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Study Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Biological Activity, and PK of ND-L02-s0201 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Reference Number: ND-L02-S0201-005

NCT Number: NCT03538301

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY, TOLERABILITY, BIOLOGICAL ACTIVITY, AND PK OF ND-L02-s0201 IN SUBJECTS WITH IDIOPATHIC PULMONARY FIBROSIS (IPF)

PROTOCOL NUMBER: ND-L02-s0201-005
EUDRACT NUMBER: 2017-004919-39

Product:	ND-L02-s0201 for Injection
Sponsor:	Nitto Denko Corporation 1-1-2, Shimohozumi, Ibaraki Osaka 567-8680, Japan
Sponsor's Authorized Representative:	[redacted]
Medical Monitor:	[redacted]
Date of Protocol:	20 October 2017
Amendment 01:	18 January 2018
Amendment 02:	12 March 2018
Amendment 03:	08 July 2019
Amendment 04:	18 September 2019
Amendment 05:	17 June 2020

1. SIGNATURE PAGE

1.1. Sponsor Approval

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Biological Activity, and PK of ND-L02-s0201 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Protocol Number:	ND-L02-s0201-005
Date of Amendment 05:	17 June 2020

This study will be conducted in compliance with the clinical study protocol and amendments, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for current Good Clinical Practice (GCP) and applicable regulatory requirements. Compliance with GCP standards provides public assurance that the rights, safety, and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

1.2. Investigator Agreement

Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Biological Activity, and PK of ND-L02-s0201 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Protocol Number:	ND-L02-s0201-005
Date of Amendment 05:	17 June 2020

By signing this page, I attest that I have read and understand the contents of Clinical Protocol ND-L02-s0201-005. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor.

2. SYNOPSIS

Name of Sponsor

Nitto Denko Corporation

Name of Investigational Product

ND-L02-s0201 for Injection (ND-L02-s0201)

Name of Active Ingredient

NDT-05-0038

Title of Study

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Biological Activity, and PK of ND-L02-s0201 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Study Number

ND-L02-s0201-005

Study Centers

Multicenter

Phase of Development

2

Objectives

Primary:

- Evaluate the safety and tolerability of ND-L02-s0201, administered at 2 dose levels, once every 2 weeks (Q2W) over 24 weeks, versus placebo, in conjunction with standard of care (SOC)

Secondary:

- Evaluate the biological activity of ND-L02-s0201 as measured by spirometry over 24 weeks
- Evaluate changes of interstitial lung abnormalities (ILA) as measured by high-resolution computed tomography (HRCT)
- Evaluate single-dose pharmacokinetic (PK) endpoints over 24 weeks in a subset of subjects
- Evaluate trough levels for accumulation over time and identify when steady state conditions are achieved

Methodology

This is a Phase 2, double-blind, placebo-controlled, randomized, multicenter, international study of 2 doses of ND-L02-s0201 for Injection to evaluate safety, tolerability, biological activity, and PK in subjects with a diagnosis of IPF with forced vital capacity (FVC) ≥ 45% of predicted and diffusion capacity of the lung for carbon monoxide (DL_{CO}) ≥ 30% of predicted and who meet all inclusion criteria and do not meet any exclusion criteria.

Two dose levels of ND-L02-s0201 will be evaluated: a low dose (45 mg) and a high dose (90 mg). Subjects will be randomly assigned to receive ND-L02-s0201 for Injection or placebo Q2W over a 24-week treatment period. Approximately 120 eligible subjects will be randomized 1:1:1 to 1 of 3 treatment arms: ND-L02-s0201 for Injection high dose (90 mg), ND-L02-s0201 for Injection low dose (45 mg), or placebo.

For the purposes of this trial, SOC is defined as administration of either nintedanib or pirfenidone, though not both. Alternatively, eligible subjects do not need to be on either medication. For subjects in Germany only (due to country specific medical practice and guidelines), subjects do not need to be on either medication, provided they have failed or not tolerated nintedanib and/or pirfenidone. Subjects receiving SOC at the time of enrollment in the study will be stratified across the 3 treatment arms via the interactive web response system (IWRS). As there is no minimum number of subjects for a given SOC stratum, balance in strata across the 3 treatment arms is required.

Discontinuation of either nintedanib or pirfenidone must have occurred at least 12 weeks before Visit 1a. If the subject has been taking either pirfenidone or nintedanib before Visit 1a, the same medication should be continued during the subject's participation in this trial. However, dose adjustment or discontinuation of SOC in accordance with the prescribing information is permitted if clinically indicated. If the subject is not taking either pirfenidone or nintedanib at Visit 1a, neither medication may be taken through Week 24 (Visit 14) or Early Termination (ET). No other investigational therapy for IPF is allowed within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a.

Pharmacokinetics:

[redacted]

Number of Subjects (planned)

Approximately 120 subjects will be enrolled into the study, with approximately 40 subjects in each of 3 arms.

[redacted]

Inclusion Criteria

To be randomized, all subjects must meet the criteria listed below.

1. Males and females between 40 and 80 years of age, inclusive, at the time of consent.
2. Diagnosis of IPF within 5 years before Visit 1a, confirmed by the Principal Investigator (PI) using American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guidelines (Raghu et al, 2011 or Raghu et al, 2018; see Section 11.2.5).
    a. Clinical management of the patient at the site must be for IPF and the PI must be convinced that all locally available information support UIP/IPF is the most likely diagnosis. It is mandatory that the PI consider overreader interpretation of Visit 1b HRCT and, if performed, SLB in order to determine that a subject is eligible for this trial.
3. Extent of fibrosis greater than emphysema on HRCT.
4. If on pirfenidone or nintedanib, unchanged dose for at least 12 weeks before Visit 1a. Subjects may not be on both pirfenidone and nintedanib.

5. FVC ≥ 45% of predicted.
6. DL_{CO} corrected for hemoglobin ≥ 30% of predicted value.
7. Pulse oximetry saturation ≥ 90%, at rest while breathing ambient air or ≤ 2 L/minute supplemental oxygen by nasal prongs/cannula (Section 11.2.1).
8. Ratio of forced expiratory volume in 1 second (FEV1) to FVC ≥ 0.70.
9. Adequate liver and renal function, as demonstrated by:
    - Total bilirubin ≤ 1.5 × upper limit of normal (ULN), unless participant has a documented history of Gilbert's syndrome
    - Aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 × ULN
    - Creatinine < 2 × ULN
    - Serum albumin > 3.5 g/dL
10. Life expectancy of ≥ 12 months.
[redacted]
12. Women of childbearing potential (WCBP) must be willing to use a highly effective method of contraception throughout the study and study follow up or for at least 90 days after the last dose of study treatment (refer to Section 10.3.2.3).
13. Women must be willing not to breastfeed for 90 days after the last dose of the study treatment.
14. Males must agree to use a condom throughout the study and for 90 days after the last dose of study treatment to prevent seminal transmission of the investigational product (IP).
15. Males with female partners of childbearing potential must agree to use a highly effective method of contraception (refer to Section 10.3.2.3) throughout the study and for 90 days after the last dose of study treatment. All men with female partners of childbearing potential will be instructed to contact the Investigator immediately if their partner becomes pregnant at any time during study participation. All men must agree not to donate semen throughout the study and for 90 days after the last dose of study treatment.
16. Willing and able to provide written informed consent and comply with the study procedures and visit schedule, including follow-up visits.

Exclusion Criteria

Potential subjects who meet any of the following criteria at Screening will be excluded from the study:

1. Best, acceptable FVC from separate Screening spirometry that differ by ≥ 200 mL. See Section 8.3.1 for more information.
2. Respiratory exacerbation(s) or hospitalization for IPF exacerbation within 3 months before Visit 1a.
3. Taking both pirfenidone and nintedanib concurrently within 12 weeks before Visit 1a.
4. Anticipated to receive a lung transplant during the subject's participation in the study.
5. Diagnosis of any connective tissue disease with a natural history that may be associated with pulmonary disease.
6. Clinical evidence of or known history of cirrhosis.
[redacted]
8. Uncontrolled cardiac disease or cardiac surgical procedure (eg, New York Heart Association Class III or IV, myocardial infarction, transient ischemic attack, uncontrolled atrial or

ventricular cardiac arrhythmias, unstable angina, stroke, coronary angioplasty, coronary artery bypass graft) within 30 days before Visit 1a.

9. Active smoker or smoking cessation within 12 weeks before Visit 1a.
10. Malignancy within the last 5 years, with the exception of curable cancer (eg, basal or squamous cell skin cancer, cervical cancer in situ, nonmedullary thyroid carcinoma) that has been adequately treated (eg, excision).
11. Evidence of any unstable or untreated, clinically significant disease or condition that, in the opinion of the Investigator, might confound the interpretation of the study or place the subject at increased risk (eg, uncontrolled hypertension, diabetes mellitus). Subjects will have to have been on stable treatment for at least 4 weeks before Visit 1a.
12. Treatment with high dose corticosteroids, cytotoxic agents (eg, chlorambucil, azathioprine, cyclophosphamide, methotrexate), unapproved IPF-targeted therapy, and cytokine modulating agents within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a.
    - A dose of ≤ 15 mg/day prednisone, or equivalent, is acceptable if unchanged for ≥ 10 weeks before Visit 1a and is expected to remain unchanged during the subject's participation in the study.
13. Receiving an investigational treatment, whether or not approved for marketing, with the last dose of that study drug within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a. Individuals allocated to receive no treatment beyond SOC in an investigational study are not excluded from this trial.
14. History of allergic reaction to any of the study drugs to be administered.
15. Pregnant or breastfeeding.
16. Veins unsuitable for repeated venipuncture or intravenous (IV) infusion (eg, veins that are difficult to locate, access, or puncture; veins with a tendency to rupture during or after puncture), in the opinion of study center personnel.
17. Known history of human immunodeficiency virus (HIV) infection, active chronic hepatitis B (eg hepatitis B surface antigen positive), and/or untreated hepatitis C antigen positive patients (with or without abnormal liver enzymes). If treated for hepatitis C viral eradication, then a viral load below the limits of quantitative detection for at least 12 weeks must be documented.
18. History of alcohol abuse and/or dependence within the last 2 years, as determined by the Investigator.
19. History within the last 2 years of significant mental illness, or dependence on any opioid or illicit drugs as defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).
20. Suspected or confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, defined as meeting one or more of the following criteria:
    a. The subject has known exposure to a person with signs or symptoms of SARS-CoV-2 infection or has tested positive for SARS-CoV-2 (suggesting current infection) within 21 days prior to the subject's Visit 1a.
    b. The subject has current signs and symptoms suggestive of SARS-CoV-2 infection.
    c. The subject has SARS-CoV-2 virus or viral antigen detected at Visit 1a using a test approved for marketing if testing is available. (Detection of antibody to SARS-CoV-2 will not be exclusionary. Refer to Section 8.3.3.1 for more guidance on SARS-CoV-2 testing.)

Screening and Rescreening Procedures

Refer to Section 8.3 for additional information on Screening and Rescreening procedures. Refer to Section 18.6 for guidance on clinical trial conduct relating to coronavirus disease (COVID-19).

Investigational Product, Dosage, and Mode of Administration

ND-L02-s0201 will be administered by IV infusion at either 45 mg or 90 mg, Q2W for 24 weeks (a total of 12 doses).

[redacted]

Duration of Treatment

All subjects will be treated with ND-L02-s0201 or placebo for 24 weeks (a total of 12 doses).

Subject's participation in the study will be approximately 40 weeks including a Screening and Baseline period of up to 6 weeks, a treatment period of 24 weeks (including the 2 weeks after the last study treatment), and a follow-up period of 10 weeks after End-of-Treatment (EOT). The end of trial will be the last subject, last visit (LSLV).

Reference Therapy, Dosage, and Mode of Administration

The reference therapy (placebo) is Sodium Chloride 0.9% for Injection (USP/EP/JP or equivalent). Reference therapy will be administered IV every 2 weeks for 24 weeks following the same procedures described for the IP.

Assessments and Measurements

Safety:

To ensure safety of the overall study an independent Data Monitoring Committee (DMC) will be established. The DMC will periodically review the available safety and tolerability of study treatment for the duration of the study (see Section 7.4).

The following safety assessments will be performed:

- Adverse events:

  [redacted]

- Safety laboratory findings:

  [redacted]

[redacted]

- Physical examinations, vital signs, and weight
- 12-Lead electrocardiograms (ECG)

[redacted]

- Concomitant medications

Biological Activity:

- Pulse oximetry (peripheral capillary oxygen saturation [SpO_2])
- FVC
- DL_{CO} (corrected for hemoglobin)
- HRCT

[redacted]

Study Endpoints

Safety:

- Incidence of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs
- Proportion of subjects discontinuing study treatment due to TEAEs

Biological Activity:

- Rate of decline in FVC over 24 weeks (measured in mL and % of predicted over unit time)
- Absolute and relative change in FVC (mL and % of predicted) at Visit 14 (Day 169) as compared with baseline

- Proportion of subjects with an FVC response (mL and % of predicted) defined as either having improvement or a decline by 0 to ≤ 5%, > 5% to ≤ 10%, and > 10% at Visit 14 (Day 169)
- Change in DL_{CO} and DL_{CO} corrected for hemoglobin
- Changes of ILA as measured by HRCT (ie, change in parenchymal feature [Baseline to Visit 14 (Day 169)]), as determined by qualitative assessment (central radiologist) and quantitative analysis (Quantitative Lung Fibrosis – QLF analysis)
- Time to first acute IPF exacerbation (ie, an unexplained worsening of dyspnea, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure [Raghu et al, 2011])
- Rate of hospitalization for respiratory ailments, rate of mortality due to all causes, and rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death

Pharmacokinetics:

[redacted]

Statistical Methods

Populations of Interest:

Safety Population: The safety population will include all subjects who receive at least 1 dose of study treatment.

ITT Population: The intent-to-treat (ITT) population will include any randomized subjects.

PK Population 1: This PK population will include subjects in the PK subset who receive at least 1 dose of study treatment and have a majority of scheduled PK samples drawn for serial PK measurements that allow for PK parameters to be generated. Subjects who do not complete the study treatment infusion (Visit 2) will be excluded from the PK analysis.

PK Population 2: This PK population will include subjects who receive the majority of the study treatment doses and also have a majority of the planned trough samples collected that allow for a comparison of trough levels across dosing weeks.

Per Protocol Population: This population will exclude nonevaluable subjects and subjects with major protocol deviations thought to impact the ability to assess the effect of study treatment. Exclusion of subjects from the Per Protocol (PP) set will be reviewed, documented, and approved before the study is unblinded to the study Sponsor. The criteria for excluding subjects from the PP population will be specified in the Statistical Analysis Plan (SAP).

Demographic and Baseline Characteristics:

The safety population will be used for summary of demographic and baseline characteristics.

Demographic and baseline laboratory results will be summarized overall and by treatment arm using descriptive statistics. Additionally, the proportion of subjects on SOC upon randomization for each treatment arm will be summarized.

Safety:

All safety analyses will be performed on the safety population.

The analysis of safety, reported for each treatment arm, will be based on the frequency of AEs and their severity for all treated subjects. The safety variables, including AEs, SAEs, and AEs of interest (coded using the Medical Dictionary for Regulatory Activities [MedDRA]), clinical laboratory tests [redacted] physical examination, ECGs, and vital signs will be summarized or tabulated by treatment arm. Some of the variables will be tabulated by treatment arm and by visit. Incidence of AEs will be further tabulated by subjects on SOC within each treatment arm.

The proportion of subjects discontinuing study treatment due to AEs will be tabulated by treatment arm.

Biological Activity:

All biological activity analyses will be performed on the ITT population.

[redacted]

Table 1: Schedule of Events

	Screening[a]		Treatment Period						EOT	Follow-Up	
Visit	**1a**	**1b**	**2**		**3**	**4**	**5, 7, 9, 11, 13 (Simple tests)**	**6, 8, 10, 12 (Detailed tests)**	**14 (or ET)**	**15**	**16**
Week	**-6 to -1**		**0**		**2**	**4**	**6, 10, 14, 18, 22**	**8, 12, 16, 20**	**24 (2 wk postdose)**	**28 (4 wk post V14/ET)**	**34 (10 wk post V14/ET)**
Study Day	**-42 to -7**		**1**	**2**	**15**	**29**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**169**	**197**	**239**
Allowable Window (days)[b]					**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Study Procedure											
Informed Consent	X[c]										
Eligibility	X	X	X								
Demographics and baseline characteristics	X										
Medical history	X										
Adverse events	X[d]	X	X	X[e]	X	X	X	X	X	X	X
IPF history and previous treatments	X										
Prior medications	X										
Concomitant medications	X[d]	X	X	X[e]	X	X	X	X	X	X	X
Physical examination (complete)	X								X		
Physical examination (abbreviated)[f]		X	X								
Height	X										
Weight	X								X		
12-lead ECG	X	X				X[g]			X		
Vital signs[h]	X	X	X		X	X	X	X	X	X	X
Pulse oximetry: SpO_2[h]	X	X	X		X	X	X	X	X	X	X
[redacted]											
Chemistry	X		X		X	X		X	X		X
Hematology	X	X[n]	X			X		X	X	X[n]	X
Urinalysis	X								X		X
Pregnancy test (urine) for WCBP[o]	X		X			X		X	X	X	X
[redacted]											
Serology (HCV Ab, HBsAg, HIV 1/2)	X										
SARS-CoV-2 test[r]	X										

	Screening[a]		Treatment Period						EOT	Follow-Up	
Visit	**1a**	**1b**	**2**		**3**	**4**	**5, 7, 9, 11, 13 (Simple tests)**	**6, 8, 10, 12 (Detailed tests)**	**14 (or ET)**	**15**	**16**
Week	**-6 to -1**		**0**		**2**	**4**	**6, 10, 14, 18, 22**	**8, 12, 16, 20**	**24 (2 wk postdose)**	**28 (4 wk post V14/ET)**	**34 (10 wk post V14/ET)**
Study Day	**-42 to -7**		**1**	**2**	**15**	**29**	**43, 71, 99, 127, 155**	**57, 85, 113, 141**	**169**	**197**	**239**
Allowable Window (days)[b]					**± 4**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Randomization			X								
[redacted]											
Premedication (optional)[w]			X		X	X	X	X			
Study treatment			X		X	X	X	X			

Abbreviations: [redacted] COVID-19 = coronavirus disease; [redacted] ECG = electrocardiogram; EOT = end-of-treatment; ET = Early Termination; [redacted] HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV 1/2 = human immunodeficiency virus type 1 or 2; [redacted] ICF = informed consent form; IPF = idiopathic pulmonary fibrosis; [redacted] QC = quality control; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted] SOC = standard of care; [redacted] V = Visit; WCBP = women of childbearing potential; [redacted]

Note: Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

[a] Screening begins with the first Visit 1a procedure (excluding signing the ICF) and may be shorter than 42 days. If possible, plan Visit 1b and schedule the [redacted] at the time of Visit 1a. To assure that an ineligible subject does not undergo an unnecessary [redacted] ALL Visit 1a procedures MUST be completed before any Visit 1b procedures may be started. [redacted]

[b] Subjects should be dosed on the study day listed in the Study Schedule (± 4 days for Visit 3 or ± 7 days for Visits 4 to 13), ensuring a minimum of 7 days between each dose. Assessments not associated with study treatment infusion may be performed on days other than the dosing day for scheduling purposes, as long as they are performed before the infusion.

[c] The ICF should be signed before Visit 1a to allow the site to instruct the subject to withhold bronchodilator use as required for the Visit 1a PFT (see Section 11.2.2) [redacted]

[d] Adverse event and concomitant medication collection will begin 24 hours before Visit 1a.

[e] On Day 2, study personnel will call subjects not returning to the site to collect any AEs and concomitant medications that may have occurred after leaving the site on Day 1.

[f] Other abbreviated physical examinations may be performed at the discretion of the Investigator on the basis of signs or symptoms. See Section 11.1.3 for more information.

[g] During Visit 4 (Day 29), ECGs will be performed once, within 30 minutes after the end of the study treatment infusion.

[h] Vital signs and SpO_2 will be measured at every study visit, except at Visit 2 (Days 2 and 3; subjects participating in the PK substudy will only have vital signs measured). On dosing days vital signs and SpO_2 will be measured thrice: once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication), midinfusion ± 5 minutes [redacted] and within 15 minutes after the end of the study treatment infusion. The frequency of monitoring vital signs may be increased as warranted by clinical management. See Section 11.1.4 and Section 11.2.1 for more information.

[redacted]

[o] A positive urine pregnancy test will be followed up with a serum pregnancy test.

[redacted]

[r] Every effort should be made to test for SARS-CoV-2 virus or viral antigen at Visit 1a if testing is available. The test used should have regulatory approval for marketing and sample collection should be performed per the assay's specifications. Depending on the site and its location, options for subject testing may vary. Refer to Section 8.3.3 for guidance on SARS-CoV-2 testing.

[redacted]

[w] Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator (see Section 18.5).

[redacted]

3. TABLE OF CONTENTS AND LIST OF TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
ALAT	Latin American Thoracic Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	clinical trial lead

Abbreviation or Specialist Term	Definition
[redacted]	[redacted]
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DMC	Data Monitoring Committee
[redacted]	[redacted]
[redacted]	[redacted]
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End-of-Treatment
EP	European Pharmacopeia
ERS	European Respiratory Society
ET	Early Termination
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FU	follow up
FVC	forced vital capacity
[redacted]	[redacted]
GCP	Good Clinical Practice
[redacted]	[redacted]
GLI	Global Lung Initiative
HBsAg	hepatitis B surface antigen
HCV Ab	hepatitis C virus antibody
[redacted]	[redacted]
[redacted]	[redacted]
HIPAA	Health Insurance Portability and Accountability Act
HIV 1/2	human immunodeficiency virus type 1 or 2
[redacted]	[redacted]
[redacted]	[redacted]
HRCT	high-resolution computed tomography
HSP47	heat shock protein 47
ICF	informed consent form

Abbreviation or Specialist Term	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILA	interstitial lung abnormalities
IND	Investigational New Drug
IP	investigational product
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
JRS	Japanese Respiratory Society
JP	Japanese Pharmacopeia
[redacted]	[redacted]
[redacted]	[redacted]
LNP	lipid nanoparticle
LSLV	last subject, last visit
MDD	multidisciplinary discussion
MedDRA	Medical Dictionary for Regulatory Activities
NCA	noncompartmental analysis
NCI	National Cancer Institute
[redacted]	[redacted]
PD	pharmacodynamic
PEF	peak expiratory flow
[redacted]	[redacted]
PFT	pulmonary function testing
PI	Principal Investigator
[redacted]	[redacted]
PK	pharmacokinetic(s)
PP	per protocol
[redacted]	[redacted]
Q2W	every 2 weeks

Abbreviation or Specialist Term	Definition
[redacted]	[redacted]
QA	quality assurance
QC	quality control
QLF	Quantitative Lung Fibrosis
[redacted]	[redacted]
QTcF	QT interval corrected using Fridericia's formula
RNAi	ribonucleic acid interference
[redacted]	[redacted]
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
[redacted]	[redacted]
siRNA	small interfering ribonucleic acid
SLB	surgical lung biopsy
SOC	standard of care
SOP	standard operating procedure
SpO_2	peripheral capillary oxygen saturation
[redacted]	[redacted]
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
TMF	Trial Master File
UIP	usual interstitial pneumonia
ULN	upper limit of normal
USP	United States Pharmacopeia
UV	ultraviolet
[redacted]	[redacted]
[redacted]	[redacted]
WBC	white blood cell

Abbreviation or Specialist Term	Definition
WCBP	women of childbearing potential
WHODDE	World Health Organization Drug Dictionary Enhanced
[redacted]	[redacted]

5. INTRODUCTION

ND-L02-s0201 for Injection is being developed for idiopathic pulmonary fibrosis (IPF) by Nitto Denko Corporation (Nitto). ND-L02-s0201 for Injection is a lipid nanoparticle (LNP) formulation [redacted]

5.1. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. It occurs primarily in older adults and is limited to the lungs. Idiopathic pulmonary fibrosis is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis (Raghu et al, 2011). The median survival of patients with IPF is generally 2.5 to 3.5 years (Ley et al, 2011). Respiratory failure resulting from disease progression is the most frequent cause of death (Ley et al, 2011).

Pulmonary fibrosis was initially thought to be the result of chronic inflammation, but current evidence indicates it is the result of an epithelial-driven and fibroblast-activated process in which inflammation may have an ancillary role (Selman et al, 2001). Type II pneumocytes and myofibroblasts in usual interstitial pneumonia (UIP) overexpress and co-express HSP47 and type I procollagen. Studies have demonstrated expression of human HSP47 is increased in fibrotic lesions of IPF, idiopathic nonspecific interstitial pneumonia, and diffuse alveolar damage (Razzaque et al, 1998; Kakugawa et al, 2005) and HSP47 is detected in the serum of patients with acute exacerbated IPF (Kakugawa et al, 2013). Myofibroblasts, through the production of HSP47-associated regulation of type I procollagen, likely play an important role in the progression of pulmonary fibrosis (Iwashita et al, 2000).

5.2. ND-L02-s0201 for Injection

ND-L02-s0201 for Injection is an LNP formulation [redacted]

5.3. Study ND-L02-s0201-005

This Phase 2 clinical study will be a randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, biological activity, and pharmacokinetics (PK) of ND-L02-s0201 for Injection in subjects with IPF. Approximately 120 subjects will be enrolled (approximately 40 subjects in each of 3 arms). Subjects will be randomized 1:1:1 to a low dose of ND-L02-s0201 (45 mg), a high dose of ND-L02-s0201 (90 mg), or placebo. Subjects will receive study treatment every 2 weeks (Q2W) for 24 weeks and will be followed until 12 weeks after the last dose.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

5.4. Nonclinical Program

Refer to the Investigator Brochure for a summary of the nonclinical information available for ND-L02-s0201.

5.5. Clinical Program

Refer to the Investigator Brochure for a summary of the clinical information available for ND-L02-s0201.

[redacted]

[redacted]

6. STUDY OBJECTIVES

6.1. Primary Objective

- Evaluate the safety and tolerability of ND-L02-s0201, administered at 2 dose levels, Q2W over 24 weeks, versus placebo, in conjunction with standard of care (SOC)

6.2. Secondary Objectives

- Evaluate the biological activity of ND-L02-s0201 as measured by spirometry over 24 weeks
- Evaluate changes of interstitial lung abnormalities (ILA) as measured by high-resolution computed tomography (HRCT)
- Evaluate single-dose PK endpoints over 24 weeks in a subset of subjects
- Evaluate trough levels for accumulation over time and identify when steady state conditions are achieved

7. INVESTIGATIONAL PLAN

7.1. Study Design

This is a Phase 2, double-blind, placebo-controlled, randomized, multicenter, international study of 2 doses of ND-L02-s0201 for Injection to evaluate safety, tolerability, biological activity, and PK in subjects with a diagnosis of IPF.

There will be 3 treatment arms. Two dose levels of ND-L02-s0201 will be evaluated in 2 arms: a low dose (45 mg) and a high dose (90 mg). A third arm will be administered placebo.

The study will consist of a Screening period lasting up to 42 days, a 24-week treatment period including an End-of-Treatment (EOT) visit 2 weeks after the final dose (Visit 14), and 2 follow-up (FU) visits 4 and 10 weeks after Visit 14. During the treatment period ND-L02-s0201 for Injection will be administered by intravenous (IV) infusion Q2W (± 4 days for Visit 3 or ± 7 days for Visits 4 to 13, ensuring a minimum of 7 days between each dose) for a total of 12 doses. Subject participation will be up to 281 days (approximately 40 weeks). The end of trial will be the last subject, last visit (LSLV).

[redacted]

7.2. Randomization

Approximately 120 eligible subjects will be randomly assigned 1:1:1 to 1 of 3 treatment arms: low dose ND-L02-s0201 for Injection (45 mg), high dose ND-L02-s0201 for Injection (90 mg), and a placebo arm. The randomization schedule will be prepared by an unblinded statistician.

[redacted]

[redacted]

7.3. Blinding

Unblinded study personnel will prepare and administer the study treatment. The Investigator and other members of staff involved with the study will remain blinded to the study treatment randomization code until the final database is locked.

[redacted]

7.4. Data Monitoring Committee

To ensure safety of the overall study an independent Data Monitoring Committee (DMC) will be established. The DMC will periodically review the safety and tolerability of study treatment for the duration of the study. The DMC will include a chairperson and pulmonologist who are experienced in IPF; all members will be experienced with clinical trials and evaluating AEs, and will not otherwise participate in the study. The DMC will also include an independent statistician.

The DMC will review all available AEs, safety laboratory data, declines in pulmonary function tests meeting thresholds defined in Section 11.2.2, [redacted] at preset times. The first scheduled meeting will occur after 25% of subjects have completed 1 month of the study (ie, Visit 4, Day 29). The second scheduled meeting will occur after 50% of subjects have completed Visit 4 (Day 29). The third scheduled meeting will occur after 75% of subjects have completed Visit 8 (Day 85). All data listed for all subjects available at the time of the meeting will be included for review.

Following review, the DMC will recommend continuation, modification, or discontinuation of the study based on observed toxicities. A DMC charter will describe the activities of this committee.

In the event of unexpected AE or serious adverse event (SAE) findings or other critical safety-related issues (eg, the coronavirus disease [COVID-19] pandemic), Nitto or the DMC may convene an ad hoc meeting. Such a meeting will outline the cause of concern and may identify a data cut-off as part of the scheduling request.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Inclusion Criteria

To be randomized, all subjects must meet the criteria listed below.

1. Males and females between 40 and 80 years of age, inclusive, at the time of consent.
2. Diagnosis of IPF within 5 years before Visit 1a, confirmed by the **Principal** Investigator (PI) using American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guidelines (Raghu et al, 2011 or Raghu et al, 2018; see Section 11.2.5).
    a. Clinical management of the patient at the site must be for IPF and the PI must be convinced that all locally available information support UIP/IPF is the most likely diagnosis. It is mandatory that the PI consider overreader interpretation of Visit 1b HRCT and, if performed, SLB in order to determine that a subject is eligible for this trial.
3. Extent of fibrosis greater than emphysema on HRCT.
4. If on pirfenidone or nintedanib, unchanged dose for at least 12 weeks before Visit 1a. Subjects may not be on both pirfenidone and nintedanib.
5. Forced vital capacity (FVC) ≥ 45% of predicted.
6. Diffusion capacity of the lung for carbon monoxide (DL_{CO}) corrected for hemoglobin ≥ 30% of predicted value.
7. Pulse oximetry saturation ≥ 90%, at rest while breathing ambient air or ≤ 2 L/minute supplemental oxygen by nasal prongs/cannula (see Section 11.2.1).
8. Ratio of forced expiratory volume in 1 second (FEV1) to FVC ≥ 0.70.
9. Adequate liver and renal function, as demonstrated by:
    - Total bilirubin ≤ 1.5 × upper limit of normal (ULN), unless participant has a documented history of Gilbert's syndrome
    - Aspartate transaminase (AST) and alanine transaminase (ALT) < 2.5 × ULN
    - Creatinine < 2 × ULN
    - Serum albumin > 3.5 g/dL
10. Life expectancy of ≥ 12 months.

[redacted]

12. Women of childbearing potential (WCBP) must be willing to use a highly effective method of contraception throughout the study and study follow up or for at least 90 days after the last dose of study treatment (refer to Section 10.3.2.3).
13. Women must be willing not to breastfeed for 90 days after the last dose of the study treatment.

14. Males must agree to use a condom throughout the study and for 90 days after the last dose of study treatment to prevent seminal transmission of the investigational product (IP).
15. Males with female partners of childbearing potential must agree to use a highly effective method of contraception (refer to Section 10.3.2.3) throughout the study and for 90 days after the last dose of study treatment. All men with female partners of childbearing potential will be instructed to contact the Investigator immediately if their partner becomes pregnant at any time during study participation. All men must agree not to donate semen throughout the study and for 90 days after the last dose of study treatment.
16. Willing and able to provide written informed consent and comply with the study procedures and visit schedule, including follow-up visits.

8.2. Exclusion Criteria

Potential subjects who meet any of the following criteria at Screening will be excluded from the study:

1. Best, acceptable FVC from separate Screening spirometry that differ by ≥ 200 mL. See Section 8.3.1 for more information.
2. Respiratory exacerbation(s) or hospitalization for IPF exacerbation within 3 months before Visit 1a.
3. Taking both pirfenidone and nintedanib concurrently within 12 weeks before Visit 1a.
4. Anticipated to receive a lung transplant during the subject's participation in the study.
5. Diagnosis of any connective tissue disease with a natural history that may be associated with pulmonary disease.
6. Clinical evidence of or known history of cirrhosis.

8. Uncontrolled cardiac disease or cardiac surgical procedure (eg, New York Heart Association Class III or IV, myocardial infarction, transient ischemic attack, uncontrolled atrial or ventricular cardiac arrhythmias, unstable angina, stroke, coronary angioplasty, coronary artery bypass graft) within 30 days before Visit 1a.
9. Active smoker or smoking cessation within 12 weeks before Visit 1a.
10. Malignancy within the last 5 years, with the exception of curable cancer (eg, basal or squamous cell skin cancer, cervical cancer in situ, nonmedullary thyroid carcinoma) who has received adequate treatment (eg, excision).
11. Evidence of any unstable or untreated, clinically significant disease or condition that, in the opinion of the Investigator, might confound the interpretation of the study or place the subject at increased risk (eg, uncontrolled hypertension, diabetes mellitus). Subjects will have to have been on stable treatment for at least 4 weeks before Visit 1a.

12. Treatment with high dose corticosteroids, cytotoxic agents (eg, chlorambucil, azathioprine, cyclophosphamide, methotrexate), unapproved IPF-targeted therapy, and cytokine modulating agents within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a.
    - A dose of ≤ 15 mg/day prednisone, or equivalent, is acceptable if unchanged for ≥ 10 weeks before Visit 1a and is expected to remain unchanged during the subject's participation in the study.
13. Receiving an investigational treatment, whether or not approved for marketing, with the last dose of that study drug within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a. Individuals allocated to receive no treatment beyond SOC in an investigational study are not excluded from this trial.
14. History of allergic reaction to any of the study drugs to be administered.
15. Pregnant or breastfeeding.
16. Veins unsuitable for repeated venipuncture or IV infusion (eg, veins that are difficult to locate, access, or puncture; veins with a tendency to rupture during or after puncture), in the opinion of study center personnel.
17. Known history of human immunodeficiency virus (HIV) infection, active chronic hepatitis B (eg hepatitis B surface antigen positive), and/or untreated hepatitis C antigen positive patients (with or without abnormal liver enzymes). If treated for hepatitis C viral eradication, then a viral load below the limits of quantitative detection for at least 12 weeks must be documented.
18. History of alcohol abuse and/or dependence within the last 2 years, as determined by the Investigator.
19. History within the last 2 years of significant mental illness, or dependence on any opioid or illicit drugs as defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).
20. Suspected or confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, defined as meeting one or more of the following criteria:
    a. The subject has known exposure to a person with signs or symptoms of SARS-CoV-2 infection or has tested positive for SARS-CoV-2 (suggesting current infection) within 21 days prior to the subject's Visit 1a.
    b. The subject has current signs and symptoms suggestive of SARS-CoV-2 infection.
    c. The subject has SARS-CoV-2 virus or viral antigen detected at Visit 1a using a test approved for marketing if testing is available. (Detection of antibody to SARS-CoV-2 will not be exclusionary. Refer to Section 8.3.3.1 for more guidance on SARS-CoV-2 testing.)

8.3. Screening and Rescreening Procedures

8.3.1. Pulmonary Function Testing

8.3.1.1. Screening

Additional information regarding pulmonary function testing (PFT) is in Section 11.2.2.
Pulmonary function testing will be performed at study visits on separate days during Screening.

[redacted]

8.3.2. Other Eligibility Criteria Assessments

Subjects with a confirmed diagnosis of IPF per this protocol's eligibility criteria who fail Screening may be rescreened once if there is a change in status that, in consideration of protocol criteria by the Investigator and Medical Monitor, would allow participation in the study.

8.3.3. COVID-19 Considerations

8.3.3.1. Screening

Refer to exclusion criterion 20 for eligibility restrictions related to suspected or confirmed SARS-CoV-2 infection.

In terms of exclusion criterion 20c, every effort should be made to test for SARS-CoV-2 virus or viral antigen at Visit 1a if testing is available. The test used should have regulatory approval for marketing and sample collection should be performed per the assay's specifications. Depending on the site and its location, options for subject testing may vary. Therefore, any of the following testing options are acceptable and are listed in order of preference:

- Local testing performed concurrent with Visit 1a.
- If local testing is not possible, testing should be performed using the central laboratory (if this option is in place and available to the site).
- If neither local nor central laboratory SARS-CoV-2 testing are available, exclusion criterion 20c may be omitted in subjects who do not meet either criterion 20a or 20b. In this case, it should be properly documented in eCRF.
- Detection of antibody to SARS-CoV-2 is not exclusionary.

If a subject has a positive result from any test to detect SARS-CoV-2 virus or viral antigen within 21 days prior to Visit 1a:

- If this finding is identified before signing the informed consent, the subject should not be consented until asymptomatic > 21 days.
- If the finding is identified after signing the consent, the subject should be considered a screen failure with the option to rescreen as detailed in Section 8.3.3.2.

If local or central SARS-CoV-2 testing is performed, the result should be available and reviewed before Visit 1b HRCT is conducted, consistent with Section 12.1. If the SARS-CoV-2 test is positive, the Visit 1b HRCT will not be performed.

8.3.3.2. Rescreening

A subject who was ineligible due to exclusion criterion 20 or details in Section 8.3.3.1, may rescreen in the following situations:

- The subject has been asymptomatic > 21 days after exposure to a person as described in exclusion criterion 20a.
- The subject's signs and symptoms of SARS-CoV-2 infection have completely resolved > 21 days prior to the planned date of Rescreening.
- The subject is asymptomatic for SARS-CoV-2 infection > 21 days after SARS-CoV-2 virus or viral antigen was detected and prior to the planned date of Rescreening.

8.3.4. High-Resolution Computed Tomography Scanning

8.3.4.1. Screening

An individual whose clinical management at the site is for IPF, may be consented for participation in this study, in the absence of obvious excluding criteria.

[redacted]

8.4. Subject Withdrawal

8.4.1. Withdrawal Criteria

Subjects may choose to withdraw from study treatment or the study at any time for any reason. In addition, subjects must have study treatment discontinued for any of the following reasons:

- The subject is unwilling or unable to adhere to the protocol.
- The subject becomes pregnant or begins breastfeeding.
- The subject experiences an SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the subject.
- [redacted]

- Another medical reason, at the discretion of the Investigator and/or the Medical Monitor that indicates continued participation is not in the best interest of the subject.

The only reason for withdrawal from the study should be subject withdrawal of consent to participate. [redacted] Subjects who discontinue study treatment should be followed for outcomes as long as they agree to continued participation in the study.

8.4.2. Withdrawal Procedures

If it is necessary for a subject to discontinue study treatment before completion, the subject should complete all ET and follow-up procedures (refer to Section 12.3 and Section 12.4) if he or she is willing and it is not medically contraindicated. At a minimum, all safety-related procedures should be performed. Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

The Investigator must notify the Sponsor and/or the Medical Monitor within 24 hours when a subject has discontinued study treatment because of an AE. Any subject who discontinued study treatment because of a treatment-related AE (whether serious or nonserious), including clinically significant abnormal laboratory test results, will be evaluated by the Investigator or a designee and will be treated and/or monitored until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or designee should inquire about the reason and will contact the subject by telephone as scheduled to collect AE information.

If the subject discontinues study treatment and also withdraws consent for disclosure of future information, no further evaluations will be performed, and no additional data will be collected. The Sponsor may retain and continue to use data collected before consent was withdrawn.

8.4.3. Documentation of Withdrawal

The reason(s) for discontinuation of study treatment or withdrawal of consent must be recorded in the subject's electronic case report form (eCRF).

8.4.4. Replacement of Subjects

Subjects who withdraw from the study will not be replaced. Subjects whose participation in the study was affected by restrictions relating to COVID-19 may be replaced if necessary to achieve this trial's objectives.

8.4.5. Stopping Rules

Subjects will be monitored for evidence of drug-induced liver injury based on regulatory guidelines.

[redacted]

8.5. Study Termination

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons or if required by the United States Food and Drug Administration (FDA) or other regulatory authorities. The Medical Monitor will review the safety of the study treatment regimen throughout the study. The study may be halted at any time for safety concerns.

9. INVESTIGATIONAL PRODUCT

Only unblinded site staff will be responsible for the receipt, storage, accountability, preparation, administration, and disposition of all IP. Unblinded site staff must be made fully aware that they are not to disclose any unblinded information to any blinded individual including the subject, site staff, sponsor, and monitors.

9.1. Identity of Investigational Product

ND-L02-s0201 for Injection is an LNP formulation [redacted]

9.3. Storage of Clinical Supplies

It is the responsibility of the Investigator to ensure that the IP is stored as specified by the Sponsor and in accordance with applicable regulatory requirements. The ND-L02-s0201 for Injection storage area must be secure with controlled access. Clinical supplies will be shipped to the study center pharmacy by the Sponsor or an approved vendor after the necessary regulatory documents have been received from the study center.

[redacted]

9.4. Drug Accountability

It is the responsibility of the Investigator to maintain IP accountability at the clinical trial site and ensure that a current record of IP disposition is maintained at the study site. It is the responsibility of the Investigator to ensure that the IP is used only in accordance with the approved protocol. Records or logs must comply with applicable regulations and guidelines, and should include the following:

- Amount received and placed in the storage area
- Amount currently in the storage area
- Lot number or batch number
- Dates and initials of the person responsible for each IP inventory entry/movement
- Amount dispensed to each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage
- Nonstudy disposition (eg, lost, wasted, not used)
- Amount returned to Sponsor or a designee, if applicable
- Amount destroyed at the study center, if applicable

The Sponsor or a designee will provide forms to facilitate inventory control if study center personnel do not have an established system that meets these requirements.

9.5. Return of Investigational Product

Refer to the study Pharmacy Manual for information regarding the return of IP.

9.6. Investigational Product Disposal at Study Center

Refer to the study Pharmacy Manual for information regarding IP disposal.

10. TREATMENT OF SUBJECTS

10.1. Dosing Regimen

ND-L02-s0201 for Injection will be administered at a dose of either 45 mg (low dose) or 90 mg (high dose). Study treatment (ND-L02-s0201 for Injection or placebo) will be dosed via IV infusion Q2W for 24 weeks as described in Table 1. Acceptable windows around dosing are ± 4 days for Visit 3 or ± 7 days for Visits 4 to 13, ensuring **a minimum of 7 days between each dose**. Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

10.2. Preparation and Administration

[redacted]

10.2.1. Dose Preparation

[redacted]

10.2.2. Dose Administration

10.2.2.1. ND-L02-s0201 for Injection or Placebo

[redacted]

[redacted]

10.2.2.2. Nintedanib

Subjects who are taking nintedanib at the start of the study should be instructed to take nintedanib in accordance with the prescribing information. Dose adjustment or discontinuation of SOC in accordance with the prescribing information is permitted if clinically indicated (see OFEV® Package Insert, 2018). On days when ND-L02-s0201 for Injection is being administered, subjects should take the morning dose of nintedanib before the infusion. On days when overnight fasting is required for sample collection, subjects should take nintedanib with their first meal of the day as prescribed (ie, after blood samples are collected).

10.2.2.3. Pirfenidone

Subjects who are taking pirfenidone at the start of the study should be instructed to take pirfenidone in accordance with the prescribing information. Dose adjustment or discontinuation of SOC in accordance with the prescribing information is permitted if clinically indicated (see ESBRIET® Package Insert, 2017). On days when ND-L02-s0201 for Injection is being administered, subjects should take the first dose of pirfenidone before the infusion. On days when overnight fasting is required for sample collection, subjects should take pirfenidone with their first meal of the day as prescribed (ie, after blood samples are collected).

10.2.3. Dose Interruption

Any interruption or other change in the study treatment infusion must be documented (see Section 10.4).

10.3. Prior and Concomitant Medications

All medications taken within 14 days before Visit 1a through end of study should be recorded in the eCRF.

10.3.1. Prior Medications

Prior medications are those taken within 14 days before Visit 1a until 24 hours before Visit 1a, or a longer period as specified in the exclusion criteria (see Section 8.2).

10.3.2. Concomitant Medications

Concomitant medications are those taken beginning 24 hours before Visit 1a.

10.3.2.1. Premedication

Refer to Section 18.5 for more information.

10.3.2.2. Pirfenidone or Nintedanib

If the subject has been taking either pirfenidone or nintedanib at an unchanged dose for at least 12 weeks before Visit 1a (Section 8.1), the same medication should be continued during the subject's participation in this trial. The dose of the medication should remain the same during the

subject's participation in the study. However, dose adjustment or discontinuation of SOC in accordance with the prescribing information is permitted if clinically indicated.

If the subject is not taking either pirfenidone or nintedanib at Screening, neither medication may be taken through Week 24 (Visit 14) or ET. After the collection of data at Week 24 (Visit 14) subjects may begin taking either medication at the discretion of the study doctor. Subjects may not be taking both pirfenidone and nintedanib during the study.

10.3.2.3. Contraceptives

Female Subjects

Female subjects of childbearing potential must use a highly effective method of contraception during participation in the study and study follow up or for 90 days after the last dose of study treatment.

Methods of contraception considered highly effective include 1 of the 5 listed below:

1. Hormonal contraception (eg, injection, implant, pill, patch, or vaginal ring as available in each country) associated with inhibition of ovulation (both estrogen and progestogen and progestogen only) in use for at least 30 days before administration of study treatment
2. Intrauterine device in use for at least 30 days before administration of study treatment
3. Intrauterine hormone-releasing system (IUS) in use for at least 30 days before administration of study treatment
4. Bilateral tubal occlusion/ligation at least 6 months before administration of study treatment
5. Partner who has been vasectomized at least 6 months before administration of study treatment

Note: A woman is considered to be of nonchildbearing potential if she meets one of the following criteria: a) postmenopausal with at least 12 months of spontaneous amenorrhea; b) has had a bilateral oophorectomy; or c) has had a hysterectomy.

Male Subjects

All males must agree to use a condom throughout the study and for 90 days after the last dose of study treatment to prevent seminal transmission of the IP.

In addition, males with female partners of childbearing potential must agree to use a highly effective method of contraception (see above) throughout the study and for 90 days after the last dose of study treatment.

10.3.2.4. Insulin

If the subject has diabetes, instruct them to adhere to the following recommendations to make sure that fasting is safe.

If the subject does not take insulin for diabetes, instruct them to:

- Not take any oral diabetes medications while fasting;
- Drink 250 mL (around 8 oz) of plain water every 4-6 hours prior to blood sampling;

- Eat a meal or snack after blood sample(s) is/are collected;
- Resume medications after eating the meal or snack.

If the subject does take insulin for diabetes, instruct them to:

- If on a basal injectable insulin dose (intermediate of long acting) the recommendation is to reduce normal insulin dose by one half or one third of the usual total morning dose depending on the fasting blood glucose in the morning after awakening;
- Omit any short-acting (eg, regular) or rapid-acting (eg, lispro, aspart, glulisine) insulin prior to blood sampling;
- If on continuous insulin infusion (insulin pump), the usual basal infusion rate does not need to be adjusted;
- Drink 250 mL (around 8 oz) of plain water every 4-6 hours prior to blood sampling;
- Eat a meal or snack after blood sample(s) is/are collected;
- Resume short-acting (eg, regular) or rapid-acting (eg, lispro, aspart, glulisine) insulin after eating the meal or snack.

10.3.2.5. Other

After enrollment into the study, every attempt should be made to avoid changes in the subject's medication regimen. Exceptions would include episodes of infections requiring treatment (eg, antibiotics or antiviral drugs), exacerbations of their underlying disease requiring immediate intervention, or any other situation requiring modification of the subject's therapy for their safety at the discretion of the treating physician or the Investigator.

10.3.3. Prohibited Medications

Subjects should not be receiving high dose corticosteroids (ie, > 15 mg/day of prednisone or its equivalent), cytotoxic agents (eg, azathioprine, cyclophosphamide, methotrexate), unapproved IPF-targeted therapy, or cytokine modulating agents while participating in this study, nor can they have received such within 8 weeks or 5 half-lives (whichever is longer) before Visit 1a.

Note: a dose of ≤ 15 mg/day prednisone, or equivalent, is acceptable if unchanged for ≥ 10 weeks before Visit 1a and is expected to remain unchanged during the subject's participation in the study.

Note: a systemic dose of corticosteroid may be administered as premedication (see Section 18.5).

[redacted]

10.4. Subject Compliance

Study treatment will be administered at the study center by study center personnel.

The time that each study treatment infusion began and ended, including the volume of study treatment administered and IV infusion rate will be recorded in source documents and eCRFs.

The infusion pump read-out should be used to record the volume of study treatment administered.

Any interruption or other change in the study treatment infusion must be documented. More specifically, the time the infusion was interrupted, the time the infusion was resumed, the total duration of the interruption, and the time that any rate change began or ended must be documented in actual time.

11. BIOLOGICAL ACTIVITY, SAFETY, PHARMACOKINETIC, AND PHARMACODYNAMIC ASSESSMENTS

To prevent missing data, if a subject does not return for a scheduled visit, every effort should be made, as per the site's standard practice, to contact the subject to determine if any steps can be taken to facilitate compliance to study visits.

[redacted]

11.1. Safety

11.1.1. Adverse Events

Adverse events will be evaluated for incidence, severity, and relationship to study treatment. [redacted]

Refer to Section 14 for AE definitions, classifications, and reporting requirements.

[redacted]

11.1.2. Safety Laboratory Tests

Safety laboratory tests will include the following:

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

Central laboratories will be used for clinical laboratory tests, although local testing may be used for emergencies and for hemoglobin for DL_{CO} correction. Details regarding specimen collection and processing will be provided in the Lab Manual. Safety laboratory tests will be analyzed throughout the study.

Blood samples and urine samples will be collected for clinical laboratory testing as shown in Table 1. If needed, additional blood samples may be taken for DL_{CO} correction. See Section 8.4.5 for guidance on how to manage subjects with elevations in transaminases.

11.1.3. Physical Examinations

Physical examinations will be conducted by the Investigator or qualified designee. A complete physical examination will include the following body systems: general appearance, eyes/ears/nose/throat/head/neck, chest and lungs (including inspection of the thorax for scars consistent with surgical lung biopsy at Screening), cardiovascular, abdomen, musculoskeletal, lymphatic, dermatologic, neurologic, psychiatric, and extremities. A complete physical examination, including recording of weight, will be conducted as shown in Table 1.

An abbreviated physical exam includes general appearance, nose/throat, jugular venous distension (sitting; absent or present), auscultation of the lungs (anterior/posterior, 4 quadrants; wheezes, crackles, rhonchi [absent or present], other sounds [describe]), auscultation of the heart, lower extremity venous distention (absent or present), pitting edema (0, 1+, 2+, 3+, or 4+). An abbreviated physical examination will be performed as shown in Table 1. Other abbreviated physical examinations may be performed at the discretion of the Investigator on the basis of signs or symptoms.

Height (not a safety assessment) will be recorded only at Visit 1a.

11.1.4. Vital Signs

Vital signs will include systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature and will be measured at every study visit as shown in Table 1. All measurements should be performed in the semisupine or sitting position after the subject has rested in that position for at least 5 minutes. When feasible, vital signs should be performed in the same position at each visit. Blood pressure may be obtained with an automated or manual blood pressure apparatus; however, the same method should be used for any given subject throughout the study. Blood pressure and heart rate should be measured in the arm opposite that used for infusion of study treatment, and the arm used should be documented.

Vital signs will be measured according to the following schedule:

- Once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication)
- midinfusion ± 5 minutes (if infusion is administered at a modified rate due to an infusion-related reaction, the timing should correspond to the middle of the modified infusion duration)
- Within 15 minutes after the end of the study treatment infusion

The frequency of monitoring vital signs may be increased as warranted by clinical management. If an AE occurs during the study treatment infusion, vital signs will be measured within 5 minutes of the start of the AE and repeated at a minimum frequency of every 15 minutes until its resolution.

11.1.5. 12-Lead Electrocardiograms

Standard single 12-lead electrocardiograms (ECGs) will be performed after subjects have been resting for 5 minutes. If possible, the same model of ECG machine using the same algorithms should be used for any given subject for all assessments throughout the study. Heart rate as well as RR, PR, QRS, QT, and QTcF (QT interval corrected using Fridericia's formula) intervals will be recorded in the eCRF. The Investigator should recalculate intervals and over read the machine interpretation, as necessary. A global interpretation of the ECG will be recorded as to whether the ECG is within normal limits or abnormal with any clinically significant findings noted.

Standard 12-lead ECGs will be performed as shown in Table 1. During Visit 4, ECGs will be performed once, within 30 minutes after the end of the study treatment infusion. Additional ECGs may be performed if clinically indicated.

Clinically significant changes not already noted or significantly worsened than documented in Medical History will be recorded as AEs.

[redacted]

11.1.11. Concomitant Medications

At each study visit after signing the informed consent through to the FU visit, subjects will be asked about medications taken.

11.2. Biological Activity

11.2.1. Pulse Oximetry

Pulse oximetry (SpO_2) will be performed with vital signs as shown in Table 1.

[redacted]

All documentation must include whether SpO_2 was measured with the subject breathing ambient air or supplemental oxygen; if on supplemental oxygen, the flow and means of administration must also be recorded. When feasible, SpO_2 measurements will be performed with the subject in the same position at each visit.

SpO_2 will be measured (with vital signs) according to the following schedule:

- Once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication)
- midinfusion ± 5 minutes (if infusion is administered at a modified rate due to an infusion-related reaction, the timing should correspond to the middle of the modified infusion duration)
- Within 15 minutes after the end of the study treatment infusion

The frequency of monitoring may be increased as warranted by clinical management. If an AE occurs during the study treatment infusion, SpO_2 will be measured within 5 minutes of the start of the AE and repeated at a minimum frequency of every 15 minutes until its resolution. [redacted]

11.2.2. Pulmonary Function Testing

11.2.2.1. General Guidelines

Pulmonary function testing will include both DL_{CO} and spirometry.

Pulmonary function testing (PFT) for this trial will be conducted in accordance with the PFT Manual that will be provided by the central PFT vendor for these services. The manual will include information on equipment and subject test instructions.

- [redacted]
- [redacted]

PFT may only be performed on subjects in this trial by site personnel who have been determined by the PFT vendor to meet certification criteria. Whenever possible, all PFTs on a single subject should be performed:

- on the same equipment
- by the same site personnel
- under the same conditions

The Global Lung Initiative (GLI) 2012 spirometry reference values (Quanjer et al, 2012) and the GLI 2017 DL_{CO} (TL_{CO}) reference values (Stanojevic et al, 2017) will be used for all PFTs.

11.2.2.2. Timing

[redacted]

Timing of PFT and Bronchodilators

All PFT on a single subject should be performed at the same time of day (± 2 hours). All PFT for this trial should be performed after withholding prescribed bronchodilators, either beta-agonists or anticholinergic agents, as follows:

- short acting agents, typically prescribed on an as needed basis, withheld 4 hours before the study visit
- twice daily agents, withheld 12 hours before the study visit
- once daily agents, withheld 24 hours before the study visit

Note that inhaled corticosteroids are not bronchodilators and may continue to be taken prior to PFT without a change in schedule.

All PFT will only be performed prebronchodilator; there will be no postbronchodilator testing.

The requirement to withhold prescribed bronchodilators prior to PFT is especially important before the first Screening PFT (Visit 1a). If a subject is taking prescribed bronchodilators, then the first Screening PFT may not be performed on the day that informed consent is obtained; it is not acceptable to alter the SOC to accommodate research specifications until after informed consent has been obtained. After informed consent has been obtained, subjects should be provided a reminder to withhold prescribed bronchodilators before each subsequent study visit when PFT will be performed. If a subject should present for PFT on any occasion other than the first Screening visit having forgotten to withhold prescribed bronchodilators for the specified time(s), PFT should be delayed as long as possible but still performed at that visit and within the window specified above; an appropriate notation must be captured in source records and the corresponding eCRF.

[redacted] In the event the repeat PFT is scheduled when the subject's status has continued to deteriorate and either the subject or the Investigator determines testing is not feasible:

- a notation that PFT was "not possible" should be entered into the corresponding eCRF and the most recent PFT results will be used for statistical analysis
- a notation that PFT was "not possible" should be recorded in source records

11.2.3. High-Resolution Computed Tomography Scanning

11.2.3.1. Timing

[redacted]

11.2.3.2. Guidelines

[redacted]

Detailed specifications will be provided in the HRCT Manual. At a minimum, all HRCT scans should:

- be performed only on scanners that have been "certified", including phantom imaging, as specified in the HRCT Manual
- all be performed on the same scanner for an individual subject, unless not feasible due to technical issues
- be performed by the same technician for an individual subject whenever possible
- be performed in the absence of radiopaque contrast
- have subjects in the same position(s) as specified in the HRCT Manual
- at full inhalation without (respiratory) motion
- employ scanner settings and reconstruction algorithm(s) as specified in the HRCT Manual

[redacted]

11.2.5. Diagnosis of Idiopathic Pulmonary Fibrosis

The diagnosis of IPF will be confirmed by the PI using ATS/ERS/JRS/ALAT consensus criteria (Raghu et al, 2011 or Raghu et al, 2018).

Clinical management of the patient at the site must be for IPF and the PI must be convinced that all locally available information support that UIP/IPF is the most likely diagnosis. It is mandatory that the PI consider overreader interpretation of Visit 1b HRCT and, if performed, SLB in order to determine that a subject is eligible for this trial.

The diagnosis of IPF may be made on the basis of HRCT and, when performed, SLB patterns in accordance with respective tables in the guidelines. Additional clinical data may also be used. In accordance with local implementation of the guidelines the diagnosis of IPF may also be established by review of the case at multidisciplinary discussion (MDD).

Documentation of the diagnosis must be included in the subject's source records.

[redacted]

[redacted]

11.3. Pharmacokinetics

Details regarding PK sample collection and processing will be provided in the Lab Manual. Samples will be batched and analyzed throughout the study.

[redacted]

[redacted]

[redacted]

11.4. Pharmacodynamics

[redacted]

12. STUDY PROCEDURES

All study visits, assessments, and procedures involving study subjects will be performed at a Sponsor-approved Investigator site, and assessments and procedures will be performed by study center personnel under the supervision of the Investigator. The Investigator may perform unscheduled assessments not specified in this protocol to ensure subject safety. All measurements performed and results obtained during the study will be recorded in the eCRF.

The informed consent form (ICF) should be signed before Visit 1a to allow the site to instruct the subject to withhold bronchodilator use as required for the PFT (Section 11.2.2) [redacted] A signed and dated ICF will be obtained from the subject as required by the protocol before any Screening procedures are conducted. A signed copy of the ICF will be given to the subject.

Subjects should be dosed on the study day listed in the Study Schedule (± 4 days for Visit 3 or ± 7 days for Visits 4 to 13), ensuring a minimum of 7 days between each dose. Assessments not associated with study treatment infusion may be performed on days other than the dosing day for scheduling purposes, as long as they are performed before the infusion.

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.1. Screening

Screening begins with the first Visit 1a procedure (excluding signing the ICF) and may be shorter than 42 days. [redacted] ALL Visit 1a procedures MUST be completed before any Visit 1b procedures may be started. [redacted]

12.1.1. Visit 1a

The following procedures will be performed:

- Record demographics and baseline characteristics.
- Record medical history (events that occurred prior to 24 hours before Visit 1a) and record AEs (events that occur beginning 24 hours before Visit 1a).
- Record IPF history and previous IPF treatments.
- [redacted]
- Record prior medication use (medications taken within 14 days before Visit 1a until 24 hours before Visit 1a; see Section 10.3.1) and concomitant medications (medications taken beginning 24 hours before Visit 1a; see Section 10.3.2).

- Conduct complete physical examination, including height and weight.
- Perform 12-lead ECG.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 before collection of blood samples.
- [redacted]
- Collect urine sample for:
  - urine pregnancy test (female subjects of childbearing potential only)
  - urinalysis
- Collect blood samples for the following tests:
  - chemistry
  - hematology
  - [redacted]
  - serology (hepatitis B surface antigen [HBsAg], hepatitis C antibody [HCV Ab], and HIV 1/2 antibodies)
- SARS-CoV-2 virus or viral antigen test (See Section 8.3.3)
- Verify and document all inclusion and exclusion criteria, and determine subject eligibility.

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.1.2. Visit 1b

The following procedures will be performed:

- Confirm all inclusion and exclusion criteria, and confirm subject's eligibility for study participation.
- Record AEs and the status of unresolved AEs.
- Record concomitant medications.
- Conduct an abbreviated physical examination.
- Perform 12-lead ECG.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 before collection of blood samples.
- [redacted]
- Collect blood for hemoglobin analysis.
- [redacted]

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2. Treatment Period (Days 1 [Baseline] to 168)

12.2.1. Visit 2 (Days 1 to 2)

[redacted]

12.2.1.1. Day 1

The following procedures will be performed on Day 1 **before** the start of the study treatment infusion:

- Confirm all inclusion and exclusion criteria and confirm subject's eligibility for study participation.
- Record AEs and the status of unresolved AEs.
- Record concomitant medications.
- Conduct an abbreviated physical examination.
- Collect urine sample for urine pregnancy test (female subjects of childbearing potential only).
- Complete randomization procedure using IWRS schedule. Store randomization assigned in the Pharmacy Manual to prevent unblinding.
- [redacted]
- Collect blood for the following tests:
  - chemistry
  - hematology

[redacted]

[redacted]

- Administer premedications, if applicable (see Section 18.5).
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication).
- Administer assigned study treatment.

The following procedures will be performed on Day 1 **during** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 midinfusion ± 5 minutes (if infusion is administered at a modified rate [redacted] the timing should correspond to the middle of the modified infusion duration).
- [redacted]

The following procedures will be performed on Day 1 **after** the end of the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 within 15 minutes after the end of the study treatment infusion.
- [redacted]

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2.1.2. Day 2

- Study personnel will call subjects not returning to the site to collect any AEs and concomitant medications that may have occurred after leaving the site on Day 1.

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2.2. Visit 3 (Day 15) All Subjects

Visit 3 will be conducted 14 ± 4 days after the previous dose of study treatment. The following study procedures will be performed at Visit 3 **before** the study treatment infusion:

- Record AEs and the status of unresolved AEs.
- Record concomitant medications.

- Collect blood for the following tests:
  - [redacted]
  - [redacted]
  - [redacted]
- Administer premedications, if applicable (see Section 18.5).
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication).
- Administer assigned study treatment.

The following study procedures will be performed at Visit 3 **during** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 midinfusion ± 5 minutes (if infusion is administered at a modified rate [redacted] the timing should correspond to the middle of the modified infusion duration).

The following study procedures will be performed at Visit 3 **after** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 within 15 minutes after the end of the study treatment infusion.

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2.3. Visit 4 (Day 29) All Subjects

Visit 4 will be conducted 14 ± 7 days after the previous dose of study treatment. The following study procedures will be performed at Visit 4 **before** the study treatment infusion:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.
- [redacted]
- Collect urine sample for urine pregnancy test (female subjects of childbearing potential only).
- Collect blood for the following tests:
  - chemistry
  - hematology

[redacted]

- Administer premedications, if applicable (see Section 18.5).
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication).
- Administer assigned study treatment.

The following study procedures will be performed at Visit 4 **during** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 midinfusion ± 5 minutes (if infusion is administered at a modified rate [redacted] the timing should correspond to the middle of the modified infusion duration).

The following study procedures will be performed at Visit 4 **after** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 within 15 minutes after the end of the study treatment infusion.
- Perform 12-lead ECG once, within 30 minutes after the end of the study treatment infusion.

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2.4. Visits 5, 7, 9, 11, and 13 (Days 43, 71, 99, 127, 155) All Subjects

Each of Visits 5, 7, 9, 11, and 13 will be conducted 14 ± 7 days after the previous dose of study treatment. The following study procedures will be performed at these visits **before** the study treatment infusion:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.
- [redacted]
- Administer premedications, if applicable (see Section 18.5).
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication).
- Administer assigned study treatment.

The following study procedures will be performed at these visits **during** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 midinfusion ± 5 minutes (if infusion is administered at a modified rate [redacted] the timing should correspond to the middle of the modified infusion duration).

The following study procedures will be performed at these visits **after** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 within 15 minutes after the end of the study treatment infusion.

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.2.5. Visits 6, 8, 10, and 12 (Days 57, 85, 113, and 141) All Subjects

Each of Visits 6, 8, 10, and 12 will be conducted 14 ± 7 days after the previous dose of study treatment. The following study procedures will be performed at these visits **before** the study treatment infusion:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.
- Collect urine sample for urine pregnancy test (female subjects of childbearing potential only)
- [redacted]
- Collect blood for the following tests:
  - chemistry
  - hematology
  - [redacted]
  - [redacted]
- [redacted]
  - [redacted]
  - [redacted]
    - [redacted]

[redacted]

- Administer premedications, if applicable (see Section 18.5).
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication).
- Administer assigned study treatment.

The following study procedures will be performed at these visits **during** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 midinfusion ± 5 minutes (if infusion is administered at a modified rate [redacted], the timing should correspond to the middle of the modified infusion duration).

The following study procedures will be performed at these visits **after** the study treatment infusion:

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 within 15 minutes after the end of the study treatment infusion.

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.3. End-of-Treatment (Visit 14 [Day 169]/Early Termination)

Visit 14/ET will be conducted 14 ± 7 days after the final dose of study treatment. The following study procedures will be performed at this visit:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.
- Perform a complete physical examination, including weight.
- Perform a 12-lead ECG.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 before collection of blood samples.

[redacted]

- Collect urine sample for:
  - urinalysis
  - urine pregnancy test (female subjects of childbearing potential only)
- Collect blood for the following tests:
  - chemistry
  - hematology

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.4. Follow Up

12.4.1. Follow-Up Visit 1 (Visit 15/Day 197)

The FU visit will be conducted 4 weeks (± 7 days) after Visit 14/ET (ie, 6 weeks [± 7 days] after the final dose of study treatment). The following study procedures will be performed at this visit:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.
- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 before collection of blood samples.
- Collect urine sample for urine pregnancy test (female subjects of childbearing potential only)

[redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

12.4.2. Follow-Up Visit 2 (Visit 16/Day 239)

The second FU visit will be conducted 10 weeks (± 7 days) after Visit 14/ET (ie, 12 weeks [± 7 days] after the final dose of study treatment). The following study procedures will be performed at this visit:

- Record AEs and the status of previously unresolved AEs.
- Record concomitant medications.

- Measure vital signs (systolic and diastolic blood pressure, heart rate, respiration rate, and oral temperature) and SpO_2 before collection of blood samples.
- [redacted]
- [redacted]
- Collect urine sample for:
  - urinalysis
  - urine pregnancy test (female subjects of childbearing potential only)
- Blood will be collected for the following tests:
  - chemistry
  - hematology
  - [redacted]
  - [redacted]

Refer to Section 18.6 for guidance on clinical trial conduct relating to COVID-19.

13. STATISTICS

In addition to this section of the study protocol, a Statistical Analysis Plan (SAP) will be developed and finalized prior to the final database lock and unblinded data analysis. The SAP will provide a detailed description for the handling of missing data, subject eligibility criteria for the analysis, and statistical methodology for the data summary and between-group comparisons.

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the safety and efficacy data is outlined below. Specific details will be provided in the SAP.

Additional sensitivity analyses may be performed due to the COVID-19 pandemic. All analyses related to COVID-19 will be conducted in accordance with regulatory guidelines. These analyses will be described in the SAP.

13.1. Study Endpoints

13.1.1. Primary Endpoint

13.1.1.1. Safety

- Incidence of TEAEs and treatment-emergent SAEs
- Proportion of subjects discontinuing study treatment due to TEAEs

13.1.2. Secondary Endpoint

13.1.2.1. Biological Activity

- Rate of decline in FVC over 24 weeks (measured in mL and % of predicted over unit time)
- Absolute and relative change in FVC (mL and % of predicted) at Visit 14 (Day 169) as compared with baseline
- Proportion of subjects with an FVC response (mL and % of predicted) defined as either having improvement or a decline by 0% to ≤ 5%, > 5% to ≤ 10%, and by > 10% at Visit 14 (Day 169)
- Change in DL_{CO} and DL_{CO} corrected for hemoglobin
- Changes of ILA as measured by HRCT (ie, change in parenchymal feature [Baseline to Visit 14 (Day 169)]), as determined by qualitative assessment (central radiologist) and quantitative analysis (Quantitative Lung Fibrosis – QLF analysis)
- Time to first acute IPF exacerbation (ie, an unexplained worsening of dyspnea, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure [Raghu et al, 2011])

- Rate of hospitalization for respiratory ailments, rate of mortality due to all causes, and rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death

13.2. Statistical Plan

13.2.1. Populations of Interest

Safety Population: The safety population will include all subjects who receive at least 1 dose of study treatment.

ITT Population: The intent-to-treat (ITT) population will include any randomized subjects.

PK Population 1: This PK population will include subjects in the PK subset who receive at least 1 dose of study treatment and have a majority of scheduled PK samples drawn for serial PK measurements that allow for PK parameters to be generated. Subjects who do not complete the study treatment infusion (Visit 2) will be excluded from PK analysis.

PK Population 2: This PK population will include subjects who receive the majority of the study treatment doses and also have a majority of the planned trough samples collected that allow for a comparison of trough levels across dosing weeks.

Per Protocol: This population will exclude nonevaluable subjects and subjects with major protocol deviations thought to impact the ability to assess the effect of study treatment. Exclusion of subjects from the Per Protocol (PP) set will be reviewed, documented, and approved before the study is unblinded to the study Sponsor. The criteria for excluding subjects from the PP population will be specified in the SAP.

13.2.2. Demographic and Baseline Characteristics

The safety population will be used for summary of demographic and baseline characteristics.

Demographic and baseline laboratory results will be summarized overall and by treatment arm using descriptive statistics. Additionally, the proportion of subjects on SOC upon randomization for each treatment arm will be summarized.

13.2.3. Safety

All safety analyses will be performed on the safety population.

The analysis of safety, reported for each treatment arm, will be based on the frequency of AEs and their severity for all treated subjects. The safety variables, including AEs, SAEs, and AEs of interest (coded using the Medical Dictionary for Regulatory Activities [MedDRA]), clinical laboratory tests [redacted] physical examination, ECGs, and vital signs will be summarized or tabulated by treatment arm. Some of the variables will be tabulated by treatment arm and by visit. Incidence of AEs will be further tabulated by subjects on SOC within each treatment arm.

The proportion of subjects discontinuing study treatment due to AEs will be tabulated by treatment arm.

13.2.4. Biological Activity

All biological activity analyses will be performed on the ITT population.

[redacted]

[redacted]

13.2.5. Pharmacokinetics

[redacted]

[redacted]

[redacted] [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted] [redacted]

[redacted]

13.3. Determination of Sample Size

Approximately 120 subjects will be enrolled into the study, with approximately 40 subjects in each of 3 arms. The study will include approximately 35-40 sites and will enroll approximately 3 to 5 subjects per site.

[redacted]

13.4. Deviation from Original Analysis Plan

All deviations from the original SAP will be provided in the final clinical study report.

14. ADVERSE EVENTS

14.1. Adverse Event Definitions

14.1.1. Adverse Event

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

14.1.2. Suspected Adverse Reaction

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

14.1.3. Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

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

14.1.4. Serious Adverse Event or Serious Suspected Adverse Reaction

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

- Death
- A life-threatening AE – see definition above
- Admission to the hospital or prolongation of existing hospitalization[1]
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

[1] Admission to the hospital for a scheduled PK blood sample collection will not be considered an SAE. If the planned hospitalization should be prolonged due to an AE, an SAE would need to be documented.

bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

14.1.5. Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

An AE or suspected adverse reaction is considered ‘‘unexpected:’’

- If it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

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

‘‘Unexpected,’’ as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

14.2. Adverse Event Classification

14.2.1. Treatment-Emergent Adverse Events

An AE is defined as treatment-emergent if it occurs at or after the first dose of study treatment and through 2 weeks after the last dose of study treatment. This also includes AEs which are observed before the first dose of study treatment and increase in severity after the first dose through 2 weeks after the last dose of study treatment.

Note: 2 weeks after the last dose of study treatment was selected because it is expected to be longer than 5 times the terminal half-life of ND-L02-s0201.

[redacted]

[redacted]

14.2.4. Respiratory Adverse Events

It is recognized that exacerbations of IPF occur and that they may be preceded by indolent symptoms. These indolent symptoms should be recorded per the site’s customary practices for reporting AE. When a subject’s status progresses to include sufficient respiratory deterioration, imaging findings, histopathology, and/or clinical interventions consistent with exacerbation of IPF, AE reporting should convert to this term as long as it is the same event. If the Investigator

determines that there is a relationship between the AE (eg, upper respiratory tract infection) and the exacerbation, the former term should be modified to indicate the relationship (eg, upper respiratory tract infection preceding IPF exacerbation or upper respiratory tract infection-related to IPF exacerbation). If the time-relationship is unclear, separate AEs are appropriate and IPF exacerbation should be captured as a new event.

14.2.5. Acute Exacerbation of IPF

Idiopathic pulmonary fibrosis exacerbation is defined as an unexplained worsening of dyspnea, evidence of hypoxemia as defined by worsened or severely impaired gas exchange, new radiographic alveolar infiltrates, and an absence of an alternative explanation such as infection, pulmonary embolism, pneumothorax, or heart failure (Raghu et al, 2011).

14.2.7. Relationship to Study Treatment, Premedication, and Standard of Care

Relationship to study treatment, premedication, and standard of care will be assessed. Hereafter referred to as drug in this section.

The Investigator's assessment of causality must be provided for all AEs (serious and nonserious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the drug caused or contributed to an AE. The possibility of a causal relationship means that there are facts, ie, evidence, or arguments to suggest a causal relationship. Adverse events with a relationship of "none" are considered not related to drug. All other AE relationship (unlikely, possible, probable, and definite) are considered related to drug.

Clinical judgement should be used to determine the relationship of drug to the AE. The Investigator should consider, for example, all relevant and/or alternative causes, including pattern of the reaction, temporal relationship, de-challenge, re-challenge, underlying disease(s), concomitant therapy(ies), concomitant illness(es), risk factor(s), and medical history.

None: No relationship between the experience and the administration of drug; related to other etiologies such as concomitant medications or subject's clinical state.

Unlikely: The current state of knowledge indicates that a relationship is unlikely. However, as a causal relationship to the drug cannot be ruled out, the causal relationship will be classified as related to drug.

Possible: A reaction that follows a plausible temporal sequence from administration of the drug and follows a known response pattern to the suspected drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

Probable: A reaction that follows a plausible temporal sequence from administration of the drug and follows a known response pattern to the suspected drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Definite: A reaction that follows a plausible temporal sequence from administration of the drug and follows a known response pattern to the suspected drug and can be confirmed with a positive re-challenge test or supporting laboratory data.

Note: AEs that occur after administration of premedication (if applicable) but before the administration of study treatment should not be reported as related to study treatment.

Refer to the country-specific package insert of Summary or Product Characteristics for the risks and side effects associated with pirfenidone, nintedanib, and premedication (if applicable).

14.2.8. Severity

Grading of AEs will be done using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50).

If an AE is not listed in the CTCAE v5.0, then the Investigator will use the terms: mild, moderate, severe, life-threatening, or death to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

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[a]
Grade 3	Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
Grade 4	Life threatening consequences	Urgent intervention indicated
Grade 5	Death	Death related to an adverse event

[a] Instrumental activities of daily life refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc

[b] Self-care activities of daily life refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.3. Exposure in Utero

The subject will be instructed to notify the Investigator if the subject or subject's partner becomes pregnant during the study, The Investigator must notify the Sponsor within 24 hours, and must complete the Pregnancy Notification Form and submit it to the Sponsor within 2 working days of being notified. The Investigator should obtain informed consent/assent from the subject or subject's partner allowing the Investigator to obtain information regarding the pregnancy and its outcome. If the subject or subject's partner provides informed consent/assent, the Investigator should follow the pregnancy until outcome. A final Pregnancy Notification Form should be completed when the outcome of the pregnancy is known.

14.4. Monitoring of Adverse Event Data

To ensure safety of the overall study an independent DMC will be established. The DMC will periodically review the safety and tolerability of study treatment for the duration of the study. Refer to Section 7.4 for details.

14.5. Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. Adverse event collection will begin 24 hours before Visit 1a. Adverse events that occur up to and including 12 weeks after administration of the last dose of study treatment, including ET, must be reported.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the Adverse Event Form for that visit. Any clinically relevant deterioration in laboratory assessments, intercurrent illness, or other clinical findings is considered an AE and must be recorded on the Adverse Event Form. In addition, an abnormal test finding will be classified as an AE if one or more of the following criteria are met:

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

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE. Laboratory data will be collected as stipulated in this protocol. Clinical syndromes associated with laboratory abnormalities will be recorded as appropriate (eg, diabetes mellitus rather than hyperglycemia).

For SAEs, a Serious Adverse Event Form must also be completed with as much information as possible and submitted in the time frame described below in Section 14.6. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the subject was hospitalized, a copy of the discharge summary and any other relevant hospital records (eg, admission report, laboratory test results, etc.) must be included as part of the subject medical file.

The clinical course of each AE will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

14.6. Notification about Serious Adverse Events and Serious and Unexpected Suspected Adverse Reactions

14.6.1. Investigator Reporting to Sponsor

All SAEs that occur during the course of the study must be reported by the Investigator to the Sponsor, designated representative, and Medical Monitor within 24 hours by fax or email. In addition, all SAEs that occur up to and including 12 weeks after administration of the last dose of study treatment must be reported to the Sponsor within 24 hours from when the Investigator becomes aware of the SAE.

Investigators must report to the Sponsor all SAEs, whether or not considered drug-related, including those listed in the Investigator Brochure. The report must include an assessment of causality.

For all SAEs, the Investigator is obligated to obtain and provide information to the Sponsor in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

14.6.2. Reporting to Regulatory Agencies and Institutional Review Boards/Independent Ethics Committees

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence of serious suspected adverse reactions over that listed in the Reference Safety Information.

It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of all serious and unexpected suspected adverse reactions involving risk to human subjects.

14.7. Emergency Identification of Study Medication

In the event of a medical emergency, when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may obtain the treatment assignment of the subject experiencing the emergency. The Investigator can unblind individual subjects via the study IWRS. The Investigator will create a secure account and receive a username and password prior to enrolling subjects. After unblinding, the Investigator should contact the Medical Monitor.

If unblinding is necessary, the Investigator must document the reasons for unblinding in the subject's source documents but should not divulge the subject's treatment assignment to any individuals except the Medical Monitor and those individuals involved in the direct care of the subject. The date and the reasons for breaking the blind must be submitted to the Sponsor within 24 hours.

If a subject's treatment assignment is unblinded, the subject should remain in the study and continue the protocol-specified follow-up evaluations.

14.8. Emergency Sponsor Contact

In a medical emergency, a qualified healthcare provider will attend to the subject's immediate clinical management, including administration of medical intervention according to the SOC.

15. ETHICS

15.1. Institutional Review Board or Independent Ethics Committee

The IRB/IEC will meet all FDA and applicable regulatory authority requirements governing IRBs/IECs in accordance with ICH GCPs.

The Investigator will provide the Sponsor (or designee) with documentation of IRB/IEC approval of the following documents before the study begins at the study site(s): protocol, ICF, and any other relevant materials intended for or directed to subjects (eg, subject diaries, advertisements). The Investigator will supply documentation to the Sponsor (or designee) of IRB/IEC requirements regarding continuing review and approval of revisions to any of these documents.

15.2. Ethical Conduct of the Study

This study will be conducted in accordance with the current IRB/IEC approved clinical protocol, ICH GCP Guidelines, and relevant policies and requirements of the national regulations and laws, including the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

15.3. Subject Information and Informed Consent

Written informed consent/assent is required from each subject before any testing under this protocol, including Screening tests and evaluations. The ICF, as specified by the clinical site's IRB/IEC, must follow the Protection of Human Subjects regulations listed in 21 Code of Federal Regulations (CFR) Part 50 and ICH E6 4.8.

The ICF will be used to explain the risks and benefits of study participation in simple terms before the subject will be entered into the study. The ICF will contain a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written informed consent must be given by the subject after the receipt of detailed information on the study. It is the responsibility of the Investigator to obtain consent/assent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject's medical record before any testing under this protocol, including Screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB/IEC and by the Sponsor or its designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor (or designee).

16. STUDY ADMINISTRATION

16.1. Administrative Structure

A list of individuals who will have key positions in this study will be saved in the Trial Master File (TMF). This list will include names, titles, and roles of selected individuals from the Sponsor (or designee) and the Contract Research Organization (CRO) that will contribute to this study.

16.2. Quality Control and Quality Assurance

16.2.1. Overview

According to the GCP Guidelines, the Sponsor is responsible for implementing and maintaining quality assurance (QA) and QC systems with written SOPs.

QC will be applied to each stage of data handling. The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s);
- Site initiation visit;
- Routine site monitoring;
- Ongoing site communication and training;
- Data management quality control checks;
- Continuous data acquisition and cleaning;
- Internal review of data; and
- QC checks of the final clinical study report (CSR).

In addition, the Sponsor's (or designee) Clinical QA Department may conduct periodic audits of the study processes, including, but not limited to study site, site visits, vendors, clinical database, and final CSR. When audits are conducted, access must be authorized to Sponsor's representatives and regulatory authorities for all study-related documents, including medical history and concomitant medication documentation.

16.2.2. Risk Management

Program risks will be evaluated on an ongoing basis by the Sponsor in accordance with ICH E6 (R2) Section 5, and any important deviations from prespecified quality limits will be documented in the clinical study report.

16.2.3. Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions for this clinical study. Monitors will work in accordance with the CRO's SOPs and have the same rights and responsibilities as monitors from the Sponsor organization. Monitors will establish and maintain regular contact between the Investigator or designee and the Sponsor.

Monitors will evaluate the competence of each study site, informing the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study, monitors will check that written informed consent/assent has been obtained from all subjects correctly and that data are recorded correctly and completely on the eCRFs. Monitors are also required to compare entries in eCRFs with corresponding source data and to inform the Investigator or designee of any errors or omissions. Monitors will also review adherence to the protocol and to regulatory requirements at the study site and discuss and deviations noted with the Investigator or designee. They will arrange for the study site to receive adequate supply of IP, review IP accountability records to IP supplies/subject use, and ensure appropriate storage conditions are maintained.

In the event that onsite monitoring visits are not allowed due to health safety concerns, monitors will remotely monitor data entry into the database by site staff and may perform source data verification (if allowed by the site) to identify SAEs that may not have been reported by sites. As soon as feasible, onsite monitoring will resume, and data monitored remotely will be source data verified.

Monitoring visits will be conducted according to the United States CFR Title 21 parts 50, 56, and 312 and ICH Guideline for GCP. The monitor will make written reports to the Sponsor following each contact with the Investigator or designee, regardless of whether it is by phone or in person.

16.2.4. Data Management/Coding

Study data will be handled according to the relevant SOPs of the data management and biostatistics departments of the Sponsor (or designee) or CRO.

AEs will be coded using MedDRA and medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced (WHODDE) drug dictionary.

16.2.5. Quality Assurance Audit

Study sites, the study database and study documentation may be subject to a QA audit by the Sponsor or designee on behalf of the Sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.

16.3. Data Handling and Recordkeeping

16.3.1. Electronic Data

When using electronic trial data handling and/or remote electronic trial data systems, the Sponsor (or designee) will:

- Ensure and document that the electronic data processing system(s) conforms to the Sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (ie, validation)
- Maintain SOPs for using these systems
- Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (ie, maintain an audit trail, data trail, edit trail)

- Maintain a security system that prevents unauthorized access to the data
- Maintain a list of the individuals who are authorized to make data changes
- Maintain adequate backup of the data
- Safeguard the blinding, if any (eg, maintain the blinding during data entry and processing)

Documentation regarding electronic systems used in this protocol is available upon request from the CRO maintaining the electronic trial data system.

16.3.2. Case Report Form Completion

Electronic data capture will be used for the study. All data will be recorded on source documentation at each study location and entered electronically by the study center personnel. Data collected on each subject will be documented on the appropriate eCRF. Completed eCRFs will be signed off by the Investigator or his/her designee.

16.3.3. Data Handling

If data are transformed during processing, records will be maintained so that it will be possible to compare the original data and observations with the processed data.

An unambiguous subject identification code will be used that allows identification of all the data reported for each subject.

16.3.4. Retention of Study Records

The Investigator must maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence, and all other supporting documentation) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the IP. These documents will be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator or designee must contact the Sponsor before disposing of any study records.

16.4. Financing and Insurance

Financing and insurance are addressed in a separate document.

16.5. Confidentiality

To maintain subject privacy, all eCRFs, study treatment accountability records, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs

and to audit the data collection process. The subject's confidentiality will be maintained in accordance with applicable laws and regulations.

Subjects will be informed that registration information, results, and other information about this study will be submitted to publicly available clinical trial registry databases in the United States, European Union, and Japan; however, protected health information of individual subjects will not be used.

All information regarding the IP supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of the IP and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

16.6. Publication Policy

The data generated by this study are considered confidential information and the property of Sponsor and shall not be published or disclosed without the prior written consent of Sponsor.

16.7. Direct Access to Source Data

The Investigators/institutions clinical sites will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections as requested by FDA or other regulatory authorities, the Sponsor, or the Sponsor designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc) in addition to eCRFs.

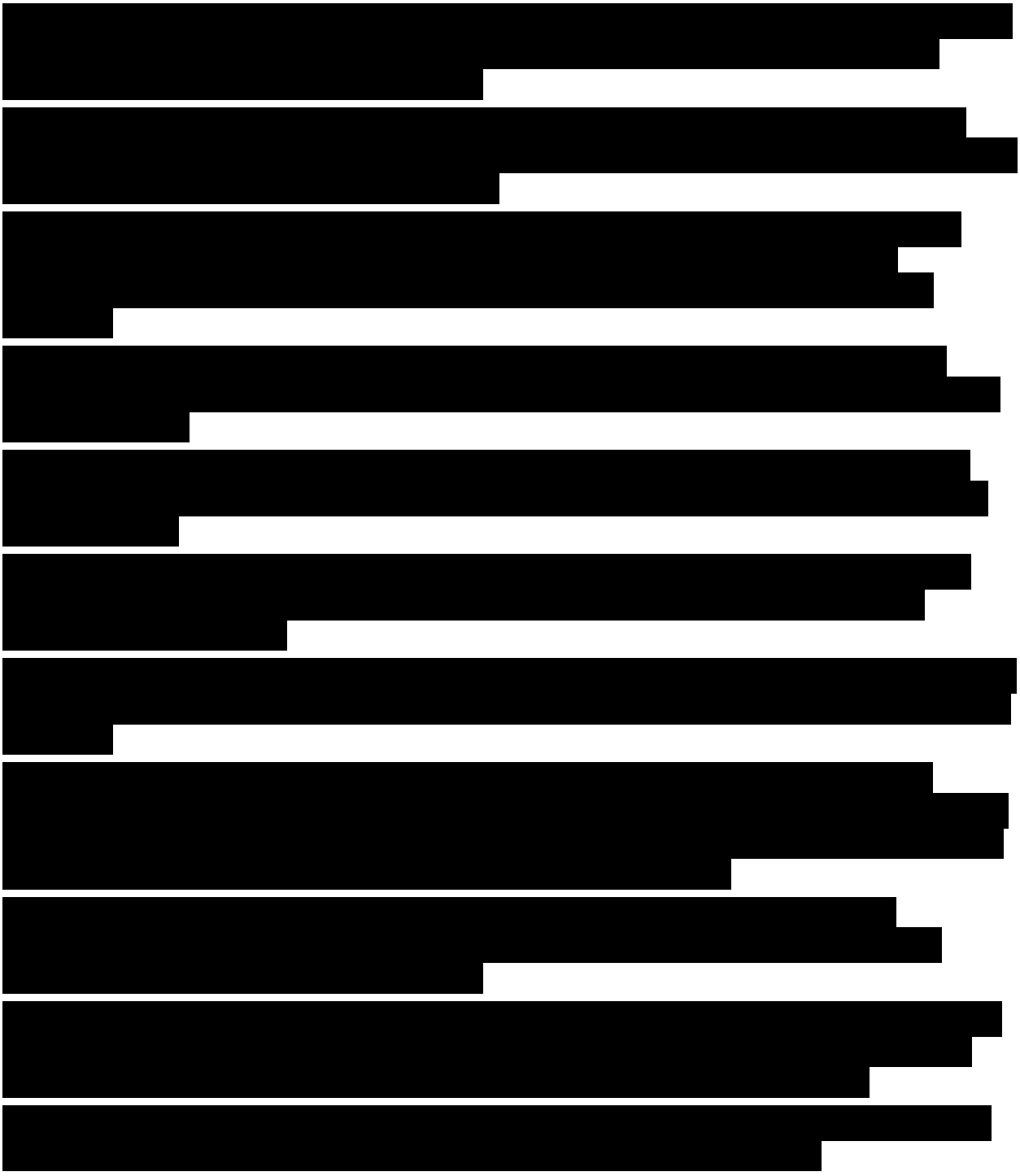
The Investigator or designee will prepare and maintain adequate and accurate source documents to support all observations and other pertinent data recorded on the eCRFs for each subject enrolled in the study.

The Investigator will allow the Sponsor (or designee) and authorized regulatory authorities to have direct access to all documents pertaining to the study.

16.8. Protocol Amendments

Changes to the conduct of the study should be prepared as a protocol amendment and implemented only upon joint approval of the Sponsor, or a representative of the Sponsor, and the Investigator. Protocol amendments should also receive written IRB/IEC approval before implementation, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, the Sponsor will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB/IEC, as appropriate.

[redacted]



18. APPENDICES

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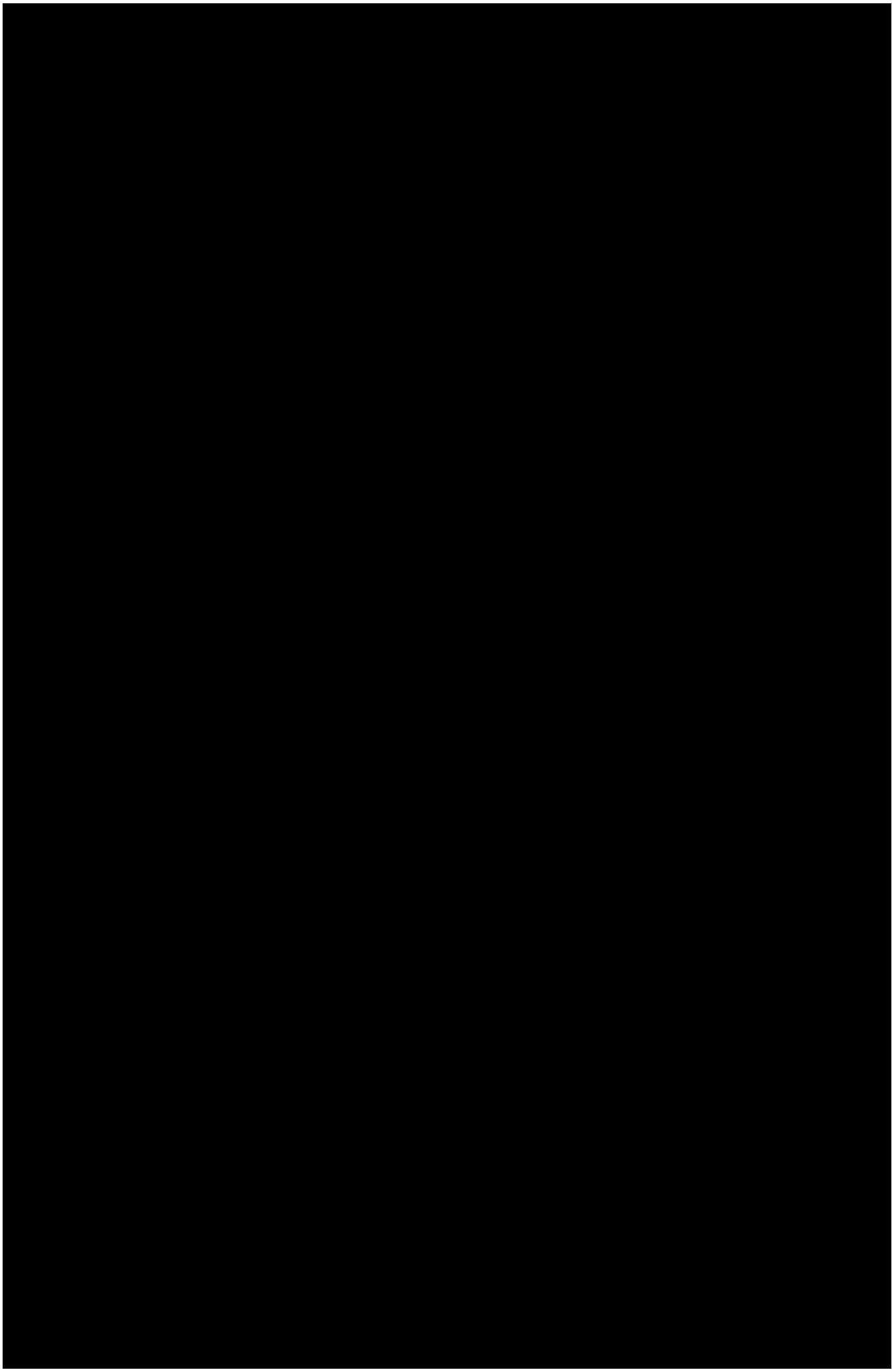

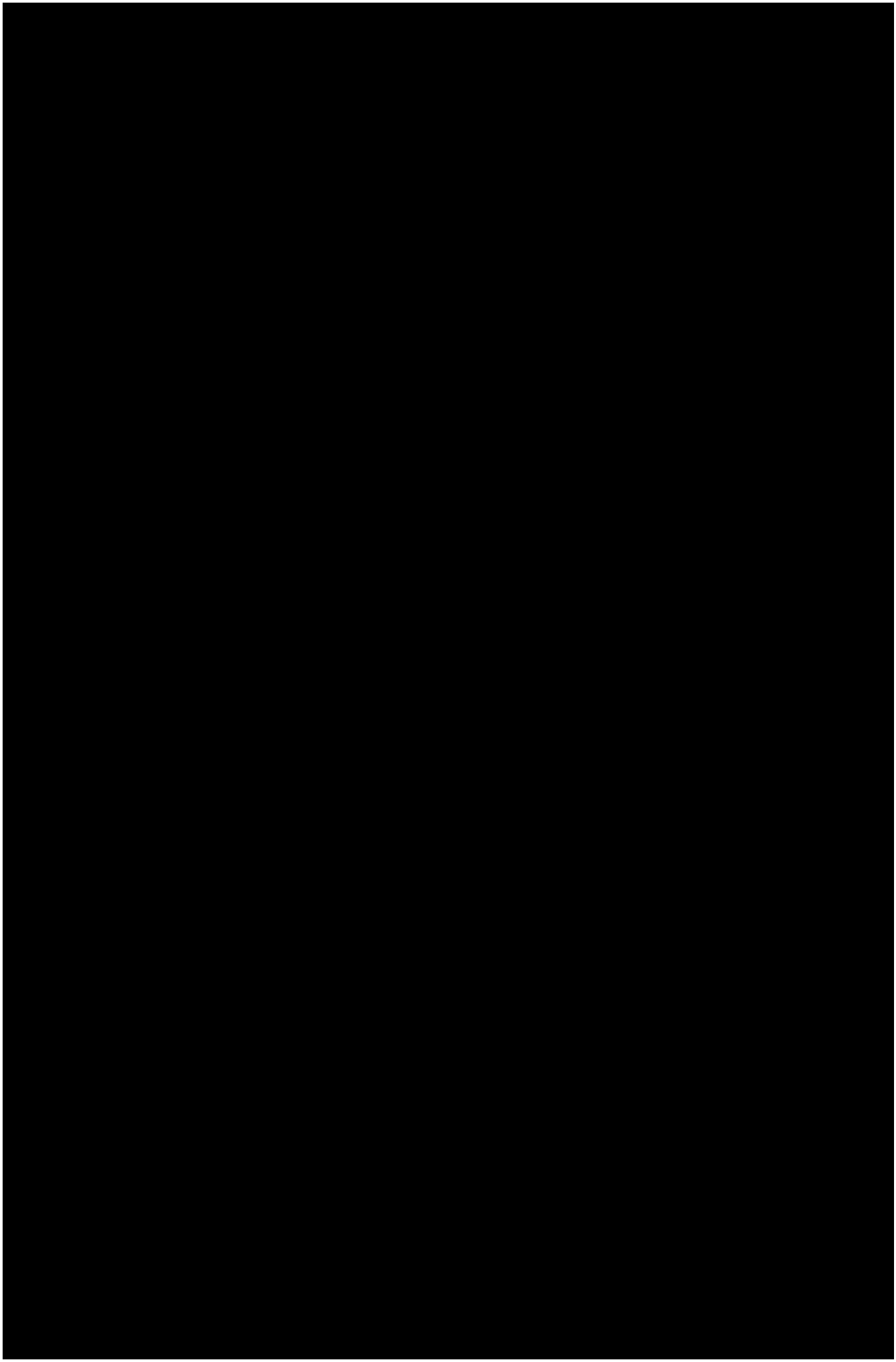

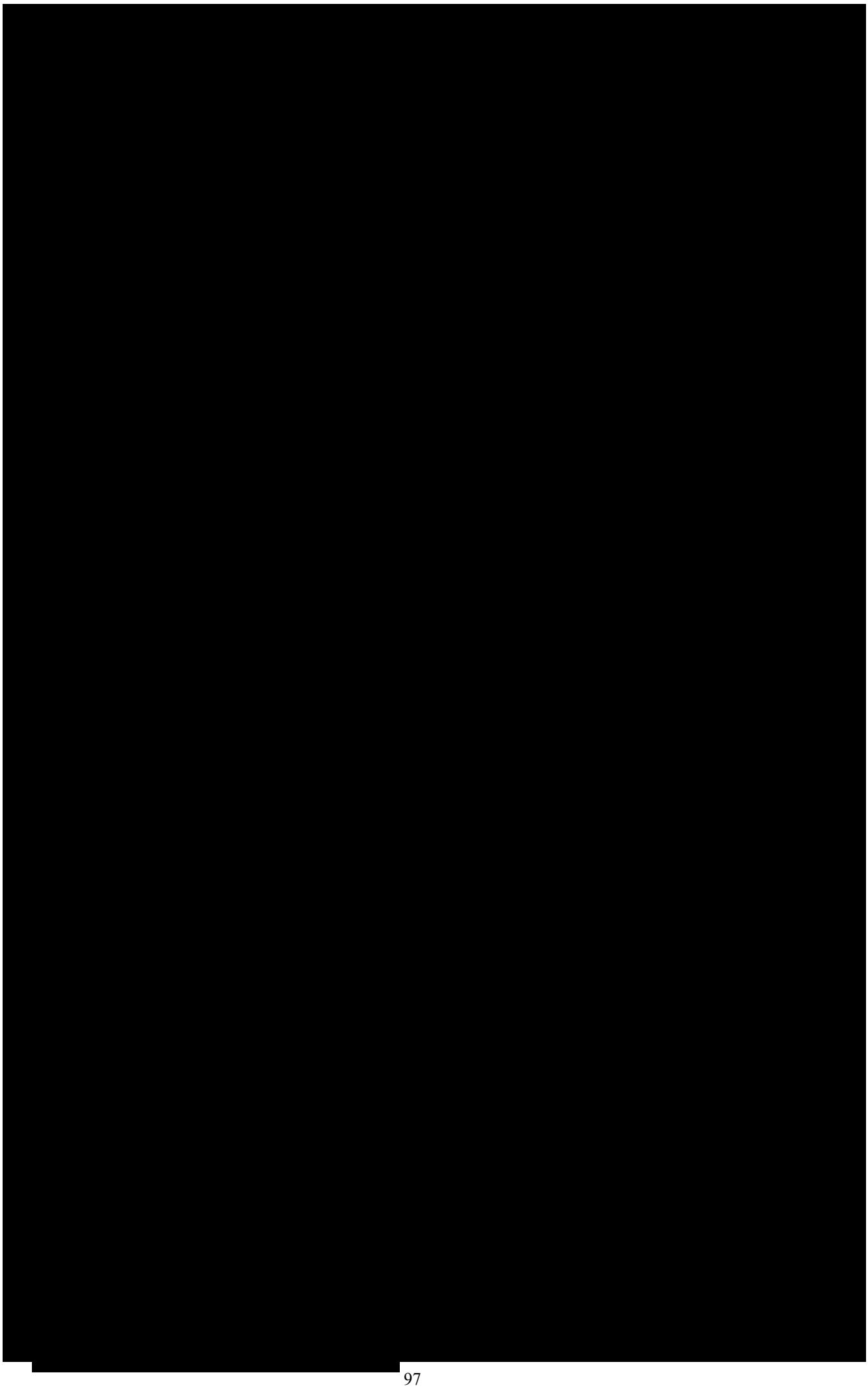

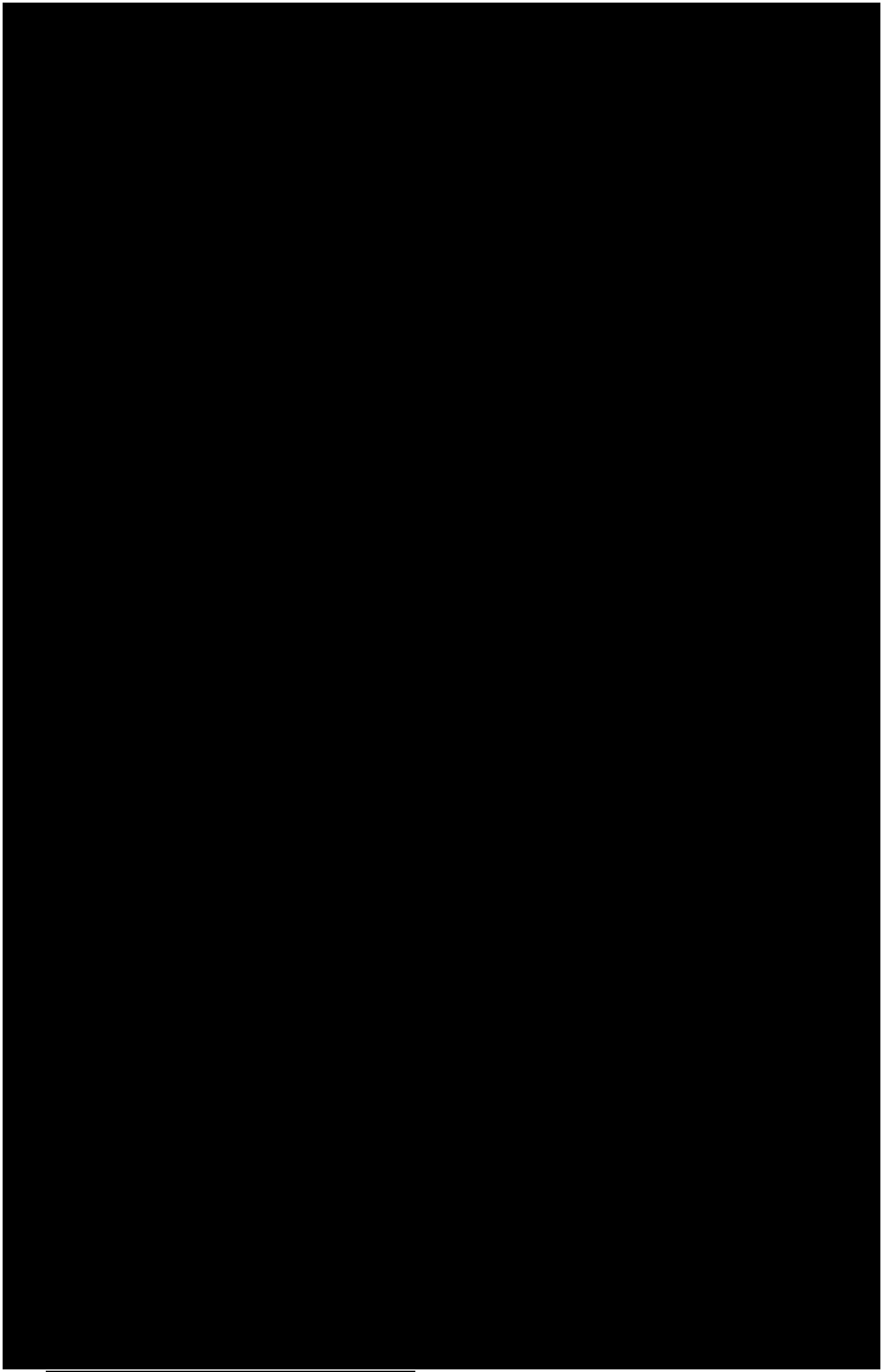

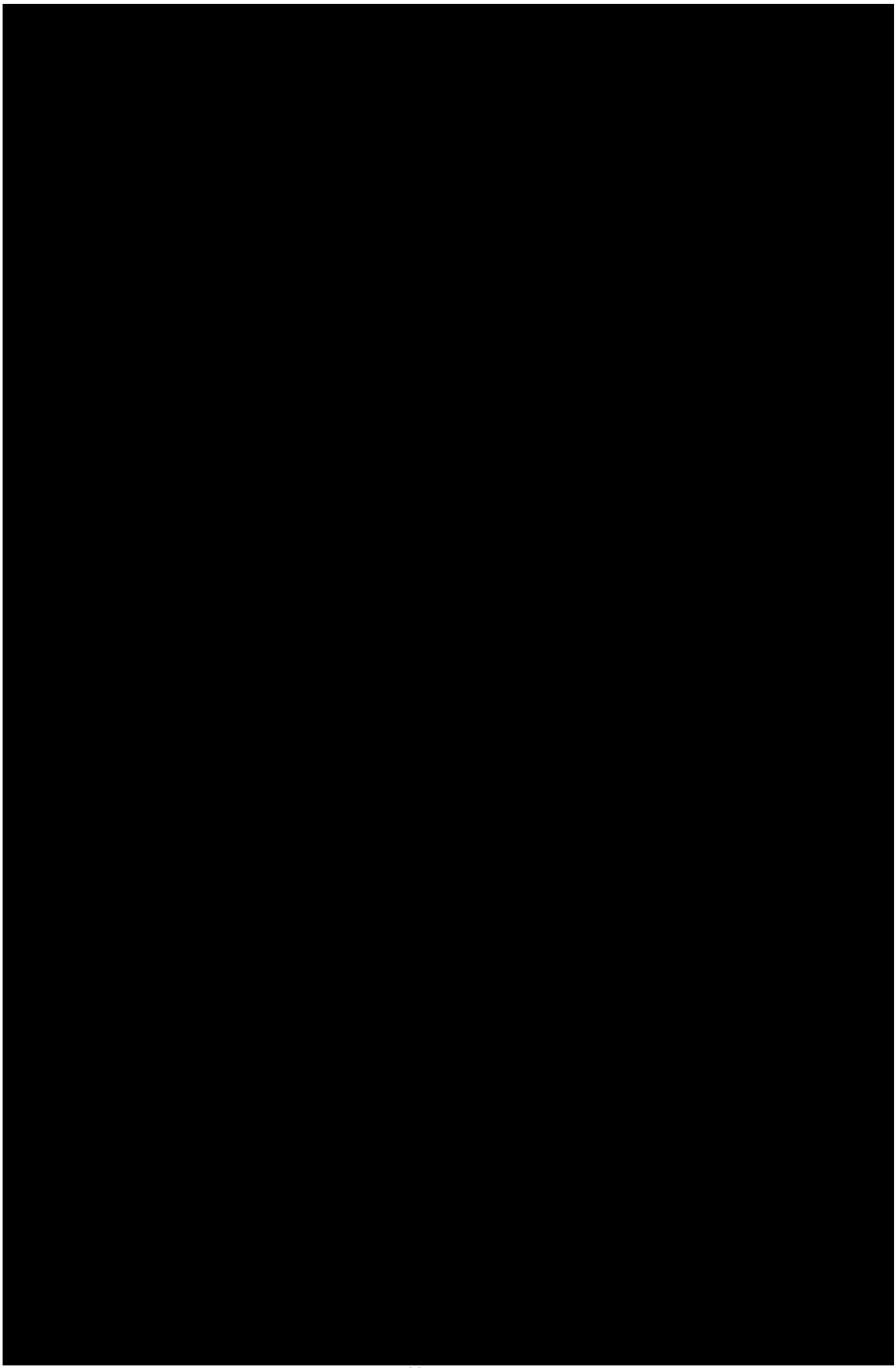

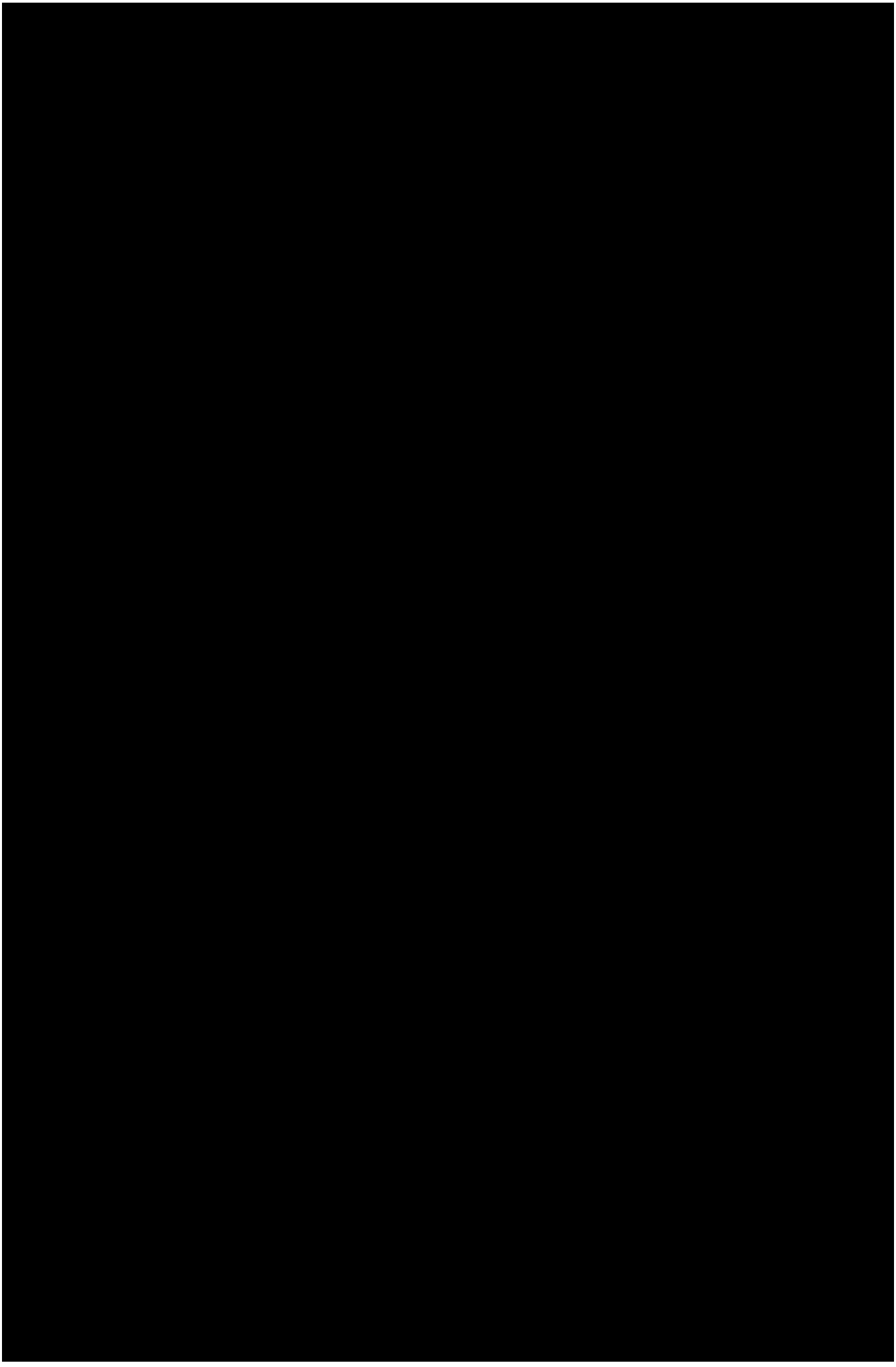

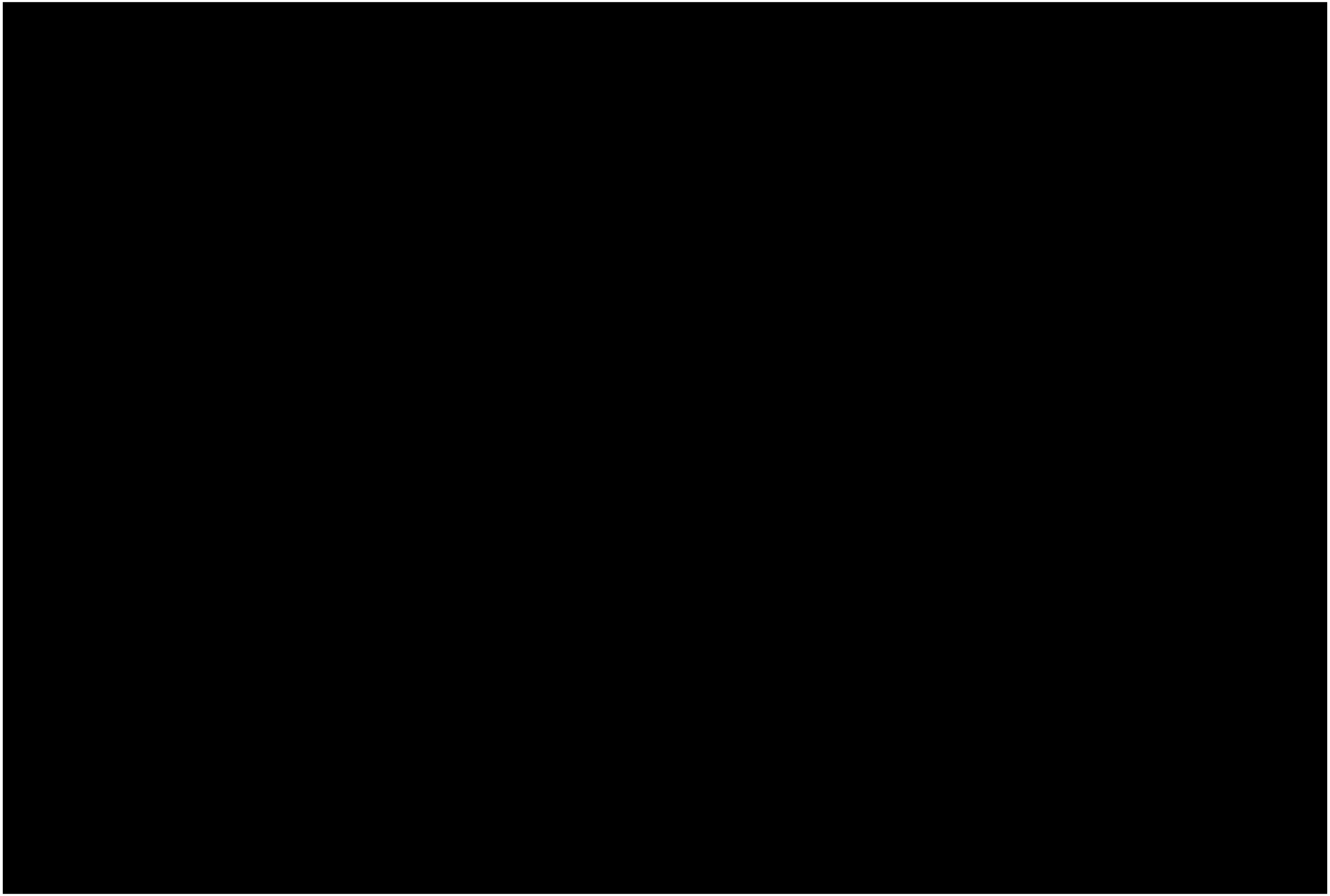

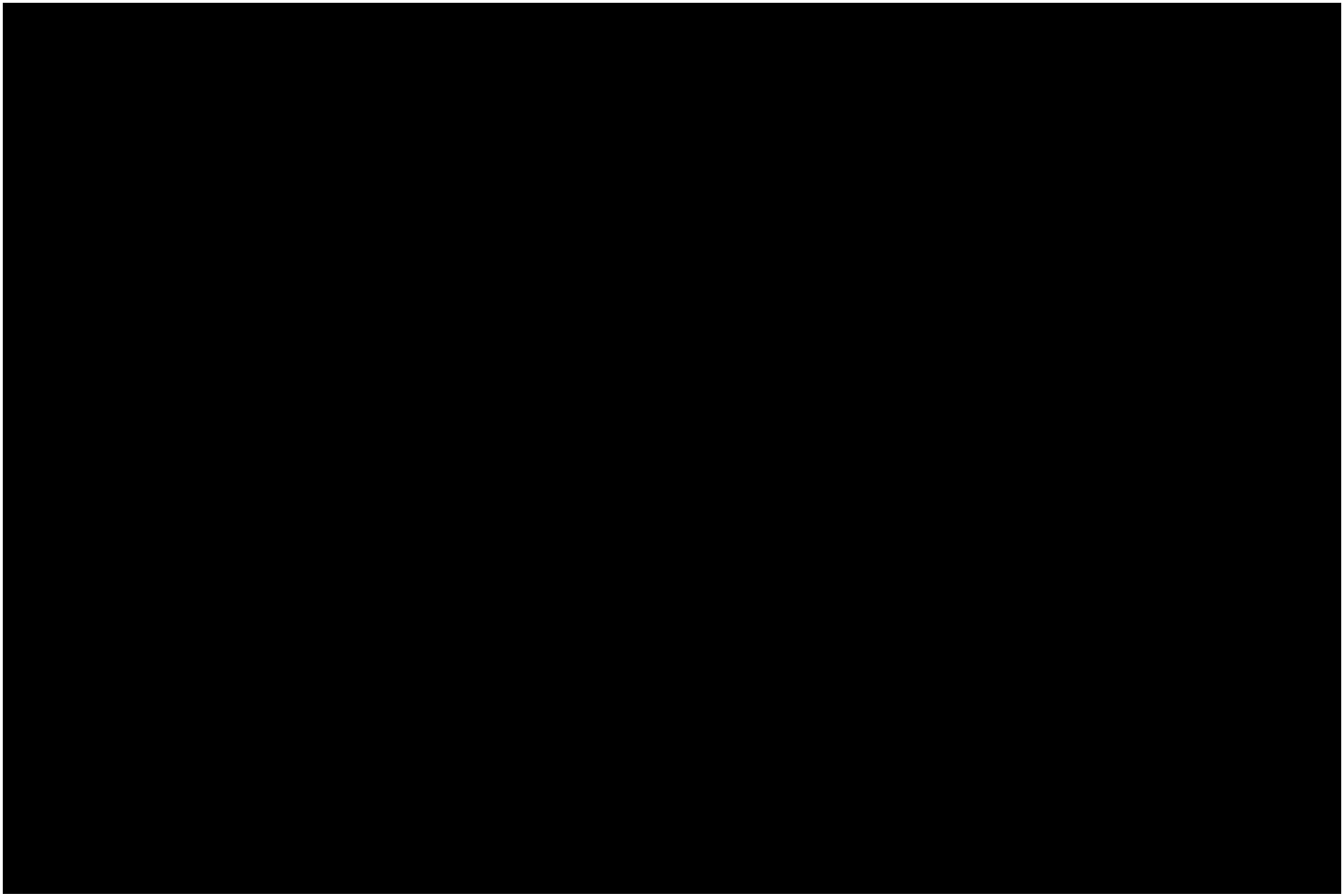

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18.5. Appendix E: Premedication

Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator.

18.5.1. Premedications

At Investigator discretion, a subject may be premedicated with:

- H_1 antagonist with local regulatory approval for marketing at a dose equivalent to 50 mg diphenhydramine AND H_2 antagonist with local regulatory approval for marketing at a dose equivalent to 20 mg famotidine

  OR

- Systemic corticosteroid.

Premedications will be obtained commercially by the study center. Whenever available, premedication should be done with preservative-free injectable formulations.

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18.5.3. Documentation

All premedication(s) administered will be reported on the appropriate eCRF.

18.6. Appendix F: Restrictions Relating to COVID-19

This section describes safety measures that were taken due to the COVID-19 pandemic. These measures will also apply to subsequent outbreaks/pandemics resulting from SARS-CoV-2 infections.

18.6.1. Restrictions to Study Conduct

The following will be taken into consideration when determining whether there are any restrictions to conducting onsite visits:

- Local government/institution and hospital readiness to allow clinical research activities
- Confirmed absence of COVID-19-related restrictions on mobility of persons (central, regional, & municipal government plus institutional) applicable to the trial candidates, subjects, or site personnel
- Ability for clinical research associate (CRA) to perform onsite routine monitoring in accordance with the Monitoring Plan.
- Confirmed ability to perform research PFT per protocol/established guidelines
- Confirmed ability to perform research HRCT per protocol/established guidelines
- Confirmed ability to process and ship central and local laboratory samples per protocol/established guidelines
- Adequate stock of study supplies including laboratory kits, personal protective equipment, and study treatment preparation and administration materials
- Unrestricted courier services

The Investigator will be responsible for determining if it is safe to proceed with onsite study visits at his/her site considering the requirements above. If the Investigator determines that onsite study procedures are not feasible based on the criteria above, they must inform the IRB/IEC and advise the CRA or clinical trial lead (CTL). Recommendations for how to proceed if there are restrictions preventing onsite visits are included Section 18.6.2.

To resume onsite study visits, the Investigator must inform the IRB/IEC and CRA or CTL after considering the guidelines above.

18.6.2. Study Visit Guidelines

18.6.2.1. Consenting and Screening

When study procedures cannot be performed onsite, the Investigator should pause consenting of new subjects and suspend screening procedures for already consented subjects. Subjects who have been consented but have not received study treatment, should be considered screen failures (with the option to rescreen at a later time). If the Investigator believes these activities may resume after considering the guidelines in Section 18.6.1, the Investigator must inform the IRB/IEC and CRA or CTL.

18.6.2.2. Managing Treatment Period Study Visits

When onsite study procedures cannot be performed for already randomized subjects, up to 2 scheduled Treatment Period visits may be conducted remotely. The implementation of remote visits allows for a maximum delay in study treatment administration of 6 weeks after the last dose. Section 18.6.2.4 describes what data should be collected at a minimum during a remote visit.

If onsite visits can resume and study treatment can be administered ≤ 6 weeks after the last dose, feasible study-related procedures should resume onsite as soon as possible per Section 12.2. In this case, the subject should proceed with the next protocol visit and follow those procedures. For example, if the subject has remote Visit 4 and Visit 5, and onsite visits can resume within 6 weeks of their last dose of study treatment, the subject will resume the study and complete Visit 6 study procedures.

18.6.2.3. Managing End-of-Treatment and Follow-Up Period Visits

Subjects Who Complete Planned Treatment Period Visits

If a subject completes all planned Treatment Period visits, remote or onsite through Visit 13, Visit 14 should be conducted per Section 12.3. If it is not safe or feasible to proceed onsite, Visit 14 may be postponed for up to 8 weeks after the last dose. If onsite Visit 14 will not be safe or feasible in ≤ 8 weeks after the last dose, the visit should be conducted remotely. If at any time circumstances change and it becomes safe and feasible for a subject to come to the site, subsequent visits should be performed onsite and follow procedures per Section 12 for the visits described below.

a. Visit 14 performed onsite or remotely ≤ 8 weeks after Visit 13
b. Visit 15 performed onsite or remotely 4 ± 1 week after Visit 14
c. Visit 16 performed onsite or remotely 10 ± 1 week after Visit 14

Subjects Who Do Not Complete Planned Treatment Period Visits

If a subject misses 2 Treatment Period visits as described in Section 18.6.2.2, and it is not expected that study treatment administration can restart ≤ 6 weeks after the last dose, perform a remote ET visit. If circumstances change and it becomes safe and feasible for the subject to come to the site, ET and Follow-Up visits should be performed onsite and follow procedures per Section 12.

a. ET visit performed onsite or remotely 2 ± 1 week after the second missed visit
b. Visit 15 performed onsite or remotely 4 ± 1 week after ET visit
c. Visit 16 performed onsite or remotely 10 ± 1 week after ET visit

18.6.2.4. Data Collection During Remote Visits

During remote visits, the following information should be collected at a minimum:

1. Concomitant medications
2. Adverse events (If the subject reports COVID-19, ask whether the infection has been confirmed via testing. If possible, the test used should be recorded.)

3. Vital signs (Has the subject been febrile? If so, how was this detected?)
4. Pulse oximetry and supplemental oxygen requirement (if subject has equipment at home)

18.6.2.5. High-Resolution Computed Tomography

[redacted]

18.6.3. Analysis Related to COVID-19

Additional sensitivity analyses may be performed due to the COVID-19 pandemic. All analyses related to COVID-19 will be conducted in accordance with regulatory guidelines. These analyses will be described in the SAP.

18.6.4. Clinical Study Report

The CSR will include information specific to the COVID-19 pandemic consistent with regulatory guidelines.