18 to 70 years (inclusive), with moderate to severe plaque psoriasis will be randomized in this study. To be eligible for the study, the subjects will need to have a history of plaque psoriasis for at least 6 months prior to the screening visit. In addition, the subjects will need to have the following characteristics at screening and on Day 1: PASI score ≥ 12, PGA score ≥ 3, and BSA involved with plaque psoriasis ≥ 10%.

All subjects will read and sign an ICF prior to any screening procedures being performed. Subjects who fulfill all inclusion criteria and none of the exclusion criteria will be included into the study. During a screening period of no longer than Day -30 to Day -1, subjects will be randomized (on Day -7) to receive either one of the four doses of NDI-034858 (2 mg, 5 mg, 15 mg, or 30 mg), or placebo on Day 1. The goal is to have approximately 50 subjects randomized per treatment group (1:1:1:1:1 ratio) on Day 1. During the treatment period, NDI 034858 (2 mg, 5 mg, 15 mg, or 30 mg) or placebo will be orally administered QD for 12 weeks. The 12-week treatment period will be followed by a 4-week safety follow-up period. The conduct of the study is illustrated in Figure 1.

For scheduled study visits, subjects will come to the study site on 8 occasions: screening, Day 1, and Weeks 1, 2, 4, 8, 12 (EOT), and 16 (EOS/ET).

Efficacy will be assessed using PASI, PGA, BSA involved with plaque psoriasis, pruritus NRS, and pain NRS for subjects with concomitant psoriatic arthritis. Quality of life will be evaluated using DLQI.

Safety will be assessed by collecting AEs, recording vital signs, performing physical examinations, and evaluating clinical laboratory and ECGs results.

Blood samples will be collected to measure plasma levels of NDI-034858 as follows:

- On Day 1 prior to dosing and 1 hour (± 5 min) postdosing;
- At Week 4 prior to dosing, 1 hour (± 5 min) postdosing, and 4 hours (± 10 min) postdosing;
- At Week 8 prior to dosing;
- At Week 12 anytime (no study treatment administration at this visit).
- At ET visit anytime (if ET visit is planned before Week 12 visit).

Urine samples will be collected on Day 1, and at Weeks 4, 12, and 16 and may be used to evaluate the effect of NDI-034858 on exploratory biomarkers.

Blood samples will be collected on Day 1, and at Weeks 4 and 12 to evaluate the effect of NDI-034858 on circulating inflammatory biomarkers.

In a subset of subjects who consent to the procedure, the effect of NDI-034858 on skin biomarkers will be evaluated by collecting three or four optional skin biopsies. Two 5-mm punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected on Day 1, and one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar, even if the lesion has cleared) at Week 12. In addition, one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies. Photographs of biopsied areas will be performed prior to biopsy.

In a subset of subjects who consent to the procedure, the effect of NDI034858 on skin biomarkers will be evaluated by collecting tape strips. Skin tape strips will be collected from lesional skin and from adjacent non-lesional skin on Day 1, and from same lesional skin at Week 12.

At certain study sites, in a subset of subjects who consent, optional medical photographs of full-body, front and back, will be taken to illustrate the outcome of the study.

No interim analysis is planned in this study.

4.2. Study Conduct During the Coronavirus Disease 2019 Pandemic

Because of the COVID-19 pandemic that has had a worldwide impact, including in North America, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity.

The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic.

- Prior to a study visit at the study site, the subject may be contacted and screened for potential exposure or infection to COVID-19 per site, local, or federal requirements. If the subject is suspected to be exposed or infected with COVID-19, the on-site visit should either be rescheduled or a virtual visit may be performed instead, as applicable (refer to Section 7.1 and Section 7.2 for details on subject discontinuation from study treatment and study, respectively).
- If a subject cannot attend their regularly scheduled study visits in person due to COVID-19 necessitating a limit on in-person contact, the investigator may perform safety and other feasible assessments by phone or video, except for the screening, Day 1, and Week 12 visits. If the screening visit cannot be performed on-site, the subject should not be screened. If the Day 1 visit cannot be performed on-site, the subject should be considered to have failed screening. Subjects who failed screening

due to COVID-19 restrictions at screening or Day 1 may be rescreened at a later time, if feasible.

- Protocol deviations due to missed study visits, missed doses, or missed study procedures as well as study discontinuations due to COVID-19 restrictions should be documented accordingly.
- Subjects should continue recording their study product administration via the Diary. Safety must be assessed during the virtual visit by collecting AEs and concomitant medications. Other safety or efficacy assessments may be performed as reasonably practicable.
- Clinical laboratory tests (serum chemistries, hematology, and urinalysis) and pregnancy tests may be performed in local laboratory if these procedures cannot be performed at the study site due to COVID-19 related limitations, including but not limited to site closure. Clinically significant abnormal laboratory results should be promptly communicated to the medical monitor within 72 hours of receipt, as per investigator's judgment. Subjects' anonymity must be maintained when communicating results to the medical monitor.
- Source documentation should note that the visit was performed virtually (not --face-to-face) and note the name of the local laboratories where laboratory tests were done.
- In the case of virtual visits, where the subject is unable to attend the scheduled visits due to extenuating circumstances, such as quarantine or immobilization, study product may be shipped direct-to-subject from the site. Direct--to-subject shipments should only occur if the investigator deems it safe for the subject to continue study drug treatment. In all cases, requirements under local regulations for maintaining required study product storage conditions and study product accountability remain.

A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

4.3. Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy, safety, and tolerability of NDI-034858 (at 2 mg, 5 mg, 15 mg, or 30 mg) compared with placebo in subjects with moderate to severe plaque psoriasis.

This Phase 2b study will be randomized to ensure random allocation of subjects to treatment groups to reduce bias. Randomization will be stratified based on prior treatment with biologics. Because efficacy assessments of plaque psoriasis have a high degree of subjectivity, the study will be double-blinded. The highest degree of subject and study site assessor blinding should be sought to achieve credible inference. It is also important to have a placebo control in this Phase 2b study to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied.

4.4. Justification for Dose

Dosing regimens for this Phase 2 dose ranging study were selected with the objective of establishing a dose/exposure response of NDI-034858 and PASI score in subjects with moderate to severe plaque psoriasis. Subjects enrolled in this study will receive one of five treatments: placebo, 2-mg NDI-034858 daily, 5-mg NDI-034858 daily, 15-mg NDI-034858 daily, and 30-mg NDI-034858 daily. Dose regimens were selected based on the preclinical assessment of NDI-034858 and exploratory assessment of PK/ PD correlation in first in human (FIH) Study 4858-101.

The primary PD measurement used for dose selection in psoriasis was the inhibition of IL-12/18 induced IFNγ production measured in an *ex-vivo* assay in the FIH. It is assumed that the inhibition of IL-12/18 assay and adequate coverage of half maximal inhibitory concentration (IC50) are associated with efficacy in psoriasis. This assumption is supported by preclinical studies of NDI-034858 and the clinical improvements observed in psoriasis clinical studies conducted using biologic therapies directed against either the p19 subunit of IL-23 or the p40 subunit it shares with IL-12 (eg, ustekinumab), as well as clinical studies conducted using compounds that target the same pathway, including BMS-986165.

Using the PK and PD data from the SAD and multiple dosing portions of the FIH studies, nonlinear regression was used to characterize the concentration-response relationship in the FIH study. Results of the analysis showed that the estimated IC50 of IL-12/18 induced IFNγ production was approximately 20 ng/mL. With the assumption that the IC50 should be similar between healthy and psoriasis subjects, over the dose range of 2-30mg, the projected trough concentration (C_{trough}) concentrations are expected to cover between 30% inhibitory concentration (IC30) and 90% inhibitory concentration (IC90). The selected treatment levels from 2 mg daily to 30 mg daily are expected to provide an approximately 15-fold range in average concentration over the dosing interval (C_{avg}). See IB for additional details.

The dose range proposed for the Phase 2 study will not exceed the range of doses tested in the SAD portions of the FIH (4858-101; 5-200 mg), nor will it exceed the range of doses tested in the multiple dose portion of the FIH study (4858-101; 20-35 mg QD). Details of the safety profile of the molecule in the 4858-101 and 4858-102 studies are discussed Section 2.1.4. Furthermore, the expected $AUC_{0\text{-}tau}$ and C_{max} resulting from these treatment levels are within the observed preclinical and clinical exposures spanned by studies 4858-101 and 4858-102. Based on toxicokinetic data, the highest C_{max} and $AUC_{0\text{-}tau}$ projected in this study maintain a greater than 5-fold margin of the observed no observed adverse effect level (NOAEL) for preclinical species and the observed NOAEL AUC in the 3-month toxicity studies (see IB for additional details).

Based on the totality of safety, pharmacokinetic, and pharmacodynamic data from the Phase 1 studies, the selected range for the present study includes doses between 2 mg and 30 mg.

4.5. End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1.

The end of the study is defined as completion of the last visit or procedure shown in the schedule of event for the last enrolled subject in the study globally for all study sites.

5. STUDY POPULATION

5.1. Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Male or female subject aged 18 to 70 years, inclusive, at the time of consent.
2. Subject has a history of plaque psoriasis for at least 6 months prior to the screening visit.
3. Subject had no significant flare in psoriasis for at least 3 months before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has moderate to severe plaque psoriasis as defined by a PASI score ≥ 12 and a PGA score ≥ 3 at screening and Day 1.
5. Subject has plaque psoriasis covering ≥ 10% of his or her total BSA at screening and Day 1.
6. Subject must be a candidate for phototherapy or systemic therapy.
7. For female subjects of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks prior to Day 1 until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (eg, combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s) (provided vasectomy was performed ≥ 4 months prior to screening), bilateral tubal ligation or occlusion, or double barrier methods of contraception (eg, male condom with cervical cap, male condom with diaphragm, and male condom with contraceptive sponge) in conjunction with spermicide.

   Note: Subjects must have been on a stable dose of combined hormonal contraceptives for at least 4 weeks before Day 1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study, and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods) is not acceptable.

   Note: A female subject of nonchildbearing potential is defined as follows:

   - Female subject who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy);

- Female subject who has had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause, and an FSH test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

8. Female subjects of childbearing potential have had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
9. For male subjects involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion 7, from Day 1 until at least 12 weeks after the last study product administration. If the female partner of a male subject uses any of the hormonal contraceptive methods listed above, this contraceptive method should be used by the female partner from at least 4 weeks before Day 1 until at least 12 weeks after the last study product administration.

   Note: Male subjects must refrain from donating sperm from Day 1 until at least 12 weeks after the last study product administration.

   Note: No restrictions are required for a male subject who underwent a vasectomy at least 4 months prior to screening and the procedure is documented. If vasectomy procedure is not documented or was performed less than 4 months prior to screening, male subjects must follow the same contraception and sperm donation requirements as for nonvasectomized subjects.
10. Subject has a BMI within the range of 18 to 42 kg/m^2, inclusive (BMI = weight [kg]/[height (m)]^2), and total body weight >50 kg (110 lb).
11. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
12. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

5.2. Exclusion Criteria

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or drug-induced psoriasis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Subject has immune-mediated conditions commonly associated with psoriasis, such as psoriatic arthritis, uveitis, inflammatory bowel disease, that require systemic treatment (including corticosteroids, immunosuppressants, or biologics).

Note: Subjects with immune-mediated conditions that do not require systemic treatment may be included in the study. Certain therapies such as NSAIDs may be permitted but should be discussed with the Medical Monitor prior to determination of subject eligibility.

5. Subject has any clinically significant medical condition, evidence of an unstable clinical condition (eg, cardiovascular, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, immunologic, or local active infection/infectious illness), psychiatric condition, or vital signs/physical/laboratory/ECG abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
6. Subject had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
7. Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
8. Subject has been hospitalized in the past 3 months for asthma, has ever required intubation for treatment of asthma, currently require oral corticosteroids for the treatment of asthma, or has required more than one short-term (≤ 2 weeks) course of oral corticosteroids for asthma within 6 months prior to Day 1.
9. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
10. Subject has a history of fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection within 4 weeks prior to Day 1.
11. Subject has an active bacterial, viral, fungal, mycobacterial infection, or other infection (including TB or atypical mycobacterial disease), or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 12 weeks prior to Day 1, or oral antibiotics within 4 weeks prior to Day 1.
12. Subject has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection, recurrent urinary tract infection, fungal infection (except for superficial fungal infection of the nailbed), or infected skin wounds or ulcers.
13. Subject has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis if that prosthesis has not been removed or replaced.
14. Subject has active herpes infection, including herpes simplex 1 and 2 and herpes zoster (demonstrated on physical examination and/or medical history) within 8 weeks prior to Day 1.
15. Subject has a history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the subject's immune status in the opinion of the investigator (eg, history of splenectomy, primary immunodeficiency).

16. Subject has positive results for HbsAg, anti-HBc, HCV, or HIV.
17. Subject has clinical or laboratory evidence of active or latent TB infection at screening.

    Note: Subjects with an history of active or latent TB will not be included in the study, unless documentation of prior and complete anti-TB treatment, appropriate in duration and type according to current local country guidelines, can be provided.

    Note: Subject will be evaluated at screening for latent TB infection with a QFT test. Latent TB is defined as a positive QFT test or two successive indeterminate QTF tests at screening.

    Note: The T-Spot.TB test (TBT) is an acceptable alternative to the QFT test in regions where the TBT is standard practice for tuberculosis screening. The medical monitor should be informed prior to using the TBT test in place of the QFT test. A negative TBT test is required if the QFT test is not performed.

18. Subject with any of the following laboratory values at the screening visit:
    a. ALT or AST values $\geq$ 3 times the ULN;
    b. Hemoglobin < 11.0 g/dL (< 110.0 g/L);
    c. White blood cell count < 3.5 x 10^9/L (< 3500/mm^3);
    d. Absolute neutrophil count of < 1.8 x 10^9/L (< 1800/mm^3);
    e. Absolute lymphocyte count of < 1.0 x 10^9/L (< 1000/mm^3);
    f. Platelet count < 100 x 10^9/L (< 100,000/mm^3);
    g. Total bilirubin > 2 times the ULN.
19. Subjects who have given > 50 ml of blood or plasma within 30 days of screening or $\geq$ 500 mL of blood or plasma within 56 days of screening (during a clinical study or at a blood bank donation).
20. Subject has used any topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar) within 2 weeks prior to Day 1.
21. Subject has used any systemic treatment that could affect psoriasis (including oral, intravenous, intramuscular, intraarticular, intrathecal, or intralesional corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; cyclosporine; oral JAK inhibitors; or apremilast) within 4 weeks prior to Day 1.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.

22. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
23. Subject has had PUVA treatment within 4 weeks prior to Day 1.

24. Subject has received any live-attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live-attenuated vaccine during the study and up to 4 weeks or 5 half-lives of the study product, whichever is longer, after the last study product administration.

    Note: Non-live-attenuated vaccines or boosters for COVID-19 (eg, RNA-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines) are allowed during the study. The study site should follow local guidelines related to COVID-19.

25. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
26. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1 (except those listed in Exclusion Criterion 27 and 28 that are to be excluded for 6 months).
27. Subject was previously enrolled in any study with NDI-034858.
28. Subject has a history of lack of response to any therapeutic agent targeting IL-12, IL-17, and/or IL-23 (eg, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab) at approved doses after at least 12 weeks of therapy, and/or received one of these therapies within 6 months prior to Day 1.
29. Subject has received rituximab or other immune-cell depleting therapy within 6 months.
30. Subject is currently being treated with strong or moderate cytochrome P450 3A (CYP3A4) inhibitors (such as itraconazole, refer to Appendix 1), or has received moderate or strong CYP3A4 inhibitors within 4 weeks prior to Day 1.
31. Subject is currently being treated with terbinafine or has received terbinafine within 4 weeks prior to Day 1.
32. Subject has consumed grapefruit within 1 week prior to Day 1.

    Note: Consumption of grapefruit must be avoided during the treatment period and for at least 1 week after last dose administration.

33. Subject has used tanning booths within 4 weeks prior to Day 1, has had excessive sun exposure, or is not willing to minimize natural and artificial sunlight exposure during the study.

    Note: Use of sunscreen products and protective apparel are recommended when sun exposure cannot be avoided.

34. Subject has a known or suspected allergy to NDI-034858 or any component of the investigational product, or any other significant drug allergy (such as anaphylaxis or hepatotoxicity).
35. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
36. For subjects consenting to biopsy collection only:

- Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
- Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
- Subject has taken anticoagulant medication, such as heparin, LMW-heparin, warfarin, or antiplatelet agents (except low-dose aspirin ≤ 81 mg which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs will not be considered antiplatelet agents and will be allowed.

5.3. Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical study but are not subsequently randomly assigned to the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

6. TREATMENT

6.1. Study Treatment Administered

This study involves a comparison of NDI-034858 at 2 mg, 5 mg, 15 mg, or 30 mg orally administered QD with a placebo. NDI-034858 will be available in 2 mg, 5 mg, and 15 mg strength capsules. All study products will be provided by the sponsor.

All study products will be administered orally daily, as assigned, for 12 weeks. On study days, the study products will be administered at the study site (if applicable). The date and time of the drug administration will be collected daily by the study site (during the visit) or via a diary provided to the subject. The subject should be instructed to take the study product at approximately the same time of the day. For Day 1 and Week 12 visits, subjects should be fasted for at least 8 hours before their visit and up to the time of the blood draw for fasting lipid panel.

Further details regarding the study products can be found in Table 3.

Table 3: Study Treatments

	Study Products				
Product name	**NDI-034858**	**NDI-034858**	**NDI-034858**	**NDI-034858**	**Placebo**
Dosage form	Capsule	Capsule	Capsule	Capsule	Capsule
Unit dose strength(s)	2 mg	5 mg	15 mg	15 mg	N/A
Dosage level(s)	2 mg	5 mg	15 mg	30 mg	N/A
Number of capsules per dose level	1 active 1 placebo	1 active 1 placebo	1 active 1 placebo	2 active	2 placebo
Route of administration	Oral	Oral	Oral	Oral	Oral
Dosing instructions	QD with approximately 240 mL of water	QD with approximately 240 mL of water	QD with approximately 240 mL of water	QD with approximately 240 mL of water	QD with approximately 240 mL of water
Physical description	Opaque white capsules	Opaque white capsules	Opaque white capsules	Opaque white capsules	Placebo is identical to the active capsules in size, shape, and color.
Source of procurement	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.

Abbreviations: N/A, not applicable; QD, once daily.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation/Storage/Handling

All study products must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study products may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

Study products will be dispensed by the study site to the subject at the visits specified in Table 1. Subjects are to return all study products (used and unused) to the study site. The capsules will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents and electronic case report form (eCRF). Each subject will be instructed on the importance of returning study product at the next study visit and on taking the product as prescribed. If a subject does not return study product, he or she will be instructed to return it as soon as possible.

6.2.2. Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. Any study product accidentally or deliberately destroyed or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained. At the conclusion of the study, all used and unused investigational products, and all medication containers will be returned or destroyed as per approved arrangements by the sponsor.

All study product accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained, as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of study products are provided in the study manual.

6.3. Randomization

At the study site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number will contain the site number and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates (eg, 02-010 for the 10th subject screened at Site 02).

Approximately 250 subjects will be randomized 1:1:1:1:1 ratio to NDI-034858 at 2 mg, 5 mg, 15 mg, or 30 mg, or placebo (approximately 50 subjects per treatment group).

Randomization will occur at Day -7 visit. Before Day -7, available eligibility information will be reviewed and Subject Eligibility Form will be submitted for approval. Subject will then be randomized. The randomization list will be generated using validated software and will be stratified based on prior treatment with biologics (yes/no). The master randomization list will be

kept secured until the study blind is broken at the end of study. This list will be uploaded into an Interactive Web Response System (IWRS). The investigator or designee will be able to acquire a randomization number for subjects by connecting to the IWRS. Of note, only eligible subjects (confirmed on Day 1) will receive the study treatment.

A cap on the number of subjects to include for optional biopsy collection and optional tape strips will be placed between 30% to 50% and 40% to 60%, respectively.

Further guidance and information can be obtained in the study manual.

6.3.1. Blinding

This study will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until after the conclusion of the study.

Breaking the blind should be considered only when knowledge of the treatment assignment is deemed essential for the subject's care. In such case of a medical emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the medical monitor prior to unblinding a subject's treatment assignment unless this could delay further management of the subject. If a subject's treatment assignment is unblinded, the medical monitor and the sponsor must be notified within 24 hours after breaking the blind. The date and reason for breaking the blind must be documented in the source document and the eCRF.

In cases of accidental unblinding, the investigator should contact the medical monitor and ensure every attempt is made to preserve the blind. Any request to unblind a subject for nonemergency purposes must be discussed with the medical monitor prior to unblinding.

The subject for whom the blind has been broken for a safety-related reason will be permanently discontinued from the study treatment. The primary reason for study treatment discontinuation (the event or condition which led to the unblinding) will be recorded.

6.3.2. Study Treatment Compliance

Study treatment compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's dosing diary, and by maintaining adequate study product dispensing and return records.

Subjects who are significantly noncompliant with treatment will be counseled and could be discontinued from the study, at the discretion of the investigator, following consultation with the sponsor. Significant noncompliance is defined as missing 3 consecutive doses (ie, 3 days in a row) or missing a total of 10 doses, or an overdose as defined in Section 8.4.10.

6.4. Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products, and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded. In addition, the last use of any prohibited medications before Day 1 must be recorded and fall within the timeframe described in the exclusion criteria.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

6.4.1. Permitted Therapies

6.4.1.1. Emollients

Subjects can apply an emollient of their choice (except those containing salicylic acid) on their skin, **including on psoriasis lesions**. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face emollient may be different). The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study.

6.4.1.2. Other Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided. However, on the day of scheduled visits, subjects cannot apply sunscreen products before their scheduled visit time.

6.4.2. Prohibited Therapies or Procedures

Table 4 lists prohibited medications that are not to be used from the defined washout periods before the first administration of study treatment at the Day 1 visit through the last study visit.

Subjects who start prohibited medications (systemic and topical) or therapies during the study may be discontinued from study treatment. Section 7.1 provides the list of prohibited medications for which a subject must be permanently discontinued from the study. Investigators should contact the medical monitor as soon as possible when any prohibited medication or therapy is initiated, to discuss the appropriate steps.

Table 4: Prohibited Therapies or Procedures

Prohibited Medications, Products, And Procedures	Washout Period Prior To First Dose (Day 1)
Therapeutic agent targeting IL-12, IL-17, and/or IL-23 (eg, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab)	6 months
Rituximab or other immune-cell depleting agents	6 months
Any marketed or investigational biological agent (except those listed above)	12 weeks or 5 half-lives (whichever is longer)
Intravenous antibiotic treatment	12 weeks
Oral antibiotic treatment	4 weeks
Nonbiological investigational product or device	4 weeks
Any live-attenuated vaccine Note: Non-live-attenuated vaccines or boosters for COVID-19 (eg, RNA-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines) are allowed during the study. The study site should follow local guidelines related to COVID-19.	4 weeks
Systemic treatment that could affect psoriasis (including oral, intravenous, intramuscular, intraarticular, intrathecal, or intralesional corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; cyclosporine; oral JAK inhibitors; or apremilast) Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.	4 weeks
Strong or moderate CYP3A4 inhibitors (such as itraconazole), see Appendix 1 for a list of prohibited medications in this class.	4 weeks
Terbinafine	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds), or excimer laser, or tanning booths	4 weeks
Topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar)	2 weeks
For subjects consenting to biopsy collection only: Anticoagulant medication, such as heparin, LMW heparin, warfarin, or antiplatelet agents (except low-dose aspirin ≤ 81 mg which will be allowed). Nonsteroidal anti-inflammatory drugs will not be considered antiplatelet agents and will be allowed.	2 weeks

Prohibited Medications, Products, And Procedures	Washout Period Prior To First Dose (Day 1)
Grapefruit Note: Consumption of grapefruit must be avoided during the treatment period and for at least 1 week after last dose administration.	1 week

Abbreviations: COVID-19, Coronavirus Disease 2019; CYP3A4, cytochrome P450 3A; IL, interleukin; JAK, Janus kinase; LMW, low molecular weight; PUVA, psoralen-ultraviolet-A; UV, ultraviolet.

7. DISCONTINUATION AND LOST TO FOLLOW-UP

7.1. Discontinuation from Study Treatment

Medical judgment should be applied to guide whether study treatment discontinuation or careful monitoring may be the most appropriate course of action. If it is deemed by the investigator that it is in the best interest of the subject to discontinue further study treatment, the medical monitor should be contacted as soon as possible for consultation.

Subjects must be permanently discontinued from study treatment for the following reasons:

- Pregnancy of a female participant
- The subject experiences a medical emergency that necessitates permanent discontinuation and/or unblinding of the subject's treatment assignment
- The subject is unwilling or unable to comply with the protocol
- At the discretion of the investigator for medical reasons or noncompliance
- Subject initiates any of the following prohibited medications (Section 6.4.2):
  - Therapeutic agent targeting IL-12, IL-17, and/or IL-23 (eg, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab)
  - Rituximab or other immune cell depleting agents
  - Other marketed or investigational biological agent not listed above
  - Live-attenuated vaccine

    Note: Non-live-attenuated vaccines or boosters for COVID-19 (eg, RNA-based vaccines, inactivated adenovirus-based vaccines, protein-based vaccines) are allowed during the study. The study site should follow local guidelines related to COVID-19.
  - Nonbiological investigational product or device
  - Intravenous antibiotic treatment
  - Systemic treatment that could affect psoriasis (including oral, intravenous, intraarticular, intrathecal, or intramuscular corticosteroids; oral retinoids; immunosuppressive/immunomodulating medication; methotrexate; cyclosporine; oral JAK inhibitors; or apremilast). Intralesional injections are prohibited medications for the duration of the study; however, their use does not require discontinuation from the study and should be discussed with the medical monitor to determine final subject disposition.
- If the subject experiences a CTCAE Grade ≥2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.4.7, for a second time after re-challenge, as detailed in the following paragraph.

Subjects must at least be temporarily discontinued from study treatment for the following reasons:

- The subject experiences a CTCAE Grade ≥2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.4.7. The subject should be followed with periodic testing until the laboratory values return to normal range, at which time dosing may be resumed. If the same subject develops CTCAE Grade ≥2 cytopenia for a second time after dosing is resumed, then the subject will be permanently discontinued from treatment but may be continued in the trial and followed until resolution of the adverse event(s).
- The subject has met study treatment discontinuation criteria for abnormalities suggestive of drug induced liver injury (DILI) as described in Section 8.4.8.

Temporary discontinuation may or may not lead to permanent discontinuation of study treatment pending results of further workup and the overall clinical assessment.

Subjects may be discontinued from study treatment for any of, but not limited to, the following reasons:

- Occurrence of a drug-related SAE (see Section 8.4.2).
- Occurrence of a severe drug-related AE (see Section 8.4.3).
- Initiation of a protocol prohibited therapy or procedure (Section 6.4.2) other than those for which the subject must be permanently discontinued from study treatment.

Study procedures should be continued to be evaluated for safety, PK, and other parameters even in the event of dosing discontinuation. The medical monitor should be contacted for consultation, including if it may be appropriate to exclude any of the planned procedures. In the event a decision is made to permanently discontinue dosing and all other interventions, please refer to the data to be collected at the ET visit of the schedule of events.

7.2. Discontinuation from Study

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit.

The investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a subject withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Subjects who discontinue the study after the first dose will be asked, if they agree, to come for a last assessment (ET visit). Subjects who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up.

Subjects who discontinue after Day 1 dosing will not be replaced.

Reasons for discontinuation may include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of an SAE, the study product is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication.
- The subject fails to comply with other protocol requirements.
- The subject is unable to continue visits or the study site is closed due to COVID-19 pandemic restrictions.
- The subject is withdrawn for any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- Other: the subject may withdraw from the study for any other reason, including withdrawal of consent.
- Study termination by the sponsor or regulatory authorities (refer to Section 7.4).

7.3. Lost to Follow-Up

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

The following actions must be taken if a subject fails to return to the clinic for a required study visit (unless this is required by the COVID-19 situation and virtual visits are scheduled instead):

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, three telephone calls

and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

- If all attempts to contact the subject fail he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4. Study Termination

The Sponsor has the right to terminate the study for any reason and at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of TEAE in this or other studies indicating a potential health risk to participants. In this case, all subjects will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical study site, inform both the subjects and the IRB/REB of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons. The study can also be terminated by IRB and/or regulatory agency for any unforeseen reasons.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Efficacy Assessments

Clinical evaluations of plaque psoriasis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.1.1. Psoriasis Area and Severity Index

The PASI will be evaluated at the visits specified in Table 1. This index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of BSA affected.[15] The PASI is a composite score ranging from 0 to 72 that that takes into account the degree of erythema, induration/infiltration, and desquamation (each scored from 0 to 4 separately) for each of four body regions, with adjustments for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. Refer to Appendix 2 for a complete description of this scale. To be eligible for this study, subjects must have a PASI score $\geq$ 12 at screening and Day 1 visit.

8.1.2. Physician's Global Assessment

The PGA of disease severity will be assessed at the visits specified in Table 1. The PGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity. A detailed description of PGA[16] scores is provided in Table 5. To be eligible for this study, subjects must have a PGA score $\geq$ 3 at screening and Day 1 visit.

Table 5: Physician's Global Assessment

Score	Grade	Description
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red; clearly distinguishable to moderate erythema; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

8.1.3. Body Surface Area

The overall BSA affected by plaque psoriasis will be evaluated (from 0% to 100%) at the visits specified in Table 1. The palmar surface of one hand (using the subject's hand and including the

fingers) represents 1% of his or her total BSA.[17] To be eligible, subjects must have a BSA affected by plaque psoriasis ≥ 10% at screening and Day 1 visit.

8.1.4. Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded at the visits specified in Table 1 using an NRS.[18,19] This will be evaluated during the visits by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pruritus is presented in Appendix 3.

8.1.5. Pain Numeric Rating Scale

The intensity of joint pain for subjects with concomitant psoriatic arthritis will be recorded at the visits specified in Table 1 using an NRS (modified from Farrar 2001).[20] This will be evaluated during the visits by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The NRS of pain is presented in Appendix 4.

8.2. Quality-of-Life Assessments/Subject Reported Outcomes

8.2.1. Dermatology Life Quality Index Questionnaire

The DLQI will be assessed at the visits specified in Table 1. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions.[21] Its use has been described in more than 1,000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled studies in dermatology. The questionnaire is provided in Appendix 5.

8.3. Safety and Other Assessments

8.3.1. Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), and body temperature (°C).

Weight (kg) will be recorded at the visits specified in Table 1. Height (cm) will only be recorded once at the screening visit.

Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE starting after dosing on Day 1.

8.3.2. Physical Examination

The following sites/systems will at least be included in the complete physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except plaque psoriasis)
- Head, eyes, ears, nose, throat
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. Any significant change will be reported as an AE in the source document and eCRF starting after dosing on Day 1.

8.3.3. Targeted Physical Examination

The following sites/systems will at least be included in the targeted physical examination that will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except plaque psoriasis)
- Respiratory
- Cardiovascular
- Abdominal

If deemed appropriate by the investigator based on the subject's condition, a complete physical examination as described in Section 8.3.2 can be performed instead of a targeted examination.

Information for all physical examinations must be included in the source document. Any significant change will be reported as an AE in the source document and eCRF starting after dosing on Day 1.

8.3.4. Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The specific tests in these panels are listed in Table 6.

Table 6: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	aPTT, HCT, Hgb, INR, MCH, MCHC, MCV, MPV, PLT, PT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, calcium, CPK, creatinine (enzymatic), GGT, glucose random, potassium, sodium, total bilirubin, direct bilirubin if total bilirubin > ULN, urea (BUN), uric acid
Fasting lipids	Cholesterol (total, LDL, and HDL), triglycerides (all fasting)
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen Microscopic analysis (as required)
Urine pregnancy test (conducted at the investigator site)	For WOCBP (at each visit, except screening)
Laboratory tests required at screening only	FSH levels for female subjects who have had a cessation of menses for at least 12 months prior to the screening visit without an alternative medical cause β-hCG for WOCBP Tuberculosis test (QuantiFERON-TB Gold) • Note: A T-Spot.TB test (TBT) may be used as an alternative to the QuantiFERON-TB Gold test as per Exclusion Criterion 17. If the TBT is used, the QuantiFERON-TB Gold test should not be performed. Serology (HBV [HBsAg, anti-HBc], HCV, HIV)

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; CPK, creatine phosphokinase; FSH, follicle-stimulating hormone; GGT, gamma--glutamyl-transferase; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; INR, international normalized ratio; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PLT, platelets; PT, prothrombin time; RBC, red blood cell (count); ULN, upper limit of normal; WBC, white blood cell (count); WOCBP, women of childbearing potential.

In case of a screening laboratory value abnormality, the test can be repeated once within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested. The QuantiFERON-TB test can only be repeated once if the result is indeterminate; tests with positive or negative results will not be repeated. The TBT may be used as an alternative to the QuantiFERON-TB test per Exclusion Criterion 17. The TBT may be repeated once only if the result is borderline (equivocal); tests with positive or negative results will not be repeated.

After the subject's first dose on Day 1, any clinically significant value will be reported as an AE. Any CTCAE Grade ≥ 2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia; clinically significant or not) or CTCAE Grade ≥ 3 elevation of CPK (clinically significant or not) will be reported as an AE and AESI (Section 8.4.7). If a subject experiences a CTCAE Grade ≥2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.4.7, dosing will be interrupted, and the subject followed with periodic testing until the laboratory values return to normal range. If the same subject develops a CTCAE Grade ≥2 cytopenia for a second time after dosing is resumed, then the subject will be permanently discontinued from treatment, but may be continued in the trial and followed until resolution of the adverse event(s).

8.3.4.1. Use of Local Laboratories

All protocol-specified laboratory tests (See Table 6) should be performed via the central laboratory. All attempts should be made to perform the laboratory assessments at the study site, via the central laboratory. In situations where the laboratory tests cannot be performed at the study site due to extenuating circumstances, such as quarantine or immobilization, the protocol-specified laboratory examinations may be conducted through a local laboratory. If the TBT is used as an alternative to the QuantiFERON-TB Gold test as per Exclusion Criterion 17, it may be performed via a local laboratory.

Use of local laboratories for any purpose beyond collection of protocol-specific laboratory tests that cannot be performed at central laboratory due to extenuating circumstances should be discussed with the medical monitor. Results from local laboratories will be recorded on the appropriate eCRF.

Follow-up safety monitoring will be conducted at the investigator's discretion. Results determined by the investigator to be SAEs or AESI, should be reported to the sponsor following the procedures described in Section 8.4.6, Section 8.4.7, and the Study Reference Manual, as applicable.

8.3.5. Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Any clinically significant value will be reported as an AE starting on Day 1.

8.3.6. Plasma Concentration of NDI-034858

Blood samples will be collected to measure plasma levels of NDI-034858 as follows:

- On Day 1 prior to dosing and 1 hour (± 5 min) postdosing;
- At Week 4 prior to dosing, 1 hour (± 5 min) postdosing, and 4 hours (± 10 min) postdosing;
- At Week 8 prior to dosing;
- At Week 12 anytime (no study treatment administration at this visit).
- At ET visit anytime (if ET visit is planned before Week 12 visit).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of plasma samples will be provided in the laboratory manual.

8.3.7. Biomarker Assessments in Urine

A urine sample that may be used to assess exploratory biomarker levels will be collected at the visits specified in Table 1 (predose, if applicable). Of note, at these visits, urine collected for urinalysis will be split and processed for both urinalysis and urine biomarkers evaluation.

The actual date and time of each urine sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of urine samples will be provided in the laboratory manual.

8.3.8. Biomarker Assessments in Blood

A blood sample to assess circulating cytokines and other inflammatory biomarker levels will be collected at the visits specified in Table 1 (predose, if applicable).

The actual date and time of each blood sample collection will be recorded. Details about the collection, processing, handling, storage, and shipping of blood samples will be provided in the laboratory manual.

8.3.9. Biomarker Assessments in Skin Biopsies

In a subset of subjects who consent to the procedure, three or four optional skin biopsies will be collected at the visits specified in Table 1 (predose, if applicable, and after all other assessments). Two 5-mm punch biopsies (one from lesional skin and one from adjacent non-lesional skin) will be collected on Day 1, and one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar, even if the lesion has cleared) at Week 12. In addition, one 5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary.

Each biopsy will be split in half. One part will be used for a limited immunohistochemistry panel (to evaluate immune cell infiltration) and the other part will be used for mRNA expression analysis.

Details about the collection, processing, handling, storage, and shipping of biopsy samples will be provided in the laboratory manual.

8.3.10. Biomarker Assessments in Skin Tape Strips

In a subset of subjects who consent to the procedure, skin tape strips will be collected from lesional skin and from adjacent non-lesional skin on Day 1, and from same lesional skin at Week 12.

8.3.11. Medical Photography

Medical photographs will be performed in a subset of subjects who consent to the procedure at the visits specified in Table 1.

Photographs will be identified as follows: study number, subject number, visit name, and date. Photographs will be uploaded and stored on a secured clinical website and will be transmitted to the sponsor for review. Additional information will be provided in the study reference manual.

8.3.11.1. Medical Photography - Biopsies

Investigator-selected target plaque areas will be biopsied. These target areas should be documented in the subject record and EDC, and the same targeted plaque areas should be followed throughout the study. All biopsied areas will be photographed prior to biopsy.

Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

8.3.11.2. Medical Photography- Full Body Front and Back

For full body photographs, all study photographs will be captured using the equipment, supplies, and guidelines provided by the sponsor or sponsors vendor.

Medical photographs, full body front and back, will be performed at selected study sites, in a subset of subjects who give written informed consent to the procedure, at the visits specified in Table 1. The full body photographs consist of four captures which include the upper posterior/anterior from the neck down and lower anterior/posterior from the toes up.

8.4. Adverse Events and Serious Adverse Events

8.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not considered related to the study product.

8.4.2. Definition of Serious Adverse Event

A SAE is any untoward medical experience occurring at any dose that results in any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the investigator).

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately -life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Prolongation of a scheduled hospitalization can be considered an SAE.

8.4.3. Classification of an Adverse Event

8.4.3.1. Relationship to Study Treatment

The investigator will assess causal relationship between each reported AE or SAE, and the experimental treatment. The investigator should consider the subject's medical history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine the causality of an AE or SAE:

- Not related: Temporal relationship of the onset of the AE or SAE, relative to the experimental treatment, is not reasonable, or another cause can explain the occurrence of the AE.
- Related: Temporal relationship of the onset of the AE or SAE, relative to the experimental treatment, is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

8.4.3.2. Adverse Event Severity

The severity of an AE or SAE is an estimate of the relative intensity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions from the National Cancer Institute (NCI) CTCAE, Version 5.0, published 27-Nov-2017 are to be used to rate the severity of an AE or SAE:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Note: A Semi-colon indicates 'or' within the description of the grade.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in severity should be documented in the medical record to allow assessment of the duration of the event at each level of severity. Adverse events characterized as intermittent require documentation of the start and stop of each incidence.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over several days, then those changes should be recorded separately (with distinct onset dates).

8.4.4. Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Study site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to dosing on Day 1 in the appropriate section of the source document and eCRF. Starting at dosing on Day 1, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to dosing on Day 1 will be considered as part of medical history and not reported as an AE. However, if the study subject's condition deteriorates after dosing on Day 1, it will be recorded as an AE.

Should a subject experience an AE at any time after dosing on Day 1 until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF.

Of note, any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from dosing on Day 1 until the end of participation in the study.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator. However, in case of an SAE, the subject should be followed until the event is resolved or stabilized as per the investigator's judgment.

8.4.5. Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

8.4.6. Serious Adverse Event Reporting

All SAEs, related to the experimental treatment or not, occurring during the study (from dosing on Day 1 to last study visit) must be reported on an SAE form to the sponsor-delegated vendor (see below contact information) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). When applicable, follow-up information should be reported to the sponsor-delegated vendor in the same manner as the original SAE report.

The SAE reporting period ends at the end of the follow-up period.

Reporting should be done by sending the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

Safety Contact Information: Innovaderm Drug Safety unit

E-mail: drugsafety@innovaderm.com

Fax: (514) 221-4199

Further to the determination of expedited criteria, the sponsor and delegate will manage the submission of individual case safety report to concerned regulatory agencies in accordance with local laws and regulations.

8.4.7. Adverse Events of Special Interest

The following are AESI:

- CTCAE Grade ≥ 2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia; clinically significant or not) defined by the following ranges:
  - Hemoglobin < 10.0 g/dL (< 100.0 g/L).
  - White blood cell count < 3.0 x 10^9/L (< 3000/mm^3).
  - Absolute neutrophil count of < 1.5 x 10^9/L (< 1500/mm^3).

  - Absolute lymphocyte count of < 0.8 x 10^9/L (< 800/mm^3).
  - Platelet count < 75 x 10^9/L (< 75000/mm^3).
- CTCAE Grade ≥ 3 elevation of CPK (clinically significant or not) defined as CPK > 5x ULN
- Major adverse cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke
- Thromboembolic events, defined as pulmonary embolism, deep vein thrombosis, and other venous and arterial thromboembolic events (eg, noncardiac, non-neurologic, fatal and nonfatal)
- Gastrointestinal perforation
- Malignancies
  - All malignancies
  - Non-melanoma skin cancer (NMSC)
  - Malignancy excluding NMSC
  - Lymphoma
- Infections
  - All infections
  - Serious infection
  - Opportunistic infection, excluding tuberculosis and herpes zoster
  - Herpes zoster
  - Active tuberculosis
- Adverse events of abnormal liver function tests
- Adverse events of renal dysfunction

Adverse events of special interest should be reported beginning on Day 1 after the first dose of study drug using the procedures detailed in Section 8.4.6. If an AESI does not meet any seriousness criteria, it must still be reported according to the SAEs reporting procedures for initial and follow-up reporting, but an AESI form would be used.

As per Section 7.1, if a subject experiences a CTCAE Grade ≥2 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.4.7 , dosing will be interrupted, and the subject followed with periodic testing until the laboratory values return to normal range. If the same subject develops a CTCAE Grade ≥2 cytopenia for a second time after dosing is resumed, then the subject will be permanently discontinued from treatment, but may be continued in the trial, and followed until resolution of the adverse events.

Immediate Reporting of AESI

1. Adverse events of special interest should be reported beginning on Day 1 after the first dose of study drug. The study site must formally notify the sponsor-delegated vendor within 24 hours of knowledge of the occurrence.
2. Even if an AESI does not meet any seriousness criteria, it must still follow the SAEs reporting procedures for initial and follow-up reporting (Section 8.4.6); however, an AESI form will be used.
3. All AESIs must be reported to the sponsor-delegated vendor within 24 hours of knowledge of the occurrence regardless of the following:
4. Whether or not the subject has undergone study-related procedures
5. The severity of the event
6. The relationship of the event to study drug
7. Refer to the Study Reference Manual's Official Study Contact List for complete contact information to report initial or follow-up information on an AESI.

8.4.8. Potential Drug Induced Liver Injury

Alanine aminotransferase or AST values ≥ 3 times the ULN will trigger the following actions and evaluations:

- The medical monitor should be contacted immediately;
- Liver tests including ALT, AST, total bilirubin, and alkaline phosphatase will be repeated from the original blood sample as soon as possible, and no longer that 72 hours after originally reported.

The following combination of signs, symptoms, or laboratory values (based on the original values, not the repeat), require at least temporary discontinuation of the study medication while workup is ongoing:

- ALT or AST ≥ 3 times the ULN and total bilirubin > 2 times the ULN in the presence of normal alkaline phosphatase;
- ALT or AST ≥ 8 times the ULN, regardless of other parameters;
- ALT or AST > 3 times the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

ALT or AST values ≥ 3 times the ULN but < 8 times the ULN without total bilirubin > 2 times the ULN or the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) do not require discontinuation of study treatment while workup is ongoing. Nonetheless, a subject may have dosing held based on investigator's medical judgement. Temporary discontinuation of study treatment may or may not lead to permanent discontinuation pending results of further workup and the overall clinical assessments. The

frequency of monitoring liver tests or relevant laboratory tests will be decided as part of the consultation between the investigator and medical monitor.

The medical monitor will work with the investigator to evaluate other possible causes of the observed liver test abnormalities. These other possible causes could include hepatitis (viral, alcoholic, or autoimmune); hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; and other concomitant treatments (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation).

8.4.9. Pregnancy Reporting

If a female subject becomes pregnant after dosing on Day 1 during the study and up to 4 weeks after the end of the study, or if a female partner of a male subject becomes pregnant after male subject dosing on Day 1 during the study and up to 12 weeks after the end of the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be permanently discontinued from the study treatment, if this occurs before the end of dosing period. The investigator must complete a study specific pregnancy form upon confirmation of a pregnancy and report it to the sponsor-delegated vendor within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). All cases of pregnancy will be reported to the sponsor-delegated vendor in a timely manner using the Pregnancy Form. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study drug period, or within 5 times the half-life or 12 weeks from their last dose of study drug, whichever is longer. The investigator will notify the pharmacovigilance unit of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.4.10. Overdose

Study product overdose is any accidental or intentional use of study product in an amount higher than the dose indicated per protocol for a given subject. Study product compliance (see Section 6.3.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study product overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.4.6, Serious Adverse Events Reporting, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures, but an overdose form would be used. The excess quantity and duration of the overdose should be recorded.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

The sample size determination is based on testing equality of two independent response rates using a 2-sided test with significance level of alpha = 0.05 and power 85%. The formula used for the calculation is the same as used in the nQuery® (ie, normal approximation with Fleiss' formula and continuity correction).

Assuming the placebo response rate at end of Week 12 is 10% (proportion of subjects achieving PASI-75), at least one of the NDI-034858 dose treatment groups will have a response rate at least 40%, and after adjustment of 15% dropout rate, a total of 250 subjects (50 per treatment group) will be randomized in the study.

9.2. Populations for Analyses

Efficacy will be evaluated on the basis of mITT analysis set. A supportive analysis will also be conducted on the PP analysis set.

Intent-to-treat (ITT) analysis set: This analysis set will include all subjects who were randomized. All subjects will be analyzed according to the treatment group to which they were randomized.

Modified intent-to-treat (mITT) analysis set: This analysis set will include all subjects who were randomized and received at least one dose of study treatment. All subjects will be analyzed according to the treatment group to which they were randomized. The mITT analysis set will be used as the primary analysis population for efficacy.

Per-protocol (PP) analysis set: This analysis set will include all subjects who were randomized, who received at least one dose of study product, and who provided evaluable data for the primary endpoint with no major protocol deviations affecting the efficacy evaluations. All subjects will be analyzed according to the treatment group that they actually received.

Safety analysis set: This analysis set will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment they received.

Pharmacokinetic (PK) analysis set: This analysis set will include all subjects who received at least one dose of NDI-034858 and have evaluable plasma concentration data.

Other analysis sets, including PD analysis set, may be defined in a separate analysis plan.

9.3. Statistical Analyses

9.3.1. General Approach

Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables and will include the number of subjects, mean, SD, median, minimum, and maximum.

Further details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values (if applicable) will be detailed in a separate SAP that will be prepared before the database is locked and any analyses are undertaken. Any deviation(s) from the SAP will be described and justified in the final Clinical Study Report, as appropriate.

All statistical tests will be two-sided and will be performed with a significant level of 0.05, unless otherwise specified in the SAP. To account for the multiplicity testing in the primary endpoint analysis, each active treatment group will be compared to the placebo group using a hierarchical testing procedure, starting with the highest dose group and ending with the lowest dose group (30-mg NDI-034858, 15-mg NDI-034858, 5-mg NDI-034858, and 2-mg NDI-034858, in order). No adjustment to alpha will be made to account for multiple testing between treatment groups for the secondary and exploratory efficacy endpoints.

9.3.2. Efficacy Analyses

The primary endpoint can be translated as a responder analysis, where a subject will be classified as responder if he or she achieves PASI-75 at Week 12. The comparison between groups for the primary endpoint will be done using a CMH, with prior treatment with biologics included as a stratification factor. The primary efficacy analysis will be performed on the mITT analysis set, while the PP analysis set will be used as a sensitivity analysis.

The secondary endpoints involving proportions of subjects will be analyzed using the same approach (CMH test) as described for the primary efficacy analysis, at each time point and based on the mITT analysis.

The continuous secondary endpoints involving absolute change from baseline will be analyzed using an MMRM based on the mITT analysis set only. The model will include treatment, visit, treatment by-visit interaction, and prior treatment with biologics as fixed effects, and baseline score as a covariate.

9.3.3. Safety Analyses

All safety analyses will be conducted using the safety analysis set. No inferential statistics will be performed on safety variables. Adverse events and SAEs will be presented and tabulated according to MedDRA classification by treatment group. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the relationship of the AE to study product, action taken with respect to the study product and the outcome.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by system organ class, preferred term, reported verbatim severity, seriousness, and investigator's assessment of the relationship to study product. For the summary of AEs by severity, each subject will be counted only once within a system organ class or a preferred term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a system organ class or a preferred term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject

will be counted only once within a system organ class or a preferred term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by treatment group, subject, detailing verbatim, system organ class, preferred term, start date, stop date, intensity, outcome, action taken with respect to study product, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. Serious adverse events will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing. Similar listings will be provided for the SAEs and AEs leading to the discontinuation from the study.

Results from vital signs, laboratory analyses, and ECGs will be tabulated by treatment and visit using descriptive statistics. The observed value at each visit, as well as the change from baseline will be presented. Shift tables describing shifts to out-of-normal range will be provided for clinical laboratory results, and normal to abnormal shift tables may be provided for vital signs.

Concomitant medications will be coded with the WHO-DD and listed by subject. Summary of medication classes will also be tabulated.

9.3.4. Pharmacokinetic Analyses

Concentration data will be listed per subject and summarized descriptively per dose.

9.3.5. Pharmacodynamic Analyses

Analyses of urine, blood, and skin biomarker levels will be described in a separate analysis plan.

9.3.6. Other Analyses

Descriptive summaries of subject disposition and baseline characteristics (including demographic data and prior concomitant therapy) will be presented by treatment group. In addition, a list of subjects who discontinued from the study along with discontinuation reason will be provided.

Protocol deviations will be summarized by treatment and category.

9.3.7. Planned Interim Analyses

No interim analysis is planned in this study.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2. Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by an IRB/REB. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or CRO) before initiation of the study and whenever subsequent modifications to the protocol are made.

10.3. Informed Consent Process

An ICF describing in detail the study treatment, study procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each i participant in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/REB approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed before the subject undergoes any study-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/REB. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

10.4. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study subjects, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study subjects and the IRB/REB and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB, Health Canada, and/or FDA.

10.5. Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. Confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained, and that subjects' identities are protected from unauthorized parties. On case report forms or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to Nimbus Lakshmi, Inc. (eg, subjects' written consent forms).

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

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

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

10.6. Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of study subjects are protected; that the reported study data are accurate, complete, and verifiable; and that the conduct of the study is following the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan.

Centralized monitoring, which consists of remote review of accumulating data from all sites, will be performed as detailed in the Centralized Monitoring Plan.

10.7. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

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

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study product accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the REB or IRB, and/or by the regulatory authorities. The investigator will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The study site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.8. Data Handling and Record Keeping

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

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 should be classified into two separate categories: investigator's study files and subject clinical source documents.

The investigator must maintain source documents for each subject in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using Medrio, a web-based EDC and reporting system. This application will be set up for remote entry. Medrio is the developer and owner of Medrio. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

10.9. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. The study monitor must ensure that prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of study results is discovered, a root cause analysis will be performed, and appropriate corrective and preventive actions will be implemented.

Protocol deviations must be sent to the reviewing IRB per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.10. Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The study will be registered on ClinicalTrials.Gov prior to the first subject being dosed.

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APPENDIX 1. PARTIAL LIST OF STRONG OR MODERATE INHIBITORS OF CYP3A4

CYP3A4 Inhibitors	
Strong*	Moderate
boceprevir	aprepitant
clarithromycin	ciprofloxacin
cobicistat	conivaptan
idelalisib	crizotinib
itraconazole	cyclosporine
ketoconazole	diltiazem
nefazodone	dronedarone
nelfinavir	erythromycin
posaconazole	fluconazole
ritonavir or any combination medication containing ritonavir	fluvoxamine
telaprevir	imatinib
telithromycin	tofisopam
troleandomycin	verapamil
voriconazole	

*Grapefruit juice is also considered a strong inhibitor of CYP3A4. Please refer to Exclusion Criteria 31 for restrictions on grapefruit or grapefruit juice consumption.

Note: Strong and moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold and ≥2 to <5-fold, respectively.

Adapted from:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; accessed 7 Apr 2021

APPENDIX 2. PSORIASIS AREA AND SEVERITY INDEX

PASI Scoring

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (plaque thickness), and desquamation (scaling), as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = no symptoms
- 1 = slight
- 2 = moderate
- 3 = marked
- 4 = very marked

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10% to <30%
- 3 = 30% to <50%
- 4 = 50% to <70%
- 5 = 70% to <90%
- 6 = 90% to 100%

Assignments for the following body regions are as follows:

- Neck: include with the head.
- Buttocks: include with the lower extremities.
- Axillae: include with the trunk.
- Genitals: include with the trunk.
- The inguinal canal separates the trunk and legs anteriorly.

The PASI score for each body region is obtained by using the formula below:

$$PASI = 0.1\ (E_h + I_h + D_h)\ A_h + 0.2\ (E_u + I_u + D_u)\ A_u + 0.3\ (E_t + I_t + D_t)\ A_t + 0.4\ (E_l + I_l + D_l)\ A_l$$

Where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

APPENDIX 3. PRURITUS NUMERIC RATING SCALE

On scale from 0 ("no itch") to 10 ("worst imaginable itch"), how was your worst itch in the past 24 hours? Please select one number.

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10 No itch Worst imaginable itch

Source: http://www.pruritussymposium.de/numericalratingscale.html

APPENDIX 4. PAIN NUMERIC RATING SCALE

Select the number that best describes your *WORST* joint pain (with regards to your psoriatic arthritis) during the past 24 hours? Please select one number.

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10
No pain — Worst imaginable pain

Source: modified from Farrar 2001

APPENDIX 5. DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check 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 **yard?**	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	□ □ □	

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

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.