Clinical Study Protocol

NCT Number: NCT05153148

Title: A Phase 2b, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Multiple -Dose Study to evaluate the Efficacy, Safety, and Tolerability of NDI-034858 in Subjects With Active Psoriatic Arthritis

Study Number: 4858-202

Document Version and Date: Version 4.0, 05 May 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A Phase 2b, Randomized, Multi-Center, Double-Blind, Placebo-Controlled, Multiple -Dose Study to evaluate the efficacy, safety, and tolerability of NDI-034858 in Subjects with active Psoriatic Arthritis

CLINICAL PROTOCOL 4858-202

EUdraCT Number: 2021-005888-52

IND Number: 158014

Sponsor:	**Nimbus Lakshmi, Inc.** a fully owned subsidiary of Takeda Pharmaceuticals U.S.A., Inc. 95 Hayden Avenue Lexington, MA, United States 02421 **Telephone: +1 781-482-9222**
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Version:	4.0, Amendment 3
Issue Date:	05 May 2023

Confidentiality Statement

This document is a confidential communication of Nimbus Lakshmi, Inc. Acceptance of this document constitutes the agreement by the recipient that no information contained herein will be published or disclosed without written authorization from Nimbus Lakshmi, Inc. Furthermore, the information is only meant for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduct of the study.

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PROTOCOL VERSION HISTORY

Version/Date: Version 1 / 06-Sep-2021

Rationale for amendment: Initial version

Main changes to the protocol: Not Applicable

Version/Date: Version 2, Amendment 1 / 27 Oct 2021

Rationale for amendment: Clarification of certain processes and correction of minor grammatical and typographical errors

Main changes to the protocol:

- Subjects with SAEs or severe AEs may be discontinued from study drug regardless of relationship to drug.
- Added homeopathic medications to the concomitant medications recorded.
- Clarified that erythrocyte sedimentation rates will be performed at the clinical sites, not the central laboratory.
- PGA [redacted] were described for clarity
- Revised stopping rules for potential hepatic laboratory abnormalities
- Global revisions for punctuation, formatting, grammatical and typographical errors

Version/Date: Version 3, Amendment 2 / 06 Apr 2022

Rationale for amendment: Inclusion of FDA requested changes. Clarification of certain processes and correction of typographical errors. See Summary of Changes document for comprehensive edits.

Main changes to the protocol:

- Revised statistical analysis methods to include estimand of interest, clarifications for definition of analysis data sets, use of the Mantel-Haenszel stratum-weighted test.
- Clarified and defined study objectives and endpoints
- Modified Inclusion Criteria 1 to remove upper age cap.
- Referenced Appendix 2 in Inclusion Criteria 8 and 10. Appendix 2 provides local contraception requirements that may apply
- Clarified washout period for biologic agents in Exclusion Criteria 4 and 9. Added Appendix 3 –DMARDS Half-life.
- Noted Exclusion Criteria 37, the T-Spot.TB (TBT) test is an acceptable alternative to the QFT test in regions where TBT is standard practice.

- Added Exclusion Criteria 42 excluding subjects with severe hepatic impairment
- Clarified in Section 6.1 that food intake is not restricted, subjects only need to fast at visits requiring a fasting lipid panel
- Added footnotes to SoA clarifying the timing of each visit is based on Day 1, allowance for use of a T-Spot.TB test, and timing for AE collection based on Day 1 dosing time.
- Update to Table 2 Potential Risks of NDI-034858, Potential risk of CPK elevation, Summary of Data/Rationale for Risk to align with the current DSUR.
- Added information to Section 6.1 defining the formulation of NDI-034858 used in this study.

Version/Date: Version 4, Amendment 3 / 05 May 2023

Rationale for amendment:

On February 08, 2023, Nimbus Lakshmi Inc. was acquired by Takeda Pharmaceuticals USA, Inc. (Takeda).

Clarification of certain processes and correction of typographical errors. See Summary of Changes for comprehensive edits.

Main changes to the protocol:

- Reflect that study sponsor, Nimbus Lakshmi Inc, is now a fully owned subsidiary of Takeda.
    - Sponsor change of address
    - NDI-034858 is now also known as TAK-279
- Stratification factor corrections for both prior treatment (“AND” to “OR”) and region “(US&Germany/Eastern Europe)” to “(US/Germany)/(Eastern Europe)”

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), and/or Independent Ethics Committee (IEC) 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/IEC 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/IEC before the changes are implemented to the study. All changes to the consent form will be IRB/REB/IEC 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.

Electronic signatures of the following individuals are provided on the last page of this document.

[redacted], MD, [redacted], Clinical Sciences
[redacted], PharmD, PhD, [redacted]. Clinical Sciences
[redacted], Statistics and Quantitative Sciences
[redacted] Pharmacovigilance

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(dd-Mon-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.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Summary of Change(s) Since the Last Version of the Approved Protocol			
Protocol Version 4.0, Amendment 3.0			
Amendment Date: 05 May 2023			**Global/Region/Country/Site Specific:** Global
Overall Reason for the Amendment The immediate reason for this protocol update is to: • Reflect that study sponsor, Nimbus Lakshmi Inc, is now a fully owned subsidiary of Takeda. o Sponsor change of address o NDI-034858 is now also known as TAK-279 • Stratification factor corrections for both prior treatment ("AND" to "OR") and region "(US&Germany/Eastern Europe)" to "(US/Germany)/(Eastern Europe)"			
Description of Each Change and Rationale			**Section(s) Affected by Change**
#	**Description of change(s)**	**Rationale for change(s)**	**Section**
1	Sponsor addressed and ownership updated	Nimbus Lakshmi Inc is now a fully owned subsidiary of Takeda Pharmaceuticals U.S.A., Inc	Cover Page
2	TAK-279 added as another name of the investigational product and active ingredient	NDI-034858 also known as TAK-279	Section 1.1 Section 2.1.2 Section 6.1, Table 3

Summary of Change(s) Since the Last Version of the Approved Protocol			
3	Prior treatment stratification with biologics "and" non-traditional DMARDs changed to "or" Commas added before ", and region" to delineate a separate stratification factor Corrected region stratification factor from "US&Germany/Eastern Europe" to "(US/Germany)/(Eastern Europe)"	Prior treatment with biologics or DMARDs as the stratification factors Region is a separate stratification factor US or Germany versus Eastern Europe are the region stratification factors	Section 1.1 Section 4.3 Section 6.3 Section 9.3.2
4	Separated "Proportion of subjects achieving at least an ACR-50 or ACR-70 response at Week 12" to "…achieving ACR-50 response at Week 12" and "…achieving ACR-70 response at Week 12"	Clarified "ACR-50 or ACR-70" secondary endpoints by separating into 2 statements	Section 1.1 Section 8.4.2
5	Fixed error linking to local laboratory tests	Link was broken	Section 8.4.4.1
6	Updated Version History	Version 4, Amendment 3 rationale added	Protocol Version History
7	Removed wet signature from Signature Page	Electronic signatures will be applied through EDMS	Signature Page
8	Updated References format	Updated References format to Harvard Copy format	Section 11
9	Formal Summary of Changes included in this table	This current table added	Protocol Amendment Summary of Changes Table

See Protocol Version History for all previous amendments.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ACR20/50/70	American College of Rheumatology 20/50/70
ADL	activities of daily living
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-CCP	Anti-cyclic citrullinated peptide antibodies
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
CASPAR	Classification Criteria for Psoriatic Arthritis
C_{max}	maximum observed concentration
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP3A	cytochrome P450 3A
DAPSA	Disease Activity Index for Psoriatic Arthritis
[redacted]	[redacted]
DDI	drug-drug interaction

Abbreviation	Definition
DMARD	disease-modifying anti-rheumatic drug
DTP	direct-to-patient
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
ESR	erythrocyte sedimentation rate
ET	early termination
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
gm	Gram
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	Hematocrit
HCV	hepatitis C virus
Hgb	Hemoglobin
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
IB	Investigator Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL	Interleukin

Abbreviation	Definition
IND	Investigational New Drug
IFNγ	interferon gamma
IRB	institutional review board
ITT	intent-to-treat
IWRS	Interactive Web Response System
JAK	Janus kinase
LEI	Leed's Enthesitis Index
MAD	multiple ascending dose
MDA	Minimal Disease Activity
MH	Mantel-Haenzel
MTX	Methotrexate
N/A	not applicable
NMSC	non-melanoma skin cancer
NOAEL	no observable adverse effect level
NSAID	non-steroidal anti-inflammatory drug
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
PASI-50/75/90	50%/75%/90% improvement from baseline in Psoriasis Area and Severity Index
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	Pharmacodynamic
PGA	Physician Global Assessment
PK	pharmacokinetic
PP	per-protocol
PPD	purified protein derivative
PRN	as needed
PsA	psoriatic arthritis
[redacted]	[redacted]
PT	preferred term
PUVA	psoralen and ultraviolet A
QC	quality control

Abbreviation	Definition
QD	once daily
RA	rheumatoid arthritis
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	spray dried dispersion
[redacted]	[redacted]
SJC	swollen joint count
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
TEAESI	Treatment-emergent adverse event of special interest
TESAE	treatment-emergent serious adverse events
Th	T helper
TJC	tender joint count
T_{max}	time to maximum observed concentration
TNF	tumor necrosis factor
TNFi	tumor necrosis factor inhibitor
TPGS	d-α-tocopheryl polyethylene glycol 1000 succinate
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UV	ultraviolet
VAS	visual analog scale
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	**Name of Investigational Product:** NDI-034858 (TAK-279)	**Name of Active Ingredient:** NDI-034858 (TAK-279)

Title of Study:

A Phase 2b, Randomized, Multi-center, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy, Safety, and Tolerability of NDI-034858 in Subjects with Active Psoriatic Arthritis

Phase of Development:

Phase 2b

Study Sites:

Approximately 80 global study sites in North America and Europe will participate in this study.

Number of Subjects (planned):

Approximately 260 subjects will be randomized in this study (approximately 65 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 (also known as TAK-279) at doses of [redacted], or placebo will be orally administered once daily (QD) for 12 weeks. NDI-034858 will be available in [redacted] strength [redacted]. 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 ratio.

Objectives:

The primary objective is:

- To assess the efficacy of NDI-034858 orally administered QD at [redacted] for 12 weeks on the rheumatological signs, symptoms and function in subjects with active psoriatic arthritis (PsA)

The secondary objectives are:

- To assess additional evaluations of efficacy of NDI-034858 orally administered QD at [redacted] for 12 weeks in subjects with active PsA
- To assess the safety and tolerability of NDI-034858 orally administered QD at [redacted] for 12 weeks in subjects with active PsA
- To evaluate the plasma concentration of NDI-034858 orally administered QD at [redacted] in subjects with active PsA

The exploratory objectives are:

- [redacted]

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	**Name of Investigational Product:** NDI-034858 (TAK-279)	**Name of Active Ingredient:** NDI-034858 (TAK-279)
[redacted]		

Endpoints:

Primary efficacy endpoint:

- Proportion of subjects achieving at least an American College of Rheumatology (ACR) 20 response at Week 12

Secondary endpoints - Efficacy:

- Proportion of subjects achieving ACR-50 response at Week 12
- Proportion of subjects achieving ACR-70 response at Week 12
- Change from baseline (Day 1) in tender joint count at Week 12
- Change from baseline (Day 1) in swollen joint count at Week 12
- Change from baseline (Day 1) in Patient Global Assessment of Psoriatic Arthritis at Week 12
- Change from baseline (Day 1) in Patient Global Assessment of Psoriatic Arthritis Pain at Week 12
- Change from baseline (Day 1) in Physician Global Assessment of Psoriatic Arthritis at Week 12
- Change from baseline (Day 1) in Health Assessment Questionnaire-Disability Index (HAQ-DI) score at Week 12
- Change from baseline (Day 1) in dactylitis count at Week 12, among subjects who have dactylitis at Day1
- Change from baseline (Day 1) in Leed's Enthesitis Index (LEI) at Week 12, among subjects who have enthesitis at Day 1
- Proportion of subjects with Minimal Disease Activity (MDA) at Week 12
- Change from baseline (Day 1) in Disease Activity Index for Psoriatic Arthritis (DAPSA) at Week 12
- Proportion of subjects achieving 75% improvement from baseline (Day 1) in Psoriasis Area Severity Index [(PASI)-75] at Week 12 among subjects with ≥3% body surface area (BSA) psoriatic involvement at Day 1
- Proportion of subjects achieving a Physician Global Assessment of Psoriasis of 0 or 1 and at least a 2 -point improvement from baseline at Week 12

Secondary endpoints - Safety:

- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs) and treatment-emergent adverse events of special interest (TEAESIs)
- Assessment of clinically relevant changes in vital signs, clinical laboratory parameters, proportion of subjects with clinically significant abnormal electrocardiograms (ECGs), and physical examinations

Secondary endpoint - Pharmacokinetics:

- Measurement of plasma concentrations of NDI-034858 in subjects receiving [redacted] of NDI-034858

Exploratory Endpoints:

[redacted]

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	**Name of Investigational Product:** NDI-034858 (TAK-279)	**Name of Active Ingredient:** NDI-034858 (TAK-279)

[redacted]

Study Design

This is a Phase 2b, randomized, multi-center, double-blind, placebo-controlled, multiple-dose study designed to evaluate the efficacy, safety, and tolerability of NDI-034858 (also known as TAK-279) in subjects with active PsA. The evaluation of plasma concentrations of NDI-034858 [redacted]

Approximately 260 male and female subjects, aged 18 and higher, with active PsA will be randomized in this study. To be eligible for the study, the subjects must have a history of PsA diagnosis with symptoms for ≥ 6 months prior to the screening visit and must meet all of the inclusion criteria, including the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, with ≥ 3 tender and ≥ 3 swollen joints at screening and baseline (Day 1) visits, and with active PsA despite previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs), traditional disease-modifying anti-rheumatic drugs (DMARDs), or one tumor necrosis factor inhibitor (TNFi).

All subjects will read and sign a written informed consent form (ICF) prior to performing any screening procedures. Subjects who fulfill all the inclusion criteria and none of the exclusion criteria will be included in the study. During a screening period of no longer than 30 days, subjects will be randomized (on Day -7) to receive either one of three doses of NDI-034858 ([redacted]), or placebo on Day 1. The goal is to have approximately 65 subjects randomized per treatment group (1:1:1:1 ratio). During the treatment period, NDI-034858 ([redacted]) 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 / early termination visit), and 16 (end of study [EOS]).

Efficacy will be assessed using the ACR20 composite measure (including tender and swollen joint count, subject assessment of PsA pain visual analog scale [VAS], patient global PsA assessment VAS, physician global assessment PsA VAS, HAQ-DI, and hsCRP) as well as the individual components. Efficacy for psoriasis among subjects who have ≥ 3% BSA involvement on Day 1 will be measured using PASI, BSA, and Physician Global Assessment of Psoriasis.

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 concentrations of NDI-034858.

[redacted]

No interim analysis is planned in this study.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

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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 criteria:

1. Subject is male or female, aged ≥18 years, at the time of consent.
2. Subject has PsA on the basis of the CASPAR with peripheral symptoms at the screening visit, as assessed by the investigator.
3. Subject has PsA symptoms for ≥ 6 months prior to screening, as assessed by the investigator.
4. Subject has ≥ 3 tender joints and ≥ 3 swollen joints at screening and Day 1 visits, as assessed by the investigator.
5. Subject has at least one lesion of plaque psoriasis ≥ 2 cm in diameter, nail changes characteristic of psoriasis, or a documented history of plaque psoriasis.
6. Subject has active PsA despite previous standard doses of NSAIDs administered for ≥ 4 weeks, or traditional DMARDs (including methotrexate and sulfasalazine) administered for ≥ 3 months, or TNFi agents administered for ≥ 3 months, or subjects are intolerant to NSAIDs or DMARDs or TNFi agents, as assessed by the investigator.
7. If subject is on concurrent PsA treatments, they must be on stable doses as described below and for the duration of the study:
    a. Methotrexate (MTX): subject must have received treatment for ≥ 3 months, with stable dose and stable route of administration (not to exceed 25 mg MTX per week) for ≥ 4 weeks prior to Day 1 until Week 16 (EOS); subjects on MTX should be taking folic acid supplementation according to local standard of care to minimize the likelihood of MTX associated toxicity.
    b. Sulfasalazine: Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to Day 1.
    c. Other traditional DMARDs not listed may be considered on a case-by-case basis after discussion with the medical monitor.
    d. Oral corticosteroids: the subject must be on a stable dose, not to exceed the equivalent of 10 mg of prednisone per day, for ≥ 2 weeks prior to Day 1. If subject is not currently using oral corticosteroids, must not have received for at least 2 weeks prior to Day 1.
    e. NSAIDs or paracetamol/acetaminophen: the subject must be on a stable dose for ≥ 2 weeks prior to Day 1. If not currently using NSAIDs, must not have received for at least 2 weeks prior to Day 1.
8. 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 screening until at least 4 weeks after the last study drug 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), tubal ligation, 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. See Appendix 2 for additional local requirements or restrictions that may apply.

    Note: Subjects must have been on a stable dose of 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

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	Name of Investigational Product: NDI-034858 (TAK-279)	Name of Active Ingredient: NDI-034858 (TAK-279)

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 test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

9. Female subjects of childbearing potential must have had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
10. 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 8, from Day 1 until at least 12 weeks after the last study drug 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 drug administration. See Appendix 2 for additional local requirements or restrictions that may apply.

    Note: Male subjects must refrain from donating sperm from Day 1 until at least 12 weeks after the last study drug 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 non-vasectomized subjects.
11. Subject has a body mass index (BMI) of >18 kg/m^2, inclusive, (BMI = weight (kg)/[height (m)]^2), and total body weight >50 kg (110 lb).
12. Subject is willing to participate and is capable of giving informed consent. Note: Signed, dated, written informed consent must be obtained prior to any study-related procedures.
13. 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:

1. Subject has other disease(s) that might confound the evaluations of benefit of NDI-034858 therapy, including but not limited to rheumatoid arthritis, axial spondyloarthritis (this does not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, Lyme disease or fibromyalgia.
2. 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 baseline (Day 1).
3. Subject has a history of lack of response to > 1 therapeutic agent targeting tumor necrosis factor.
4. Subject has received infliximab, golimumab, adalimumab, or certolizumab pegol, or any biosimilar of these agents, within 8 weeks or 5 half-lives (see Appendix 3), whichever is longer, prior to baseline (Day 1).
5. Subject has received etanercept, or any biosimilar of etanercept, within 4 weeks prior to baseline (Day 1).

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6. Subject has received rituximab or any immune-cell-depleting therapy within 6 months prior to baseline (Day 1).
7. Subject has received any marketed or investigational biological agent, other than those specified in other inclusion/exclusion criteria, within 12 weeks or 5 half-lives (whichever is longer, see Appendix 3) prior to baseline (Day 1).
8. Subject is currently receiving a non-biological investigational product or device or has received one within 4 weeks prior to baseline (Day 1).
9. Subject has received apremilast or other non-biologic systemic treatment for PsA within 4 weeks prior to baseline (Day 1), other than MTX, sulfasalazine, corticosteroids, NSAIDs, or paracetamol/acetaminophen, which are allowed at stable doses as described in Inclusion Criterion 7. Subject has received leflunomide within 95 days of baseline (Day 1) if no elimination procedure was followed or adhere to an elimination procedure (eg, 11 days with cholestyramine or 30 days washout with activated charcoal as per local label). For subjects not receiving MTX and sulfasalazine at Screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1).
10. Subject has received intraarticular injection (including corticosteroids), intramuscular steroids, intralesional steroids, or intravenous steroids within 4 weeks prior to baseline (Day 1). For subjects not receiving MTX and sulfasalazine at screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1).
11. Subject has received high potency opioid analgesics (eg, methadone, hydromorphone, or morphine) within 2 weeks prior to baseline (Day 1).
12. Subject has used any topical medication that could affect PsA or psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], Janus kinase [JAK] inhibitors, or tar) within 2 weeks prior to baseline (Day 1).
13. Subject has used any systemic treatment that could affect PsA or psoriasis (including oral retinoids, immunosuppressive/immunomodulating medication, cyclosporine, oral JAK inhibitors, or apremilast) within 4 weeks prior to baseline (Day 1), unless otherwise excluded or allowed by protocol.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
14. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to baseline (Day 1).
15. Subject has had psoralen and ultraviolet A (PUVA) treatment within 4 weeks prior to baseline (Day 1).
16. Subject has received Chinese traditional medicine within 4 weeks prior to baseline (Day 1).
17. Subject has received any live-attenuated vaccine, including for Coronavirus Disease-19 (COVID-19), within 4 weeks prior to baseline (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 drug, whichever is longer, after the last study drug 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.
18. 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 baseline (Day 1).
19. Subject has consumed grapefruit or grapefruit juice within 1 week prior to baseline (Day 1).

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

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20. Subject has used tanning booths within 4 weeks prior to baseline (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.

21. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
22. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or drug-induced psoriasis.
23. 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.
24. 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.
25. Subject had a major surgery within 8 weeks prior to baseline (Day 1or has a major surgery planned during the study.
26. Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
27. Subject has an estimated creatinine clearance of < 40 mL/min based on the Cockcroft-Gault equation or a history of renal failure as defined by the investigator

    – Cockcroft Gault equation:

    Creatinine Clearance (estimated) / Conventional mL/min =

    (140 - Age [years]) x Weight (kg) x Factor a) / (72 x serum creatinine [mg/dL])

    Note: Factor a = 0.85 in females and 1.00 in males.

28. Subject was hospitalized in the 3 months prior to screening 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 baseline (Day 1).
29. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to baseline (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.
30. Subject has a history of fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection within 4 weeks prior to baseline (Day 1).
31. Subject has an active bacterial, viral, fungal, mycobacterial infection, or other infection (including tuberculosis [TB] or atypical mycobacterial disease), or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 12 weeks prior to baseline (Day 1), or oral antibiotics within 4 weeks prior to baseline (Day 1).
32. 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 (with the exception of superficial fungal infection of the nailbed), or infected skin wounds or ulcers.
33. 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.

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34. 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.
35. 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).
36. Subject has positive results for hepatitis B surface antigens, antibodies to hepatitis B core antigens, hepatitis C virus (HCV), or human immunodeficiency virus. Samples testing positive for HCV antibodies will require polymerase chain reaction (PCR) qualitative testing for HCV RNA. Any HCV RNA PCR result that meets or exceeds detection sensitivity is exclusionary.
37. Subject has clinical or laboratory evidence of active or latent TB infection at screening.

    Note: Subjects will be evaluated for TB infection by QuantiFERON-TB Gold (or a purified protein derivative [PPD] skin test, or equivalent, (or both if required per local guidelines) and chest X-ray. The PPD skin test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless local guidelines require both tests). Chest X-ray may be taken at screening or completed within 3 months prior to the screening visit, with documentation showing no evidence of infection or malignancy as read by a qualified physician.

    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.

    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. Latent TB is defined as a positive QFT test or two successive indeterminate QFT tests at screening.
38. Subject with any of the following laboratory values at the screening visit:
    a) Alanine aminotransferase or aspartate aminotransferase 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
39. 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).
40. 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).
41. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to baseline (Day 1).
42. Subject has known history of moderate to severe hepatic impairment, Class B or C, by Child-Pugh scoring system.

Statistical methods:

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Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables including the number of subjects, mean, standard deviation, 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. No adjustment to alpha will be made to account for multiple testing between treatment groups.

Study Drug Exposure and Compliance:

Exposure to study drug and study drug compliance will be summarized for each treatment group for the Safety Analysis Set.

Efficacy Analyses:

The primary endpoint can be translated as a responder analysis, where a subject will be classified as responder if they achieve ACR20 at Week 12. Comparison of the primary endpoint will be made between each dose group and the placebo group using a two-sided Mantel-Haenszel (MH) test of the risk difference in two proportions stratified by the randomization stratification factors (prior treatment with biologics or non-traditional DMARDs [yes/no], and region [(USA/Germany)/(Eastern Europe)]. The estimated MH risk difference will be summarized along with the two-sided 95% CI using MH stratum weights (Mantel, 1959) and the Sato variance estimator (Sato, 1989). The primary efficacy analysis will be performed on the full analysis set (FAS), while the intent-to-treat and per protocol sets will be used as a supplementary analysis. Use of the FAS dataset as primary is to assess the clinical question of interest in the protocol to determine treatment effect for dosing and efficacy. Estimands and additional sensitivity analyses will be described in the SAP.

A descriptive analysis will be performed in demographic subgroups including age, gender, race, and BMI to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and the randomization stratification factor will also be conducted and described in the SAP.

The secondary endpoints involving proportions of subjects will be analyzed using the same approach (MH test of the difference) as described for the primary efficacy analysis and based on the FAS.

The continuous secondary endpoints involving change from baseline will be analyzed using a mixed model for repeated measures based on the FAS. The model will include fixed effects for treatment group, visit, and treatment group-by-visit interaction, with baseline score and the randomization stratification factor as covariates, and the change from baseline as the dependent variable. Additional details on sensitivity analyses and missing data imputation of the secondary endpoints will be provided in the SAP.

Safety Analyses:

Name of Sponsor/Company: Nimbus Lakshmi, Inc.	Name of Investigational Product: NDI-034858 (TAK-279)	Name of Active Ingredient: NDI-034858 (TAK-279)

All safety analyses will be performed on the Safety Analysis Set. No inferential statistics are planned for safety variables.

Adverse events will be coded using Medical Dictionary for Regulatory Activities version 24.0 or higher and summarized by system organ class (SOC) and preferred term (PT). Collection of Adverse Events will begin after dosing on Day 1. Analysis and reporting for AEs will be based on TEAEs. A TEAE is defined as an AE occurring (onset date/time) at the time of or after dosing on Day 1. Adverse events with missing start and/or end dates and/or times (if applicable) will be handled as described in the SAP.

All TEAEs will be listed for each subject. Separate listings will be presented for TEAEs, TESAEs, and TEAESIs. Each category will be presented for events leading to discontinuation of study drug and events leading to study discontinuation. All listings will be done by treatment group and subject, detailing verbatim, SOC, PT, start date, stop date (if resolved), intensity, seriousness, outcome, action taken with respect to study drug, and relationship to study drug. The AE onset will also be shown relative (in number of days) to the day of study drug administration.

Results from vital signs, laboratory analyses, ECGs, and physical examination will be listed by subject and timepoint. Descriptive summaries of vital signs, laboratory analyses, ECGs and physical examination will also be provided.

Exploratory Analyses:

[redacted]

Other Analyses:

Descriptive summaries of subject disposition and baseline characteristics (including demographic data and medical and surgical history) will be presented by treatment group, and also listed. Protocol deviations will be listed and summarized by treatment and category.

Medications will be coded using the World Health Organization Drug Dictionary and listed by subject. A summary of concomitant medications by treatment group and medication class will also be tabulated.

Pharmacokinetic Analyses:

Plasma concentration data will be listed per subject and summarized descriptively per dose for each scheduled sampling time point.

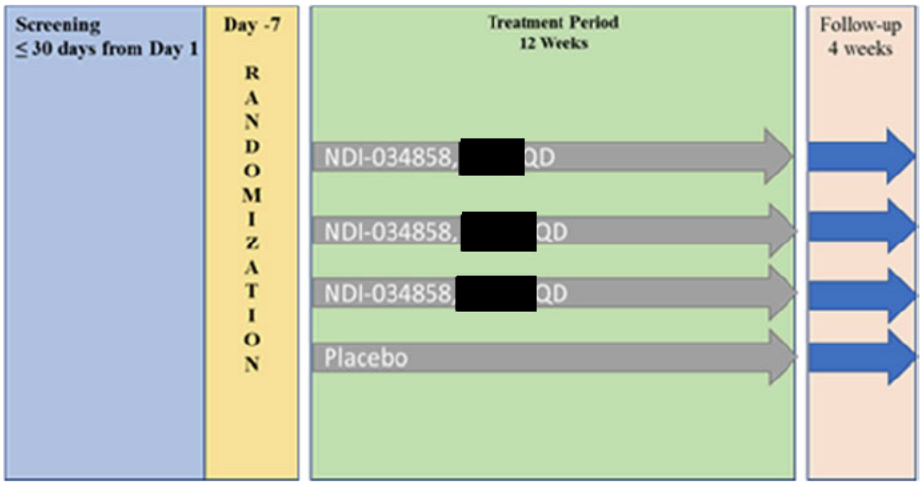
Sample Size Consideration:

A sample size of 65 per treatment group across all sites will have 83% power using a two-sided test for difference in the two proportions, assuming a type I error rate of 0.05, a 55% response rate for each NDI-034858 dose group as a proportion of ACR20 response, and a placebo ACR20 response rate of 30%. A total number of 260 subjects (65 per treatment group) are planned to be randomized into the study with a 1:1:1:1 allocation.

The sample size was calculated in nQuery 8.7 using a two-sample Z-Test (Chi-Square Test) pooled for difference of proportions.

1.2. Study Diagram

Figure 1: Study Diagram



QD = once daily
Note: Study drug should be taken at the same time each day whenever possible.

1.3. Schedule of Assessments

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the written informed consent form (ICF). No treatment or study-related procedures will be initiated before the ICF 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 drug administration, if applicable. There is no study drug administration the day of the Week 12 visit. Patient reported assessments (Health Assessment Questionnaire – Disability Index [HAQ-DI], [redacted] must be completed prior to other efficacy assessments.

The Coronavirus Disease-19 (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 subject's record and entered into electronic data capture (EDC).

An unscheduled visit may be conducted for clinical reasons such as the appearance of new symptoms or an adverse event (AE); for laboratory testing pertaining to subject safety; to return study drug, particularly if there is an issue concerning loss of or damage to study drug; administrative reasons wherein the subject requests a visit for clarification of any study procedure; or other similar type of situation.

Table 1: Schedule of Assessments

Study Time Frame/ Visit	Screening Period		Treatment Period[a]						Follow-up
	Screening Day –30 to Day -1 Visit 1	Day --7[b]	Day 1 Visit 2	Week 1 Visit 3	Week 2 Visit 4	Week 4 Visit 5	Week 8 Visit 6	Week 12 EOT/ET Visit 7	Week 16 EOS Visit 8
Windows (days)		(±1)	(±1)	(±2)	(±2)	(±2)	(±3)	(±3)	(±4)
Informed consent	X								
Demographics	X								
Medical and surgical history	X		X						
Inclusion and exclusion criteria	X		X						
Pregnancy test[c]	X		X	X	X	X	X	X	X
Serology (HIV, HBV [HBsAg, antiHBc], HCV)	X								
QuantiFERON-TB Gold test[d]	X								
Chest X-ray[e]	X								
Rheumatoid factor and anti-CCP	X								
Vital signs[f]	X		X	X	X	X	X	X	X
Complete physical examination	X							X	
Targeted physical examination[g]			X	X	X	X	X		X
Clinical laboratory tests (hematology, chemistry, UA, FSH[h])	X		X	X	X	X	X	X	X
Fasting lipid panel			X					X	

Table 1: Schedule of Assessments

Study Time Frame/ Visit	**Screening Period**		**Treatment Period[a]**						**Follow-up**
	Screening Day –30 to Day -1 Visit 1	**Day --7[b]**	**Day 1 Visit 2**	**Week 1 Visit 3**	**Week 2 Visit 4**	**Week 4 Visit 5**	**Week 8 Visit 6**	**Week 12 EOT/ET Visit 7**	**Week 16 EOS Visit 8**
Windows (days)		**(±1)**	**(±1)**	**(±2)**	**(±2)**	**(±2)**	**(±3)**	**(±3)**	**(±4)**
High sensitivity CRP and ESR	X		X	X	X	X	X	X	X
Electrocardiogram[i]	X		X	X	X	X	X	X	
Tender and swollen joint counts (TJC 68, SJC 66)	X		X	X	X	X	X	X	X
CASPAR	X								
Dactylitis			X	X	X	X	X	X	X
Patient global assessments of PsA, and PsA pain (VAS)			X	X	X	X	X	X	X
Physician global assessment of PsA (VAS)			X	X	X	X	X	X	X
HAQ-DI			X	X	X	X	X	X	X
LEI			X	X	X	X	X	X	X
PASI/ PGA of psoriasis/BSA			X		X	X	X	X	X
[redacted]									
MDA			X			X	X	X	
Randomization		X							

Table 1: Schedule of Assessments

Study Time Frame/ Visit	Screening Period		Treatment Period[a]						Follow-up
	Screening Day –30 to Day -1 Visit 1	Day --7[b]	Day 1 Visit 2	Week 1 Visit 3	Week 2 Visit 4	Week 4 Visit 5	Week 8 Visit 6	Week 12 EOT/ET Visit 7	Week 16 EOS Visit 8
Windows (days)		(±1)	(±1)	(±2)	(±2)	(±2)	(±3)	(±3)	(±4)
On-site study drug administration[j]			X	X	X	X	X		
Dispense study drug			X	X	X	X	X		
Collection of study drug				X	X	X	X	X	
Subject dosing diary distribution/collection/ review			X	X	X	X	X	X[k]	
Blood samples for NDI-034858 concentration			X[l]			X[m]	X[n]	X[o]	
[redacted]									
Concomitant medication	X		X	X	X	X	X	X	X
Adverse events evaluation			X[p]	X	X	X	X	X	X

BSA = body surface area; CASPAR = Classification Criteria for Psoriatic Arthritis; CCP = cyclic citrullinated peptides; CRP = C-reactive protein; EOS = end of study; EOT = end of treatment; ESR = erythrocyte sedimentation rate; ET = early termination; [redacted]; FSH = follicle stimulating hormone; HAQ-DI = Health Assessment Questionnaire – Disability Index; HBsAg = Hepatitis B serum antigen; HBc = hepatitis B core; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LEI = Leed's Enthesitis Index; MDA = Minimal Disease Activity; PASI = Psoriasis Area Severity Index; PsA = psoriatic arthritis; PGA = Physician Global Assessment; [redacted]; SJC = swollen joint count; TJC = tender joint count; UA = urinalysis; VAS – visual analog scale

Note: Day 1 assessments will be used to confirm eligibility for the study. Subjects who do not meet continuing eligibility on Day 1 will not be allowed into the study.

[a] Study Visit Weeks are scheduled based on Day 1. The Week 1 visit is 7 days ±2 days from Day 1; Week 2 is 14 days ±2 days from Day 1; Week 4 is 28 days ±2 days from Day 1; Week 8 is 56 days ±3 days from Day 1; Week 12 is 84 days ±3 days from Day 1; and Week 16 is 112 days ±4 days from Day 1.
[b] Day -7 is not a subject visit and is only planned for randomization and to allow time for study drug shipment to the site.
[c] For female subjects of childbearing potential only, serum pregnancy test at screening, and urine pregnancy test at the other visits.
[d] A T-Spot.TB test may be used as an alternative to the QuantiFERON-TB Bold test as per Exclusion Criterion 37.
[e] Chest x-ray may be performed at screening or within 3 months prior to the screening visit, read and documented by a qualified physician as no evidence of infection or malignancy.
[f] Including height and weight. Height will be measured only at screening.
[g] Targeted examination includes: heart, lungs, abdomen, lower extremities, and lymph nodes.
[h] FSH to be performed at screening only, for females who have had a cessation of menses for ≥12 months prior to the screening visit without an alternative medical cause.
[i] In addition to the time points specified in the schedule of assessments, an ECG may be performed at any time during the study if in the opinion of the investigator it is clinically warranted.
[j] Study drugs will be taken at home QD for 12 weeks, except on visit days, when the study drugs will be administered on-site. No drug administration will occur on the day of Week 12 visit.
[k] Subject dosing diary will be collected and reviewed at Week 12 visit. Subject dosing diary will not be distributed at Week 12.
[l] Samples to be taken predose and 1 hour (±5 min) postdose on Day 1.
[m] Samples to be taken predose, 1 hour (±5 min) postdose, and 4 hours (± 10 min) postdose at Week 4.
[n] Samples to be taken predose at Week 8.
[o] Samples to be taken anytime at Week 12 (no study drug administration at this visit).
[p] Adverse event collection will begin after dosing on Day 1.

2. INTRODUCTION

2.1. Background

2.1.1. Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic, systemic inflammatory disease that manifests as peripheral arthritis, axial disease, dactylitis, enthesitis, and skin and nail lesions (Mease et al. 2018). There is an estimated prevalence of 0.3 to 1% of the general population with psoriatic arthritis, with approximately 50% of subjects experiencing bone erosions within 2 years (Kavanaugh et al. 2014). Psoriatic arthritis is present in up to 30% of psoriasis subjects (Ogdie et al. 2020) with disability from irreversible joint damage and deformities in many subjects (Mease et al. 2018). In addition, PsA is also associated with increased mortality (Duarte et al. 2012).

Psoriatic arthritis substantially impacts function, quality of life, and work productivity. If left untreated, the joint inflammation results in joint destruction and disability. The goals of treatment are to ameliorate the signs and symptoms of PsA, improve function, prevent structural damage, and enhance quality of life and productivity. The significant morbidities associated with PsA are typically treated with non-steroidal anti-inflammatory drugs (NSAIDs), traditional disease-modifying anti-rheumatic drugs ([DMARDs], e.g., methotrexate or sulfasalazine), and/or biologics such as tumor necrosis factor inhibitors (TNFi) or interleukin (IL)-12/23 or IL-17 inhibitors. There are limited data supporting the use of traditional DMARDS for PsA and these may not prevent structural damage. The biologics require parenteral delivery which are inconvenient for subjects. In addition, despite these therapies, a low percentage of subjects achieve remission, many have variable efficacy regarding the multiple co-morbid manifestations of PsA or are intolerant to available therapies (Kavanaugh et al. 2014; Mease et al. 2018).Thus, there continues to be a significant unmet need for a safe and efficacious oral PsA therapy.

2.1.2. NDI-034858

NDI-034858 (also known as TAK-279) 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).

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 (Watford et al. 2004). 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 (Stark and Darnell 2012). The cytokine signaling pathways regulated by TYK2 play key roles in several immune-mediated disorders. Most relevant for PsA pathogenesis, the cytokine IL-23 is central for the expansion and survival of T-helper (Th)17 cells and innate lymphoid cells, both of which have been shown to play key pathogenic roles in autoimmunity (Sutton et al. 2012). IL-23 stimulation drives the production of key proinflammatory cytokines

by Th17 cells, including IL-17A, IL-17F, and IL-22, which are involved in propagating the inflammation in PsA.

2.1.3. Study Rationale

NDI-034858 has the potential to add value to the treatment algorithm of PsA, particularly considering the lack of highly efficacious oral agents. A safe, well-tolerated, and highly efficacious oral therapy for PsA would provide an appealing treatment option for both subjects and physicians.

Inhibition of TYK2 by NDI-034858 is expected to impact PsA pathogenesis primarily through its effects on the IL-23/Th17/Th22 axis. In addition, safety and efficacy data in Phase 2 PsA study presented to date for a TYK2 inhibitor (BMS-986165 or deucravacitinib) (Armstrong et al. 2021; Papp et al. 2018), 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.

Treatment for PsA has changed dramatically over the last decade, with traditional synthetic DMARDs, glucocorticoids, biologic therapies (ie, tumor necrosis factor [TNF] and IL inhibitors), biosimilar and targeted synthetic DMARDs, and other new targeted agents (Kavanaugh et al. 2014; Mease et al. 2018). Given the early efficacy and safety profile of NDI-034858 in psoriasis, and the evidence of effects of another TYK2 inhibitor in PsA, the potential for NDI-034858 to be effective in PsA is high.

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 (MAD) 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 MADs of 20 mg and 35 mg given QD for 14 days. An additional open-label cohort was also included to evaluate the comparative bioavailability [redacted], to assess the pharmacokinetics (PK) of single oral doses [redacted] of NDI-034858 in healthy subjects under fed and fasted conditions. [redacted].

2.1.4.1.1. Safety Results in Study 4858-101

In Study 4858-101, 47 subjects (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%) subjects treated with NDI-034858 experienced at least one treatment-emergent adverse event (TEAE), compared with 3 of 12 (25%) treated with placebo. The most common adverse events (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 subjects. No adverse trends were noted in safety laboratory tests, electrocardiograms (ECGs), vital signs, or physical examination findings.

In Study 4858-101, 16 subjects (healthy volunteers) were enrolled in multiple-dose cohorts (12 treated with either 20 mg or 35 mg of NDI-034858 daily for 2 weeks and 4 treated with placebo daily for 2 weeks). Treatment with NDI-034858 was generally safe and well tolerated. A total of 12 of 12 (100%) subjects treated with NDI034858 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 NDI-034858. All events of acneiform dermatitis or papular rash were deemed to be drug related. They were all mild in intensity and resolved within 1 to 2 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 subject 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 examination 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 serious adverse events (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}) ranging from 3 to 5 hours postdose in SAD Cohorts 1 to 6 and MAD Cohorts 7 and 8. CCI [redacted]

For Cohorts 1 to 3 (doses of 5, 20, and 75 mg NDI-034858), the mean maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner CCI [redacted] 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 CCI [redacted]

Similarly, for Cohorts 1 to 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-inf}) increased in an approximately dose-proportional manner [redacted]

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-tau}) was 2.9 and 2.4, respectively. [redacted]

[redacted] the terminal half-life ($t_{1/2}$) was consistent across the dose levels tested and ranged from [redacted].

[redacted]

2.1.4.1.3. Pharmacodynamic Results in Study 4858-101

The pharmacodynamic (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 [redacted]

2.1.4.2. Study 4858-102

Study 4858-102 was a Phase 1, randomized, multi-center, double-blind, placebo-controlled (MAD) study of NDI-034858 in subjects with moderate-to-severe plaque psoriasis. The study objective was to provide preliminary evidence of safety, tolerability, PK, PD, and early efficacy in a moderate-to-severe plaque psoriasis population.

There were a total of 26 subjects enrolled in the study, 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 [redacted]), 10 mg [redacted]), or 30 mg [redacted]

2.1.4.2.1. Efficacy Results in Study 4858-102

Exploratory efficacy data in psoriasis (Psoriasis Disease Activity Index [PASI], static Physician Global Assessment [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 ([redacted] for 5 mg, [redacted] for 10 mg, [redacted] 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 [redacted]
- 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 1 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 SAEs. 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 with the exception of one severe (Grade 3) AE 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 AE 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 tuberculosis (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

CCI

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.

Nonclinical 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 4858-202.

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 returned to normal within 3 days of discontinuation of study medication and was not associated with any AEs 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.	In Study 4858-202: Subjects with absolute neutrophil count of < 1.8 x 10^9/L (< 1800/mm^3) are excluded from participation. 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. Subjects must be permanently discontinued from study treatment for cytopenia ≥ Grade 3.
CPK elevation	Six events of CTCAE Grade 2 to 3 elevations of CPK occurred in 6 subjects administered NDI-034858 or placebo in Studies 4858-101, 4858-102, and 4858-104. Four of the 6 events occurred in subjects administered NDI-034858 and 2 occurred in subjects administered placebo. Three of the 6 events were Grade 3 at maximum (1 in a subject administered NDI-034858, and 2 in subjects who received placebo). The Grade 3 CPK elevations resolved without need for further intervention. No clinically significant increases in serum creatinine or abnormalities on urinalysis accompanied these elevations in CPK. There was no apparent temporal association with study drug administration.	In Study 4858-202: CPK will be monitored per protocol. CPK elevation ≥ Grade 3 is an AESI. Subjects with an SAE or severe AE may be discontinued from study drug.
Drug interaction	CCI [redacted]	In Study 4858-202: Strong and moderate inhibitors of CYP3A4 are prohibited in Study 4858-202.

Table 2: Potential Risks of NDI-034858

Potential Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
	CCI [redacted]	Exclusion criteria in Study 4858-202 ensure adequate wash out of strong and moderate inhibitors of CYP3A4.

AE = adverse event; AESI = adverse event of special interest; CPK = creatine phosphokinase; CYP3A -= cytochrome P450 3A; CCI [redacted].

CCI [redacted]

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. CCI [redacted]. 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. CCI [redacted]

2.2.2. Known Potential Benefits

NDI-034858 has the potential to treat a variety of autoimmune and inflammatory disorders, including PsA. These diseases present serious, long-term health risks with high unmet medical need and risk of significant morbidity and impact on function. NDI-034858 was evaluated in a developing model of adjuvant-induced arthritis in male Lewis rats demonstrating inhibition of TYK2-dependent signaling and improvements in articular and paw inflammatory swelling. 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 4858-202.

In a Phase 2 PsA study of the allosteric TYK2 inhibitor deucravacitinib, substantial efficacy was demonstrated in terms of improvement of the signs and symptoms of PsA in the treated arms compared with placebo (Mease et al. 2020). In addition, efficacy data from Phase 3 psoriasis trials of deucravacitinib demonstrated that deucravacitinib has superior efficacy to apremilast (Mease et al. 2020), the only Food and Drug Administration (FDA)-approved oral medication for moderate-to-severe plaque psoriasis. Thus, nonclinical data, early clinical data from NDI-034858 in psoriasis, and data from Phase 2/3 studies of deucravacitinib in PsA and psoriasis, another allosteric TYK2 inhibitor, support the potential for NDI-034858 to treat psoriatic arthritis.

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 PsA and psoriasis studies from deucravacitinib, which validated blockade of TYK2 as a therapeutic approach for treatment of moderate-to-severe plaque psoriasis.

In summary, the collective nonclinical and clinical evidence supporting the inhibition of TYK2 as a therapeutic approach in PsA 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 PsA. The benefit/risk for further development of NDI-034858 in PsA is therefore warranted.

3. OBJECTIVES AND ENDPOINTS

3.1. Primary Objective

To assess the efficacy of NDI-034858 orally administered QD at [redacted] for 12 weeks on the rheumatological signs, symptoms, and function in subjects with active PsA.

3.2. Secondary Objectives

The secondary objectives are:

- To assess additional evaluations of efficacy of NDI-034858 orally administered QD at [redacted] for 12 weeks in subjects with active PsA
- To assess the safety and tolerability of NDI-034858 orally administered QD at [redacted] for 12 weeks in subjects with active PsA
- To evaluate the plasma concentration of NDI-034858 orally administered QD at [redacted] in subjects with active PsA

3.3. Exploratory Objectives

[redacted]

- [redacted]
- [redacted]

3.4. Endpoints

3.4.1. Primary Efficacy Endpoint

- Proportion of subjects achieving at least an American College of Rheumatology (ACR) 20 response at Week 12

3.4.2. Secondary Efficacy Endpoints

- Proportion of subjects achieving ACR-50 response at Week 12
- Proportion of subjects achieving ACR-70 response at Week 12
- Change from baseline (Day 1) in tender joint count at Week 12
- Change from baseline (Day 1) in swollen joint count at Week 12
- Change from baseline (Day 1) in Patient Global Assessment of Psoriatic Arthritis at Week 12
- Change from baseline (Day 1) in Patient Global Assessment of Psoriatic Arthritis pain at Week 12

- Change from baseline (Day 1) in Physician Global Assessment of Psoriatic Arthritis at Week 12
- Change from baseline (Day 1) in Health Activities Questionnaire – Disability Index (HAQ-DI) score at Week 12
- Change from baseline (Day 1) in dactylitis count at Week 12, among subjects who have dactylitis at Day 1
- Change from baseline (Day 1) in Leed's Enthesitis Index (LEI) at Week 12, among subjects who have enthesitis at Day 1
- Proportion of subjects with Minimal Disease Activity (MDA) at Week 12
- Change from baseline (Day 1) in Disease Activity Index for Psoriatic Arthritis (DAPSA) at Week 12
- Proportion of subjects achieving 75% improvement from baseline (Day 1) in Psoriasis Area Severity Index [(PASI)-75] at Week 12 among subjects with ≥ 3% body surface area (BSA) psoriatic involvement at Day 1
- Proportion of subjects achieving a Physician Global Assessment of Psoriasis of 0 or 1 and at least a 2-point improvement from baseline (Day 1) at Week 12.

3.4.3. Secondary Endpoints – Safety

- Incidence of TEAEs, TESAEs, TEAESIs
- Assessment of clinically relevant changes in vital signs, clinical laboratory parameters, and proportion of subjects with clinically relevant abnormal ECGs, and physical examinations

3.4.4. Secondary Endpoints – Pharmacokinetics

- Measurement of plasma concentrations of NDI-034858 in subjects receiving [redacted] of NDI-034858

3.4.5. Exploratory Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2b, randomized, multi-center, double-blind, placebo-controlled, multiple-dose study designed to evaluate the efficacy, safety, and tolerability of NDI-034858 in subjects with active PsA. The evaluation of plasma concentrations of NDI-034858 [redacted]

Approximately 260 male and female subjects, aged 18 and higher, with active PsA will be randomized in this study. To be eligible for the study, the subjects must have a history of PsA with symptoms for ≥ 6 months prior to the screening visit and must meet all of the inclusion criteria, including the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, with ≥ 3 tender and ≥ 3 swollen joints at screening and baseline (Day 1) visits, and with active PsA despite previous therapy with NSAIDs, traditional DMARDs, or one TNFi.

All subjects will read and sign a written informed consent form (ICF) prior to performing any screening procedures. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be included in the study. During a screening period of no longer than 30 days, subjects will be randomized (on Day -7) to receive either one of three doses of NDI-034858 ([redacted]), or placebo on Day 1. The goal is to have approximately 65 subjects randomized per treatment group (1:1:1:1 ratio). During the treatment period, NDI-034858 ([redacted]) 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] / early termination visit [ET]), and 16 (end of study [EOS]).

Efficacy will be assessed using the ACR20 composite measure (including tender and swollen joint count, patient assessment of PsA pain visual analog scale (VAS), patient global PsA assessment VAS, physician global PsA assessment, HAQ-DI, and hsCRP) as well as the additional components. Efficacy for psoriasis among subjects who have ≥ 3% BSA) involvement on Day 1, will be measured using PASI, PGAs, and BSA.

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 concentrations of NDI-034858 as follows:

- On Day 1 (Visit 2) prior to dosing and 1 hour (± 5 min) postdosing
- Week 4 (Visit 5) prior to dosing, 1 hour (± 5 min) postdosing, and 4 hours (± 10 min) postdosing
- Week 8 (Visit 6) prior to dosing
- Week 12 (Visit 7) any time as study-drug dosing is completed, or at ET, whenever possible

[redacted]

No interim analysis is planned in this study.

4.2. Study Conduct During the Coronavirus Disease 2019 Pandemic

As a consequence of the Coronavirus Disease-2019 (COVID-19) pandemic that has had a worldwide impact, including cases 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).
- In the event that 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 drug 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 a 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. Local laboratory results (See Section 8.4.4) should be entered into the electronic case report form (eCRF) and 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 (ie, 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 patient is unable to attend the scheduled visits in order to protect the life or well-being of the patient, study product may be shipped direct-to-patient (DTP) from the site. Home delivery of investigational product must not raise any new safety risks. DTP shipments should only occur if the investigator deems it safe for the patient to continue study drug treatment. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational 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 [redacted]) compared with placebo in subjects with PsA.

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 or non-traditional DMARDs (yes/no), and region. Because efficacy assessments of PsA 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

[redacted]

4.5. End of Study Definitions

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 EOS is defined as completion of the last visit or procedure shown in the Schedule of Events 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. Subject is male or female, aged ≥18 years, at the time of consent.
2. Subject has PsA on the basis of the CASPAR with peripheral symptoms at the screening visit, as assessed by the investigator.
3. Subject has a history of PsA symptoms for ≥ 6 months prior to the screening visit, as assessed by the investigator.
4. Subject has ≥ 3 tender joints and ≥ 3 swollen joints at screening and Day 1 visits, as assessed by the investigator.
5. Subject has at least one lesion of plaque psoriasis ≥ 2 cm in diameter, nail changes characteristic of psoriasis, or a documented history of plaque psoriasis.
6. Subject has active PsA despite previous standard doses of NSAIDs administered for ≥ 4 weeks, or traditional DMARDs (including methotrexate and sulfasalazine) administered for ≥ 3 months, or TNFi agents administered for ≥ 3 months, or subjects are intolerant to NSAIDs or DMARDs or TNFi agents, as assessed by the investigator.
7. If subject is on concurrent PsA treatments, they must be on stable doses as described below and for the duration of the study:
    a. Methotrexate (MTX): subject has received treatment for ≥ 3 months, with stable dose and stable route of administration (not to exceed 25 mg MTX per week) for ≥ 4 weeks prior to Day 1 until Week 16 (EOS); subjects on MTX should be taking folic acid supplementation according to local standard of care to minimize the likelihood of MTX associated toxicity.
    b. Sulfasalazine: Maximum dose of 3 gm/day. Minimum duration of therapy 2 months and dose stable for 4 weeks prior to Day 1.
    c. Other traditional DMARDs not listed may be considered on a case-by-case basis after discussion with the medical monitor
    d. Oral corticosteroids: the subject must be on a stable dose, not to exceed the equivalent of 10 mg of prednisone per day, for ≥ 2 weeks prior to Day 1. If subject is not currently using oral corticosteroids, must not have received for at least 2 weeks prior to Day 1.
    a. NSAIDs or paracetamol/acetaminophen: the subject must be on a stable dose for ≥ 2 weeks prior to Day 1. If not currently using NSAIDs, must not have received for at least 2 weeks prior to Day 1.
8. For female subjects of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to us a highly effective contraceptive method from screening until at least 4 weeks after the last study drug 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), tubal ligation, 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. See Appendix 2 for additional local requirements or restrictions that may apply.

Note: Subjects must have been on a stable dose of 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).

9. Female subjects of childbearing potential have had a negative serum pregnancy test at screening and negative urine pregnancy test at Day 1.
10. 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 8, from Day 1 until at least 12 weeks after the last study drug 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 drug administration. See Appendix 2 for additional local requirements or restrictions that may apply.

    Note: Male subjects must refrain from donating sperm from Day 1 until at least 12 weeks after the last study drug 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.
11. Subject has a body mass index (BMI) of >18 kg/m^2, inclusive, (BMI = weight [kg]/[height (m)]^2), and total body weight >50 kg (110 lb).

12. Subject is willing to participate and is capable of giving informed consent. Note: Signed, dated, written informed consent must be obtained prior to any study-related procedures.
13. 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 has other disease(s) that might confound the evaluations of benefit of NDI-034858 therapy, including but not limited to rheumatoid arthritis (RA), axial spondyloarthritis (this does not include a primary diagnosis of PsA with spondylitis), systemic lupus erythematosus, Lyme disease, or fibromyalgia.
2. Subject has a history of lack of response to any therapeutic agent targeting IL-12, IL17, and/or IL23 (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 baseline (Day 1).
3. Subject has a history of lack of response to > 1 therapeutic agent targeting TNF.
4. Subject has received infliximab, golimumab, adalimumab, or certolizumab pegol, or any biosimilar of these agents, within 8 weeks or 5 half-lives (see Appendix 3), whichever is longer, prior to baseline (Day 1).
5. Subject has received etanercept, or any biosimilar of etanercept, within 4 weeks prior to baseline (Day 1).
6. Subject has received rituximab or any immune-cell-depleting therapy within 6 months prior to baseline (Day 1).
7. Subject has received any marketed or investigational biological agent, other than those specified in other inclusion/exclusion criteria, within 12 weeks or 5 half-lives (whichever is longer, see Appendix 3) prior to baseline (Day 1).
8. Subject is currently receiving a non-biological investigational product or device or has received one within 4 weeks prior to baseline (Day 1).
9. Subject has received apremilast or other non-biologic systemic treatment for PsA within 4 weeks prior to baseline (Day 1), other than MTX, sulfasalazine, corticosteroids, NSAIDs, or paracetamol/acetaminophen, which are allowed at stable doses as described in Inclusion Criterion 7. For subjects not receiving MTX and sulfasalazine at screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1). Subject has received leflunomide within 95 days of baseline (Day 1) if no elimination procedure was followed or adhere to an elimination procedure (eg, 11 days with cholestyramine or 30 days washout with activated charcoal as per local label). For subjects not receiving MTX and sulfasalazine at Screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1).

10. Subject has received intraarticular injection (including corticosteroids), intramuscular steroids, intralesional steroids, or intravenous steroids within 4 weeks prior to baseline (Day 1). For subjects not receiving MTX and sulfasalazine at screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1). For subjects not receiving MTX and sulfasalazine at screening, MTX and sulfasalazine are excluded within 4 weeks prior to baseline (Day 1).
11. Subject has received high potency opioid analgesics (eg, methadone, hydromorphone, or morphine) within 2 weeks prior to baseline (Day 1).
12. Subject has used any topical medication that could affect PsA or psoriasis (including corticosteroids, retinoids, vitamin D analogues (such as calcipotriol), JAK inhibitors, or tar) within 2 weeks prior to baseline (Day 1).
13. Subject has used any systemic treatment that could affect PsA or psoriasis (including oral retinoids, immunosuppressive/immunomodulating medication, cyclosporine, oral JAK inhibitors, or apremilast) within 4 weeks prior to baseline (Day 1), unless otherwise excluded or allowed by protocol.

    Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
14. Subject has received any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to baseline (Day 1).
15. Subject has had psoralen and UV A (PUVA) treatment within 4 weeks prior to baseline (Day 1).
16. Subject has received Chinese traditional medicine within 4 weeks prior to baseline (Day 1)
17. Subject has received any live-attenuated vaccine, including for COVID-19, within 4 weeks prior to baseline (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 drug, whichever is longer, after the last study drug 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.
18. 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 baseline (Day 1).
19. Subject has consumed grapefruit or grapefruit juice within 1 week prior to baseline (Day 1).

    Note: Consumption of grapefruit must be avoided during the treatment period and for at least 1 week after last study drug administration.
20. Subject has used tanning booths within 4 weeks prior to baseline (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.

21. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
22. Subject has evidence of erythrodermic, pustular, predominantly guttate psoriasis, or drug -induced psoriasis.
23. 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.
24. 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.
25. Subject had a major surgery within 8 weeks prior to baseline (Day 1or has a major surgery planned during the study.
26. Subject has a history of Class III or IV congestive heart failure as defined by New York Heart Association Criteria.
27. Subject has an estimated creatinine clearance of < 40 mL/min based on the Cockcroft-Gault equation or a history of renal failure as determined by the investigator

    – Cockcroft-Gault equation:

    Creatinine Clearance (estimated) / Conventional mL/min =

    (140 - Age [years]) x Weight (kg) x Factor a) / (72 x serum creatinine [mg/dL])

    Note: Factor a = 0.85 in females and 1.00 in males.
28. Subject was hospitalized in the 3 months prior to screening 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 baseline (Day 1).
29. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to baseline (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.
30. Subject has a history of fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection within 4 weeks prior to baseline (Day 1).
31. 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 baseline (Day 1), or oral antibiotics within 4 weeks prior to baseline (Day 1).

32. 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 (with the exception of superficial fungal infection of the nailbed), or infected skin wounds or ulcers.
33. 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.
34. 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.
35. 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).
36. 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). Samples testing positive for HCV antibodies will require polymerase chain reaction (PCR) qualitative testing for HCV RNA. Any HCV RNA PCR result that meets or exceeds detection sensitivity is exclusionary.
37. Subject has clinical or laboratory evidence of active or latent TB infection at screening.

    Note: Subjects will be evaluated for TB infection by QuantiFERON-TB Gold (or a purified protein derivative [PPD] skin test or equivalent, or both if required per local guidelines) and chest X-ray. The PPD skin test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason (unless local guidelines require both tests). Chest X-ray may be taken at screening or completed within 3 months prior to the screening visit, with documentation showing no evidence of infection or malignancy as read by a qualified physician.

    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.

    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. Latent TB is defined as a positive QFT test or two successive indeterminate QFT tests at screening.
38. Subject with any of the following laboratory values at the screening visit:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥ 3 times the upper limit of normal (ULN)
    - Hemoglobin < 11.0 g/dL (< 110.0 g/L)
    - White blood cell count < 3.5 x 10^9/L (< 3500/mm^3)

- Absolute neutrophil count of < 1.8 x 10^9/L (< 1800/mm^3)
- Absolute lymphocyte count of < 1.0 x 10^9/L (< 1000/mm^3)
- Platelet count < 100 x 10^9/L (< 100,000/mm^3)
- Total bilirubin > 2 times the ULN

39. 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).
40. 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).
41. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to baseline (Day 1).
42. Subject has known history of moderate to severe hepatic impairment, Class B or C, by Child-Pugh scoring system.

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 screening number than the initial screening number. All screening procedures will be performed at the new screening visit except for chest X-ray if performed within 3 months of the new screening visit, including signature of a new consent form.

6. TREATMENT

6.1. Study Treatment Administered

This study involves a comparison of NDI-034858 at [redacted] orally administered QD with a placebo. NDI-034858 will be available in [redacted] strength [redacted]. All study drugs will be provided by the sponsor.

All study drugs will be administered orally daily, as assigned, for 12 weeks. On study days, the study drugs will be administered at the study site (if applicable). The date and time of drug administration will be collected by the study site during each visit and daily via a diary provided to the subject. The subject should be instructed to take the study drug at approximately the same time of the day with no food restrictions. For Day 1 and Week 12 visits, subjects should have fasted for at least 8 hours before their visit and up to the time of the blood draw for fasting lipid panel.

Additional detail regarding the study drugs is provided in Table 3.

Table 3: Study Drugs

Drug name	Study Drugs			
	NDI-034858 (TAK-279)	NDI-034858 (TAK-279)	NDI-034858 (TAK-279)	Placebo
Dosage form	[redacted]	[redacted]	[redacted]	[redacted]
Unit dose strength(s)	[redacted]	[redacted]	[redacted]	N/A
Dose level(s)	[redacted]	[redacted]	[redacted]	N/A
Number of [redacted] per dose level	1 Active 1 placebo	1 active 1 placebo	2 active	2 placebo
Route of administration	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
Physical description	[redacted]	[redacted]	[redacted]	Placebo is identical to the active [redacted] in size, shape, and color.
Source of procurement	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.	Nimbus Lakshmi, Inc.

N/A = not applicable; QD = once daily.

The NDI-034858 clinical formulation is a [redacted]

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 drugs 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 drugs may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

Study drugs will be dispensed by the study site to the subject at the visits specified in Table 1. Subjects are to return all study drugs (used and unused) to the study site. The [redacted] will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents and eCRF. Each subject will be instructed on the importance of returning study drug at the next study visit and taking the drug as prescribed. If a subject does not return study drug, 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 drug received initially and of the study drug dispensed/used. Any study drug 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 drugs, and all study-drug containers will be returned or destroyed as per approved arrangements by the sponsor.

All study drug accountability forms and treatment logs must be retained in the investigator's study files. Drug 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.

Additional guidance and information for final disposition of study drugs are provided in the pharmacy 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, 02010 for the 10th subject screened at Site 02).

Approximately 260 subjects will be randomized in a 1:1:1:1 ratio to NDI-034858 at [redacted], or placebo (approximately 65 subjects per treatment group).

Randomization will occur at the Day -7 visit. The randomization list will be generated using validated software and will be stratified based on prior treatment with biologics or non-traditional DMARDs (ie, yes/no), and region. 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 drug.

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 cases 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 drug. The primary reason for study drug 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 drug 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.

6.4. Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural drugs, homeopathic medications, 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

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
- The use of oral corticosteroids and concomitant PsA treatments (ie, MTX and sulfasalazine) are described in Section 5.1, number 7.
- 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.

6.4.1.1. 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.

6.4.2. Prohibited Therapies or Procedures

Prohibited medications that are not to be used from the defined washout periods before the first administration of study drug at the Day 1 visit through the last study visit are provided in Table 4.

Subjects who start prohibited medications (systemic and topical) or therapies that have been demonstrated to be effective for treatment of PsA or plaque psoriasis during the study may be discontinued from study drug. Investigators should contact the medical monitor as soon as possible when a prohibited medication is initiated, to discuss the appropriate steps. Subjects who start prohibited medications or therapies for other reasons during the study may be discontinued from study drug if an impact on efficacy assessment or safety of the subjects is expected.

Table 4: Prohibited Therapies or Procedures

Prohibited Medications, Products, And Procedures	Washout Period Prior To First Dose (Day 1)
DMARD Therapies	
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
Therapeutic agent targeting TNF-α (eg, infliximab, golimumab, adalimumab, or certolizumab pegol) or any biosimilar of these agents	8 weeks
Leflunomide if no elimination procedure was followed. Or if an elimination procedure is used then 11 days with cholestyramine or 30 days washout with activated charcoal as per local label.	8 weeks
Apremilast or other non-biologic systemic treatment for PsA, other than MTX, sulfasalazine, corticosteroids, NSAIDs, or paracetamol/acetaminophen, which are allowed at stable doses as described in inclusion criterion (Sutton et al. 2012)	4 weeks
Etanercept or any biosimilar of etanercept	4 weeks
Investigational Drugs or Vaccines	
Any marketed or investigational biological agent (except those listed above)	12 weeks or 5 half-lives (whichever is longer)
Any live-attenuated vaccine, including for COVID-19 or plans or receive a live-attenuated vaccine Note: Non-live-attenuated vaccines 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 or 5 half-lives (whichever is longer)
Non-biological investigational drug or device	4 weeks
Steroids and Similar Therapies	
Systemic treatment that could affect psoriasis or PsA (oral retinoids, immunosuppressive/immunomodulating medication, 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
Intraarticular injection (including corticosteroids), intramuscular steroids, intralesional steroids, or intravenous steroids	4 weeks
Topical medication that could affect psoriasis (including corticosteroids, retinoids, vitamin D analogues [such as calcipotriol], JAK inhibitors, or tar)	2 weeks

Table 4: Prohibited Therapies or Procedures

Prohibited Medications, Products, And Procedures	Washout Period Prior To First Dose (Day 1)
Antibiotics/Antifungals/CYP3A4 inhibitors	
Intravenous antibiotic treatment	12 weeks
Strong or moderate CYP3A4 inhibitors (such as itraconazole); see Appendix 1 for a list of prohibited medications in this class.	4 weeks
Oral antibiotic treatment	4 weeks
Grapefruit or grapefruit juice Note: Consumption of grapefruit must be avoided during the treatment period and for at least 1 week after last dose administration.	1 week
All Other Prohibited Medications/Therapy	
PUVA treatment, UV-B phototherapy (including tanning beds), or excimer laser, or tanning booths, 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.	4 weeks
Chinese traditional medicine	4 weeks
High potency opioid analgesics (eg, methadone, hydromorphone, or morphine)	2 weeks

COVID-19 = coronavirus Disease-2019; CYP3A4 = cytochrome P450 3A; IL = interleukin; JAK = Janus kinase; MTX = methotrexate; NSAIDs = nons-steroidal inflammatory drugs; PsA – psoriatic arthritis; PUVA = psoralen-ultraviolet-A; RNA = ribonucleic acid; TNF-α – tumor necrosis factor alpha; UV = ultraviolet.

7. DISCONTINUATION AND LOST TO FOLLOW-UP

7.1. Discontinuation from Study Drug

Medical judgment should be applied to guide whether study drug 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 drug, the medical monitor should be contacted as soon as possible for consultation.

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

- Pregnancy of a female subject
- 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 for noncompliance.
- Subject experiences a Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, and thrombocytopenia; clinically significant or not) as defined in Section 8.5.7.
- 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
  - Non-biological investigational drug or device
  - Intravenous antibiotic treatment
  - Systemic treatment that could affect psoriasis or PsA (including corticosteroids, oral retinoids, immunosuppressive/immunomodulating medication, methotrexate, cyclosporine, oral JAK inhibitors, or apremilast)

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

- The subject has met study drug discontinuation criteria for abnormalities suggestive of drug induced liver injury as described in Section 8.5.8.

If abnormalities suggestive of drug-induced liver injury as described in Section 8.5.8 are found to be related to study drug, the subject will be permanently discontinued from study drug.

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

- Occurrence of an SAE (see Section 8.5.2).

- Occurrence of a severe AE (see Section 8.5.3).
- 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 drug.

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 Assessments.

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 AE follow-up.

Subjects who discontinue will not be replaced.

Reasons for discontinuation from the study may include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of an SAE, the study drug is to be discontinued for 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.
- The subject becomes pregnant at any time during the study.
- 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 TEAEs in this or other studies indicating a potential health risk to subjects. In this case, all subjects will be discontinued from the study. The investigator will immediately, upon discontinuation of the study by the sponsor, in its entirety or at a clinical study site, inform both the subjects and the IRB/REB/IEC of the discontinuation, provide them with the reasons for the discontinuation 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/REB/IEC and/or regulatory agency for any unforeseen reasons.

If more than one subject meets the criteria based on Hy's Law (Section 8.5.8) and these are confirmed to be study-drug related after comprehensive safety review, the sponsor will terminate the trial.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Screening Assessments

8.1.1. Classification Criteria for Psoriatic Arthritis

The CASPAR will be assessed at the Screening Visit only. The CASPAR consists of established inflammatory articular disease with at least 3 points from the following:

Feature	Points assigned
Current psoriasis	2
A history of psoriasis (in the absence of current psoriasis)	1
A family history of psoriasis (in the absence of current psoriasis and history of psoriasis)	1
Dactylitis	1
Juxta-articular new-bone formation	1
Rheumatoid factor negativity	1
Nail dystrophy	1

8.1.2. Chest X-ray

Chest X-rays will be performed as a safety assessment during screening if specified in Table 1. Any evidence of TB will be reported. Chest X-ray may be taken at screening or completed within 3 months prior to the screening visit with documentation showing no evidence of infection or malignancy as read by a qualified physician.

8.1.3. Tuberculosis Testing

QuantiFERON-TB Gold or a PPD skin test or equivalent (or both if required per local guidelines) will be performed at screening. The PPD skin test should be utilized only when a QuantiFERON-TB Gold Test is not possible for any reason, unless local guidelines require both tests.

The T-Spot.TB test (TBT) performed by the site's local laboratory, using the site laboratory supplies, 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.

8.1.4. Rheumatoid Factor

A blood sample will be taken to test for presence of rheumatoid factor (RF). An RF test can help with diagnosing immune disorders and estimate disease severity. This test will be used as part of the CASPAR. Subjects with RA are not eligible for the study.

8.1.5. Anti-Cyclic Citrullinated Peptide

A blood sample will be taken to test for presence of anti-cyclic citrullinated peptides (anti-CCP). The anti-CCP test is predictive of progression of disease, indicating more erosive disease or increases in joint involvement.

8.2. Efficacy Assessments

Clinical evaluations of PsA will be performed by an experienced and qualified physician (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor, who is not involved in the study conduct or direct patient care should perform all clinical efficacy assessments on a given subject whenever possible.

8.2.1. Primary Efficacy Endpoint - American College of Rheumatology 20

The ACR20 is a composite measure defined as both improvement of 20% in the number of tender (68) and number of swollen (66) joints, and a 20% improvement in three of the following five criteria: patient global assessment of psoriatic arthritis, physician global assessment of psoriatic arthritis, patient global assessment of psoriatic arthritis pain, disability history questionnaire (ie, HAQ-DI) and an acute phase reactant (ie, erythrocyte sedimentation rate [ESR] or hsCRP). For this primary endpoint, hsCRP will be used. The ACR-20 will be derived corresponding with collection of the listed assessments and timepoints as specified in Table 1.

8.2.2. Secondary Efficacy Endpoints

8.2.2.1. American College of Rheumatology 50/70

The ACR-50 and ACR-70 are a composite measure defined as both improvement of 50% or 70%, respectively, in the number of tender (68) and number of swollen (66) joints, and a 50% or 70%, respectively, improvement in three of the following five criteria: patient global assessment of psoriatic arthritis, physician global assessment of psoriatic arthritis, patient global assessment of psoriatic arthritis pain, disability history questionnaire (ie, HAQ-DI) and an acute phase reactant (ie, hsCRP). For these endpoints, hsCRP will be used. The ACR-50 and ACR-70 will be derived corresponding with collection of the listed assessments and timepoints as specified in Table 1.

8.2.2.2. Tender Joint Count 68 and Swollen Joint Count 66

The TJC 68 and SJC 66 (SJC minus hip joints, which cannot be assessed for swelling) are a total score of points assigned for presence of tenderness or swelling in the following:

- Temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, hip (TJC only), knee, ankle, tarsus, typically assigned 2 points each
- Metacarpophalangeal, finger proximal interphalangeal, metatarsophalangeal, toe proximal interphalangeal, typically assigned 10 points each
- Distal interphalangeal, typically assigned 8 points

8.2.2.3. Patient Global Assessment of Psoriatic Arthritis

Subjects will rate their assessment of their PsA using a VAS where 0 is 'very good, no symptoms' and 100 is 'very poor, severe symptoms'.

8.2.2.4. Patient Global Assessment of Psoriatic Arthritis Pain

Subjects will rate their assessment of their PsA pain using a VAS where 0 is 'no pain' and 100 is 'most severe pain'.

8.2.2.5. Physician Global Assessment of Psoriatic Arthritis

The investigator or qualified sub-investigator will assess the patients' overall disease status, taking into account signs, symptoms, and function, of all components of joint and skin which is affected at the time of the visit and will rate this overall status using a VAS scale where 0 is 'very good, asymptomatic, and no limitation of normal activities' and 100 is 'very poor, very severe symptoms which are intolerable, and inability to carry out all normal activities'.

8.2.2.6. Health Assessment Questionnaire – Disability Index

The HAQ-DI will be assessed at the visits specified in Table 1. The HAQ-DI is comprised of eight domains: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are two or three questions per section. Scoring within each section is from 0 (without any difficulty) to 3 (unable to do). For each section the score given to that section is the worst score within the section (ie, if one question is scored 1 and another 2, then the score for the section is 2). In addition, if an aide or device is used or if help is required from another individual, then the minimum score for that section is 2. If the section score is already 2 or more then no modification is made. The eight scores of the eight sections are summed and divided by eight. The result is the DI or disability index.

8.2.2.7. Dactylitis Count

The dactylitis count consists of totaling the number of single digits in the hands and feet with tenderness.

8.2.2.8. Leed's Enthesitis Index

The LEI will be assessed at the visits specified in Table 1. The LEI is comprised of review of six bilateral sites: Achilles tendon insertions, medial femoral condyles, and lateral epicondyles of the humerus. Tenderness at each site is quantified on a dichotomous basis: 0 means nontender and 1 means tender.

8.2.2.9. Physician Global Assessment of Psoriasis

The PGA will be assessed at the visits specified in Table 1. The PGA is measured using a 0 to 4 scale with a 0 score meaning cleared and a 4 score meaning severe and a ≥ 2 grade improvement from baseline at a specified timepoint, specifically Week 12 in this study.

8.2.3. Exploratory Efficacy Endpoints

8.2.3.1. [redacted]

[redacted]

8.2.3.2. [redacted]

[redacted]

8.2.3.3. [redacted]

[redacted]

8.2.3.4. [redacted]

[redacted]

8.2.3.5. [redacted]

[redacted]

8.2.3.6. [redacted]

[redacted]

8.2.3.7. [redacted]

8.2.3.8. [redacted]

8.2.3.9. [redacted]

8.3. Patient Reported Outcomes

8.3.1. [redacted]

8.3.2. [redacted]

8.4. Safety and Other Assessments

8.4.1. 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 beginning on Day 1 after study drug administration related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.4.2. 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 beginning after study drug administration on Day 1 will be reported as an AE in the source document and eCRF.

8.4.3. 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 8.4.2 can be performed instead of a targeted examination.

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

8.4.4. 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 5.

Table 5: Clinical Laboratory Testing

Laboratory Evaluation	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)
Specialty evaluations	hsCRP, ESR, Rheumatoid factor, anti-CCP
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 37. If the TBT is used, the QuantiFERON-TB Gold test should not be performed. Serology (HBV [HBsAg, anti-HBc], HCV[a], HIV)

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; anti-CCP = cyclic citrullinated peptide antibodies; CPK = creatine phosphokinase; hsCRP = high sensitivity C-reactive Protein; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl-transferase; HBsAg = hepatitis B surface antigens; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HDL = high-density lipoprotein; 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; PCR = polymerase chain reaction, 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

[a] Samples testing positive for HCV antibodies will require PCR qualitative testing for HCV RNA. Any HCV RNA PCR result that meets or exceeds detection sensitivity is exclusionary.

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 37. The TBT may be repeated once only if the result is borderline (equivocal); tests with positive or negative results will not be repeated.

Any clinically significant value will be reported as an AE beginning after study drug administration on Day 1. Any CTCAE Grade ≥ 3 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 AE of special interest (AESI, Section 8.5.7). Any CTCAE Grade ≥ 3 cytopenia (anemia, leukopenia, neutropenia, lymphopenia, or thrombocytopenia) will lead to permanent discontinuation of study drug (Section 7.1).

8.4.4.1. Use of Local Laboratories

All protocol-specified laboratory tests (See Section 8.4.4) should be performed via the central laboratory except for ESR which is performed locally. The central laboratory will provide supplies for the ESR. The test will be performed, and results read at the local laboratory. For all other tests, attempts should be made by the study site to perform the laboratory assessments via the central laboratory. In situations where the laboratory tests cannot be performed at the study site due to unexpected conditions, extreme difficulty, or other unforeseen situations, the protocol-specific 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 37, it will be performed via a local laboratory.

Please note: other use of local laboratories should be limited to testing for safety when visits to the site are not possible, such as quarantine or immobilization of the subject, and is not meant to be a replacement for the central laboratory.

Results determined by the investigator to be clinically significant laboratory abnormalities should be reported to the medical monitor ≤ 24hours of the investigator's receipt. Follow-up safety monitoring will be conducted at the investigator's discretion. Results determined by the investigator to be SAEs or AESIs, should be reported to the sponsor following the procedures described in Section 8.5.6, Section 8.5.7.

Unscheduled visits for laboratory testing should also be performed via the central laboratory and all efforts should be made to do so. In cases where this is not possible, the local laboratory may be used as above.

Results from local laboratories will be collected, recorded on the appropriate eCRF, and entered in the database.

8.4.5. Electrocardiogram

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

8.4.6. Plasma Concentrations of NDI-034858

Blood samples will be collected to measure plasma levels of NDI-034858 as specified in Table 1.

Plasma concentrations will be reported. 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.

8.4.7. [redacted]

[redacted]

8.5. Adverse Events and Serious Adverse Events

8.5.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical drug 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 drug, whether or not considered related to the study drug.

8.5.2. 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 dyscrasias, or 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.

Laboratory abnormalities suggestive of drug-induced liver injury as described in Section 8.5.8 are to be considered SAEs/important medical events.

8.5.3. Classification of an Adverse Event

8.5.3.1. Relationship to Study Drug

The investigator will assess causal relationship between each reported AE or SAE, and the experimental drug. The investigator should take into account 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 drug, 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 drug, is reasonable, follows a known response pattern to the drug, and an alternative cause is unlikely.

8.5.3.2. 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 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 noninvasive 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 self care 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 a number of days, then those changes should be recorded separately (with distinct onset dates).

8.5.4. 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 drug (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 the administration of study drug on Day 1 in the appropriate section of the source document and eCRF. Starting on Day 1 after dosing with NDI-034858, 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 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.

8.5.5. 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.

8.5.6. Serious Adverse Event Reporting

All SAEs, related to the experimental drug or not, occurring during the course of the study (from Day 1 after dosing, to last study visit) must be reported immediately without undue delay but not later than 24 hours of 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 in the same manner as the original SAE report.

All SAEs will be entered in the electronic data collection tool on the appropriate SAE electronic case report form (eCRF). If the electronic system is unavailable, a paper SAE report form should be completed and sent to Parexel Safety Services by email at NSISafety@parexel.com or fax to +1 781 434 5957. As soon as the electronic system is available, all SAE information should be entered into the eCRF.

The sponsor will be responsible for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) for study drug NDI-034858 to ethics committees and regulatory authorities in accordance with current local requirements. The reference document for SUSAR reporting will be the most current version of the IB.

Any SAE occurring after the End of Study visit, and that is considered by the investigator to be causally related to study drug, must be reported to the sponsor according to SAE reporting procedures. The SAE reporting period for non-study related SAEs ends at the end of the follow-up period.

8.5.7. 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, non-fatal myocardial infarction, and non-fatal stroke

- Thromboembolic events, defined as pulmonary embolism, deep vein thrombosis, and other venous and arterial thromboembolic events (eg, non-cardiac, 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 starting on Day 1 (first day of dosing) using the procedures detailed in Section 8.5.6. 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, and the AESI/overdose checkbox must be completed.

As per Section 7.1, the above mentioned CTCAE Grade ≥ 3 cytopenia requires permanent discontinuation of study drug.

8.5.7.1. Immediate Reporting of AESIs

Adverse events of special interest should be reported starting after dosing on Day 1 (day of first dose). The study site must formally notify the sponsor within 24 hours of knowledge of the occurrence.

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 8.5.6); however, the AESI/overdose checkbox on the eCRF must be selected.

All AESIs must be reported to sponsor within 24 hours of knowledge of the occurrence regardless of the following:

1. Whether or not the subject has undergone study-related procedures
2. Whether or not the subject has received study drug

3. The severity of the event
4. The relationship of the event to study drug

Refer to the Investigator Site File Study Contact List for complete contact information to report initial or follow-up information on an AESI.

8.5.8. Potential Drug Induced Liver Injury

ALT 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 than 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:

- Criteria based on Hy's Law:
  - ALT or AST ≥ 3 times the ULN, or ≥ 3 times the baseline value if greater than the ULN at baseline AND
  - total bilirubin > 2 times the ULN, or > 2 times the baseline value if greater than the ULN at baseline, OR international normalized ratio > 1.5
  - in the presence of alkaline phosphatase < 2 times the ULN
- ALT or AST ≥ 8 times the ULN, or ≥ 8 times the baseline value, if greater than the ULN at baseline, regardless of other parameters
- ALT or AST ≥ 3 times the ULN, or ≥ 3 times the baseline value, if greater than the ULN at baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Total bilirubin or direct bilirubin > 3 times the ULN, or > 3 times the baseline value, if greater than the ULN at baseline

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 drug while workup is ongoing. Nonetheless, a subject may have dosing held based on investigator's medical judgement. If abnormalities suggestive of drug-induced liver injury as described in this section are confirmed and found to be related to study drug, the subject will be permanently discontinued from study drug and will be followed up with appropriate care until resolution.

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).

8.5.9. Pregnancy Reporting

If a female subject becomes pregnant 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 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 drug, 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 within 24 hours of confirmation of the pregnancy; the contact information is the same as for SAE reporting. All cases of pregnancy will be reported to the sponsor 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.

8.5.10. Overdose

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

Any study drug 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 8.5.6, 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 SAE reporting procedures but an AESI/overdose checkbox must be completed. The excess quantity and duration of the overdose should be recorded.

9. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, United States).

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints. The SAP supersedes any differences in the protocol.

9.1. Statistical Hypotheses

This protocol is designed to evaluate the superiority of three doses ([redacted] QD) of NDI-034858 to placebo for the treatment of rheumatological signs, symptoms and function in patients with active psoriatic arthritis.

For each dose within each endpoint, the null hypothesis is that there is no difference between NDI-034858 and placebo, and the alternative hypothesis is that there is a difference between NDI-034858 and placebo.

9.1.1. Multiplicity Adjustment

No multiplicity adjustment is planned in this study due to the non-pivotal nature of the study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Table 6: Analysis Sets

Population (Analysis Set)	Description
Enrolled Population (EP)	All subjects who signed the informed consent
Intent-to-Treat (ITT) Analysis Set	All randomized subjects. Subjects will be included into the analysis as randomized.
Full Analysis Set (FAS)	All randomized subjects who receive at least one dose of study drug. Subjects will be included into the analysis as randomized.
Per-Protocol (PP) Set	All FAS subjects who are compliant, as defined in Section 6.3.2, with study treatment and are without any major protocol deviations that could impact the primary endpoint.
Safety Analysis Set	All subjects who receive at least one dose of study drug. Subjects will be included into the analysis based on actual treatment received, regardless of the treatment randomized.
PK Analysis Set	All subjects in the Safety Analysis Set with at least one evaluable post-dose PK assessment.

PK = pharmacokinetics

The Full Analysis Set (FAS) will be used for all efficacy and baseline analyses. The Per Protocol (PP) Set will be determined prior to database lock and the PP and ITT Sets will be used as supplementary analyses of the primary endpoint. Additional analyses may be conducted on the PP set in order to evaluate the impact of major protocol deviations.

All safety analyses will be based on the Safety Analysis Set. All PK tabulations and statistical analyses will be based on the PK Analysis Set.

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

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analyses will include tabulations of summary data, inferential analyses, by-subject listings, and figures.

All statistical tests will be two-sided and will be performed at the 5% level of significance, unless otherwise stated. Frequency counts (n and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated for each quantitative variable, unless otherwise stated. All data will be summarized by treatment group.

The baseline value for analysis and reporting will be based on the last (non-missing) measurement before dosing on Day 1. If any safety measurements are repeated after dosing on Day 1, then the first (non-missing) value of any repeated measurements will be used in the descriptive statistics and in the calculation of changes from baseline.

9.3.2. Efficacy Analyses

The primary endpoint can be translated as a responder analysis, where a subject will be classified as responder if they achieve ACR20 at Week 12. Comparison of the primary endpoint will be made between each dose group and the placebo group using a 2-sided Mantel-Haenszel (MH) test of the risk difference in two proportions stratified by the randomization stratification factors (prior treatment with biologics or non-traditional DMARDs [yes/no], and region [(USA/Germany)/(Eastern Europe)]). The estimand MH risk difference will be summarized along with the two-sided 95% CI using MH stratum weights (Mantel and Haenszel 1959) and the Sato variance estimator (Sato 1989). The primary efficacy analysis will be performed on the FAS, while the ITT and PP sets will be used as a supplementary analysis. Use of the FAS dataset as primary is to assess the clinical question of interest in the protocol to determine treatment effect for dosing and efficacy. Handling of intercurrent events and missing data will be addressed in detail within the SAP. Estimands and additional sensitivity analyses will be described in the SAP.

A descriptive analysis will be performed in demographic subgroups including age, gender, race, and body mass index to assess the consistency of the treatment effect. Additional subgroup analyses based on baseline disease characteristics and the randomization stratification factor will also be conducted and described in the SAP.

The secondary endpoints involving proportions of subjects will be analyzed using the same approach (MH test of the difference) as described for the primary efficacy analysis and based on the FAS.

The continuous secondary endpoints involving change from baseline will be analyzed using a mixed model for repeated measures based on the FAS. The model will include fixed effects for treatment group, visit, and treatment group-by-visit interaction, with baseline score and the randomization stratification factor as covariates, and the change from baseline as the dependent variable. Additional details on sensitivity analyses and missing data imputation of the secondary endpoints will be provided in the SAP.

9.3.3. Study Drug Exposure and Compliance

Exposure to study drug and study drug compliance will be summarized for each treatment group for the Safety Analysis Set.

9.3.4. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. No inferential statistics will be performed for safety variables. Additional details will be provided in the SAP.

9.3.4.1. Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 or higher and summarized by system organ class (SOC) and preferred term (PT). Collection of AEs will begin after dosing on Day 1. Analysis and reporting for AEs will be based on TEAEs. A TEAE is defined as an AE occurring (onset date/time) at the time of or after dosing on Day 1. Adverse events with missing start and/or end dates and/or times (if applicable) will be handled as described in the SAP.

All TEAEs will be listed for each subject. Separate listings will be presented for TEAEs, TESAEs, and TEAESIs. Each category will be presented for events leading to discontinuation of study drug and events leading so study discontinuation. All listings will be done by treatment group and subject, detailing verbatim, SOC, PT, start date, stop date (if resolved), intensity, seriousness, outcome, action taken with respect to study drug, and relationship to study drug. The AE onset will also be shown relative (in number of days) to the day of study drug administration.

An overview of all TEAEs will be presented by treatment group. The overview will include the following:

- Number and percentage of subjects with TEAEs
- Number and percentage of subjects with drug-related TEAEs
- Number and percentage of subjects with TEAEs leading to discontinuation of study drug
- Number and percentage of subjects with TEAEs leading to study discontinuation
- Number and percentage of subjects with TESAEs
- Number and percentage of subjects with drug-related TESAEs

- Number and percentage of subjects with TESAEs leading to discontinuation of study drug
- Number and percentage of subjects with TESAEs leading to study discontinuation
- Number and percentage of subjects by intensity of TEAEs (CTCAE grades 1, 2, 3, 4, 5)
- Number and percentage of subjects with TEAEs leading to death
- Number and percentage of subjects with TEAESIs
- Number and percentage of subjects with drug-related TEAESIs
- Number and percentage of subjects with TEAESIs leading to discontinuation of study drug
- Number and percentage of subjects with TEAESIs leading to study discontinuation

Summaries of TEAEs by treatment group, SOC, and PT will be presented for the following:

- All TEAEs
- Drug-related TEAEs
- TEAEs leading to discontinuation of study drug
- TEAEs leading to study discontinuation
- TESAEs
- Drug -related TESAEs
- TESAEs leading to discontinuation of study drug
- TESAEs leading to study discontinuation
- TEAEs by intensity (CTCAE grades 1, 2, 3, 4, 5)
- TEAEs leading to death
- TEAESIs, overall and by categories
- Drug-related TEAESIs
- TEAESIs leading to discontinuation of study drug
- TEAESIs leading to study discontinuation

9.3.4.2. Electrocardiogram

Electrocardiogram measurements will be listed by subject and timepoint including changes from baseline, any repeated/unscheduled measurements and the investigator's assessment of clinically significant changes. Descriptive statistics (n, mean, SD, minimum, median, maximum) will be provided presented by treatment group and timepoint for both absolute values and changes from baseline. Clinically significant electrocardiogram measurements will also be summarized by treatment group.

9.3.4.3. Vital Signs

Vital signs measurements will be listed by subject and timepoint including changes from baseline and any repeated/unscheduled measurements. Descriptive statistics (n, mean, SD, minimum, median, maximum) will be provided by treatment group and timepoint for both absolute values and changes from baseline. Clinically significant vital signs measurements will also be summarized by treatment group.

9.3.4.4. Safety Laboratory Tests

Laboratory safety assessments will be listed by subject and timepoint including changes from baseline, flags for any measurements that are outside the reference ranges and any repeated/unscheduled assessments. Descriptive statistics (n, mean, SD, minimum, median, maximum) will be provided by treatment group and timepoint for both absolute values and changes from baseline. A shift from baseline table describing shifts to out-of-normal range will be provided by treatment group and timepoint.

Urinalysis results will be listed by subject and timepoint including changes from baseline for numeric variables, flags for any measurements that are outside the reference ranges and any repeated/unscheduled assessments. The results of any microscopic urinalysis assessments will be included in the listing.

The results of pregnancy, serology, and TB will be listed for each subject.

9.3.4.5. Physical Examination

Physical examination results will be listed and summarized descriptively by subject and body system.

9.3.5. Exploratory Analyses

[redacted]

9.3.6. Other Analyses

Descriptive summaries of subject disposition and baseline characteristics (including demographic data and medical and surgical history) will be presented by treatment group. In addition, a listing of subjects who discontinued from the study along with discontinuation reason will be provided. Listings of baseline characteristics and prohibited medications will also be provided.

Protocol deviations will be listed and summarized by treatment group and category.

Medications will be coded using the world Health Organization Drug Dictionary (WHO DD) and listed by subject. A summary of concomitant medications by treatment group and medication class will also be tabulated.

9.3.6.1. Pharmacokinetic Analyses

Concentration data will be listed per subject and summarized descriptively per dose for each scheduled sampling time point.

9.3.7. Planned Interim Analyses

No interim analysis is planned in this study.

9.3.8. Sample Size Determination

A sample size of 65 per treatment group across all sites will have 83% power using a two-sided test for the difference in the two proportions, assuming a type I error rate of 0.05, a 55% response rate for each NDI-034858 dose group as a proportion of ACR20 response, and a placebo ACR20 response rate of 30%. A total number of 260 subjects (65 per treatment group) are planned to be randomized into the study with a 1:1:1:1 allocation.

The sample size was calculated in nQuery 8.7 using a two-sample Z-Test (Chi-Square Test) pooled for difference of proportions.

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/IEC. 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 also 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 individual participating 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/IEC 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/IEC. 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/IEC and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to 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 to 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/REBIEC, Health Canada, European Medicines Agency, 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/REB/IEC, regulatory agencies, or pharmaceutical company supplying study drug 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/REB/IEC, 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 in compliance with 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 consist 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 drug 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, IEC 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 Medidata RAVE electronic data capture (EDC), a web-based EDC and reporting system. This application will be set up for remote entry. Medidata is the developer and owner of RAVE EDC. The EDC software was 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 a 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/REB/IEC per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB/REB/IEC 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
Posaconzole	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 Criterion 20 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. CONTRACEPTION

LOCAL REQUIRMENTS: EU Member States

For Female Subjects

A female subject who does not meet either the definition of postmenopausal as defined in the Inclusion Criteria or who is not permanently surgically sterile is considered of childbearing potential and is required to use highly effective contraception from screening until at least 4 weeks after the last study drug administration.

Highly effective contraceptive methods:

- Combined estrogen and progestin containing hormonal contraceptives (eg, oral contraceptive, patch, vaginal ring, injectable, or implant), or
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, or
- Intrauterine devices or intrauterine systems, or
- Vasectomized partner(s) (provided vasectomy was performed ≥ 4 months prior to screening), or
- Tubal ligation

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) and withdrawal are not acceptable.

For Male Subjects

A male subject who is surgically sterile (vasectomy with medical assessment confirming surgical success) OR who has a female partner who is postmenopausal or permanently sterile, no contraception is required.

A male subject who is sexually active with female partner(s) of childbearing potential must agree to use one of the highly effective contraceptive methods from Study Day 1 until at least 12 weeks after the last study drug as follows:

- Condom use and female partner(s) using at least one of the contraceptive measures as defined in above for female study subjects of childbearing potential, OR
- True abstinence: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods) and withdrawal are not acceptable.

Male subjects are responsible for informing his partner(s) of the risk of becoming pregnant and for reporting any pregnancy to the study doctor. If a pregnancy occurs, a partner authorization form requesting pregnancy outcome information will be requested from the pregnant partner.

It is important to note that contraception recommendations described are specifically intended to prevent pregnancy during exposure to the investigational study drug. Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

APPENDIX 3. SELECT DMARDS HALF-LIFE

Table 7 lists those DMARDS that have a washout period based on half-life in the exclusion criteria.

Table 7: DMARDS Half-life

DMARD	Half-life
Adalimumab (Humira (adalimumab) Injection for Subcutaneous Use 2019)	Mean terminal half-life is approximately 2 weeks, ranging from 10-20 days across studies with doses 0.25 mg/kg to 10 mg/kg
Certolizumab (Cimzia (certolizumab pegol) for Injection for Subcutaneous Use 2018)	Terminal elimination half-life is approximately 14 days for all doses tested
Golimumab (Simponi Aria® (golimumab) 2021)	Median terminal half-life is approximately 2 weeks for doses tested, 0.1 mg/kg to 10 mg/kg
Infliximab (Infliximab 2021)	Half-life is 7.7 to 9.5 days for doses tested, 3 mg/kg, 5 mg/kg and 10 mg/kg
Leflunomide (Arava® (leflunomide) 2021)	Median half-life of 18-19 days for the active metabolite (teriflunomide)

APPROVALS

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURE OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER

The electronic signature of the medical monitor is provided below.

[redacted], MD, [redacted], Clinical Sciences

DocuSigned by:
[redacted]