

Document Type: Final Statistical Analysis Plan

Document Date: 13 May 2022

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

Statistical Analysis Plan

Nitto Denko Corporation

Protocol ID: ND-L02-s0201-005

[REDACTED]
Document Version: 1.0

Document Date: May 13, 2022

[REDACTED]
[REDACTED]

1.	Source Documents.....	8
2.	Protocol Details	8
2.1	Study Objectives.....	8
2.2	Overall Study Design	8
2.3	Sample Size and Power	9
3.	Efficacy and Safety Variables.....	9
3.1	Primary Endpoints.....	9
3.2	Secondary Endpoints.....	9
3.4	Efficacy and Safety Variables.....	10
3.4.1	Spirometry	10
3.4.2	Diffusion Capacity of the Lung for Carbon Monoxide (DLco)	11
3.4.3	High Resolution Computed Tomography (HRCT).....	11
3.4.5	Extent of Exposure	13
3.4.6	Adverse Events (AEs).....	14
3.4.7	Laboratory Evaluations	15
3.4.8	Vital Signs and Pulse Oximetry.....	16
3.4.9	Physical Examination.....	17
3.4.10	12-Lead Electrocardiograms	17
3.4.11	Other Safety Assessments.....	17
4.	Pharmacokinetic variables.....	19
5.	Analysis populations.....	21
5.1	Safety Population (SAF)	21

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

5.2	Intent-to-treat Population (ITT)	21
5.3	Pharmacokinetic Population 1 (PK1)	21
5.4	Pharmacokinetic Population 2 (PK2)	21
5.5	Per Protocol Population (PP)	21
6.	Data Handling	22
6.1	Time points and Visit Windows	22
6.2	Handling of Dropouts, Missing Data, and Outliers	22
7.	Statistical Methods	23
7.1	General Principles	23
7.2	Subject Disposition and Data Sets Analyzed	25
7.3	Protocol Deviations	25
7.4	Demographics and Other Baseline Characteristics	25
7.4.1	Medical History	27
7.4.2	Previous and Concomitant Medications	27
7.5	Efficacy	28
7.5.1	Primary Efficacy Analysis	28
7.5.2	Secondary Efficacy Analysis	28
7.5.3	Sensitivity Analysis	32
7.5.4	Subgroup Analysis	32
7.6	Safety	34
7.6.1	Extent of Exposure	34
7.6.2	Adverse Events	35
7.6.3	Laboratory Evaluations	37
7.6.4	Vital Signs and Pulse Oximetry	38
7.6.5	Electrocardiograms	38
7.6.6	Physical Examination	39
7.6.7	Other Safety Analyses	39
7.6.9	Impact of COVID-19 Pandemic	40
7.7	Interim Analysis	40

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

8. Changes in Planned Analysis	40
--------------------------------------	----

Appendices.....	42
-----------------	----

Appendix 1: GAP Algorithm for IPF Stage and Predicted Mortality	42
---	----

Appendix 2: Schedule of visits.....	44
-------------------------------------	----

Appendix 3: FVC and %FVC Baseline Determination	47
---	----

Appendix 4: HRCT Assessment	48
-----------------------------------	----

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

[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]	[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]	[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] [REDACTED]	[REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED] [REDACTED]	[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Glossary of Abbreviations

Abbreviation	Term
████	████████████████████
AE	Adverse event
AEOI	Adverse events of special interest
AIC	Akaike's information criterion
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AR(1)	First-order autoregressive
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
████	████████████████████
bpm	beats per minute
CI	Confidence Interval
COVID-19	Coronavirus disease
CS	Compound symmetry
CTCAE	Common Terminology Criteria for Adverse Events
DLco	Diffusion capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eDISH	Evaluation of drug induced serious hepatotoxicity
EOT	End-of-Treatment
ET	Early Termination
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
████	████████████████████
HRCT	High-resolution computed tomography
ILA	Interstitial lung abnormalities
ILD	interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
████	████████████████████
KW	Kruskal-Wallis
KM	Kaplan-Meier
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation

Sponsor Protocol ID: ND-L02-s0201-005

Abbreviation	Term
NCI	National Cancer Institute
PD	Pharmacodynamics
PFT	Pulmonary function testing
████	██
PK	pharmacokinetic(s)
PP	Per protocol
████	██
Q2W	Every 2 weeks
QLF	Quantitative lung fibrosis
QOL	Quality of life
QTcF	QT interval corrected using Fridericia's formula
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Standard Deviation
████	██
SLB	Surgical lung biopsy
SOC	System Organ Class
SpO ₂	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures and Listings
TOEP	Toeplitz
UIP	Usual interstitial pneumonia
ULN	Upper limit of normal
VA	Alveolar volume
WBC	White blood cell
WHO	World Health Organization
████	██

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol Amendment	17 June 2020	5.0
eCRF	19 February 2021	Prod 3.00

2. Protocol Details

2.1 Study 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

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)

- [REDACTED]
- [REDACTED]

2.2 Overall Study Design

This is a Phase 2, double-blind, placebo-controlled, randomized, multicenter, international study of 2 doses of ND-L02-s0201 for Injection, consisting of 3 treatment arms: 2 dose levels of ND-L02-s0201, a low dose (45 mg) and a high dose (90 mg), will be evaluated in 2 arms; a third arm will be administered placebo. This study will evaluate safety, tolerability, biological activity, and PK in subjects with a diagnosis of idiopathic pulmonary fibrosis (IPF) with forced vital capacity (FVC) $\geq 45\%$ of predicted and diffusion capacity of the lung for carbon monoxide (DL_{CO}) $\geq 30\%$ of predicted.

Approximately 120 eligible subjects will be randomized 1:1:1 to 1 of following 3 treatment arms:

- ND-L02-s0201 for Injection high dose (90 mg)

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- ND-L02-s0201 for Injection low dose (45 mg)
- Placebo.

The randomization via the interactive web response system (IWRS) will be stratified by the receipt of standard of care at the enrollment of the study, defined as administration of either nintedanib or pirfenidone, or no standard of care. As there is no minimum number of subjects for a given strata of standard of care, balance in strata across the 3 treatment arms is required.

Eligible subjects who meet the inclusion criteria and do not meet any of the exclusion criteria and have provided informed consent will be enrolled in the study. Subjects will participate in the study for approximately 40 weeks consisting of a Screening and Baseline period of up to 6 weeks, a treatment period of 24 weeks including a total of 12 doses and an End-of-Treatment visit 2 weeks after the final dose (Visit 14), and a follow-up visit 4 and 10 weeks after Visit 14, or until they withdraw from the study or the study is terminated by the Sponsor. 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. Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator.

2.3 Sample Size and Power

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.

3. Efficacy and Safety Variables

3.1 Primary Endpoints

Safety

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

3.2 Secondary Endpoints

Biological Activity

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- Rate of decline in FVC from baseline to Visit 14 (Day 169) (measured in L and % of predicted over unit time)
- Absolute and relative change in FVC (L and % of predicted) at Visit 14 (Day 169) as compared with baseline
- Proportion of subjects with an FVC response (L and % of predicted) defined as either having improvement or a decline by 0% to $\leq 5\%$, $> 5\%$ to $\leq 10\%$, and by $> 10\%$ at Visit 14 (Day 169)
- Change in DL_{CO} (mL/min/mmHg) and DL_{CO} (mL/min/mmHg) corrected for hemoglobin at Visit 14 (Day 169)
- Changes of ILA as measured by HRCT (i.e., 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 (i.e., 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]) or death
- Rate of hospitalization for respiratory ailments and time to first hospitalization for respiratory ailments or death
- Rate of mortality due to all causes and overall survival
- Rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death and time to deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death

[REDACTED]

- [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]

3.4 Efficacy and Safety Variables

3.4.1 Spirometry

Spirometry variables include forced vital capacity (FVC) and percent predicted FVC (%FVC). FVC will be measured in units of liters (L) and rounded to 2 decimal places. %FVC will be measured in percent and rounded to 2 decimal places. The spirometry

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

variables will be provided by an external vendor in a data transfer and the results will not be entered into the EDC system.

In the event that no baseline measurement is designated, then the baseline measurement will be the last non-missing value before the first infusion of study treatment.

3.4.2 Diffusion Capacity of the Lung for Carbon Monoxide (DLco)

Diffusion capacity of the lung for carbon monoxide (DLco) in mL*(CO/min/mmHg) will be provided by an external vendor in a data transfer, and the results will not be entered in the EDC system. DLco will be provided with and without correction for hemoglobin and results will be rounded 2 decimal places.

In the event that no baseline measurement is designated, then the baseline measurement will be the last non-missing value before the first infusion of study treatment. Values not designated as "Accepted" in the vendor data transfer will be excluded from statistical analyses. When more than two valid test values are obtained at a study visit in the event a PFT that has passed QC shows declines from baseline that need confirmatory testing, the average of both values will be included in the summary table.

3.4.3 High Resolution Computed Tomography (HRCT)

High resolution computed tomography (HRCT) data will be provided by a central reader and will include variables from qualitative and quantitative analyses of HRCT scans

Results of HRCT analyses will be provided by an external vendor in a data transfer and will not be entered in the EDC system

3.4.3.1 Qualitative HRCT Variables

The qualitative HRCT variables will include central reader estimates of the extent of lung region abnormalities by lung (left and right) and region (upper, mid, and lower).

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Possible values (as %) for each region will include "Absent", "1-25", "26-50", "51-75", and "76-100". Results for unreadable scans will be reported as "Unknown".

The central reader's assessment of overall change in interstitial lung disease (ILD) from baseline to Visit 14 (or ET) will have possible values of "Much Better", "Better", "Same", "Worse", "Much Worse", or "Unknown".

[REDACTED]

[REDACTED]

3.4.3.2 Quantitative HRCT Variables

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Extent of exposure to study treatment will be summarized descriptively as:

- Treatment compliance is calculated as:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- Treatment compliance = $100 * \text{total actual cumulative dose of administered (mg)} / \text{total cumulative dose of the planned (mg)}$ during the study.

Where the cumulative dose of planned dose is defined as number of planned doses until last dose subject received multiplying by assigned dose (45 mg for low dose treatment arm and 90 mg for high dose treatment arm). The total planned dose is defined as the number of infusions planned until subject's last dose (i.e. if subject's last dose is at Week 22, then the subject's expected number of infusions would be 12).

If date of first dose date is missing, then the randomization visit will be used. The last dose is the date of the last dose administered as of the data cut-off date.

3.4.6 Adverse Events (AEs)

All AEs recorded on the eCRF will be coded using the latest version of MedDRA dictionary, per the Data Management Plan, throughout the study and classified as either pre-treatment AEs or TEAEs as follows:

- Pre-treatment AEs are events that started prior to the first dose of any study treatment, including pre-medication.
- TEAEs are events that occur on or after the first dose of any study treatment including pre-medication through two weeks after the last dose of study treatment or adverse events which start before the first dose of study treatment, but increase in severity after the first dose through two weeks after the last dose of study treatment.

Assessment of AE severity will be based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). The severity of all AEs is recorded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening consequences (Grade 4), or death (Grade 5), per CTCAE grading. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and study treatment is assessed as definite, probable, possible, unlikely, or none. A drug-related AE is an AE considered by the investigator as definitely, probably, possibly, or unlikely related to study treatment. If the relationship is unknown or missing, it is also considered as related to study treatment.

AEs of special interest (AEOI) include [REDACTED]
[REDACTED] respiratory adverse events, and acute exacerbation of idiopathic pulmonary fibrosis.

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

3.4.7 Laboratory Evaluations

The following hematology, serum chemistry, and urinalysis analytes recorded in the eCRF will be analyzed in this study. Absolute values will be compared to the laboratory reference range and classified as

- lower than reference range, clinically significant;
- lower than reference range, not clinically significant;
- normal in reference range;
- higher than reference range, not clinically significant;
- higher than reference range, clinically significant.

All values classified as high or low will be flagged on the listings. The baseline value will be defined as last scheduled or unscheduled value prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

[illegible]

3.4.8 Vital Signs and Pulse Oximetry

The following vital signs will be evaluated at the time points specified in study calendar.

- systolic and diastolic blood pressure (mmHg);
- heart rate (bpm);
- respiratory rate (breaths/min);
- oral temperature (°C).
- weight (kg) and height (cm). Height will be recorded only at first visit (visit 1a).
- SpO₂ (%).

The baseline value will be defined as last scheduled or unscheduled value collected prior to start of treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if

the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

3.4.9 Physical Examination

Complete and abbreviated physical examinations will be evaluated in this study. A complete physical examination includes 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. 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+). Any clinically significant abnormal result after baseline should be recorded as an AE.

3.4.10 12-Lead Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia's corrected QT (QTcF) interval (msec).

An overall investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant"). Clinically significant changes not already noted or significantly worsened than documented in Medical History will be recorded as AEs.

The baseline value will be defined as last scheduled or unscheduled value collected prior to start of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables. When triplicate ECG tracings are obtained at a study visit or timepoint, the triplicate average (or if fewer, average of ECGs available) will be included in the analysis.

3.4.11 Other Safety Assessments

The following other safety assessments will be performed:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation

Sponsor Protocol ID: ND-L02-s0201-005

- [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]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation

Sponsor Protocol ID: ND-L02-s0201-005

[REDACTED]

[REDACTED]

- I [REDACTED]
[REDACTED]
[REDACTED]
- I [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- I [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]
[REDACTED]	[REDACTED]

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

[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] [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]

5. Analysis populations

5.1 Safety Population (SAF)

The safety population (SAF) will include all subjects who receive at least 1 dose of study treatment. Subjects will be analyzed according to the study treatment they actually received.

5.2 Intent-to-treat Population (ITT)

The ITT population will include any randomized subjects with treatment assignment according to the planned randomization.

5.3 Pharmacokinetic Population 1 (PK1)

PK population 1 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. A majority of samples is defined by sampling to at least 4 hours after end of infusion. Subjects who do not complete the study treatment infusion (Visit 2) will be excluded from the PK analysis.

5.4 Pharmacokinetic Population 2 (PK2)

PK population 2 will include subjects who have at least 3 of the 7 planned trough samples collected for subjects in the PK subset and both 2 planned trough samples collected for non-PK subjects to allow for a comparison of trough levels across dosing weeks.

5.5 Per Protocol Population (PP)

The per protocol population (PP) will exclude non-evaluable subjects and subjects with important protocol deviations thought to impact the ability to assess the effect of study treatment.

Evaluable subjects are defined as subjects who received at least one dose of study treatment (not including pre-medication) and have baseline and at least one post baseline FVC or have baseline and at least one post baseline DLco.

Non-evaluable subjects are subjects who do not meet the evaluable criteria.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations that may significantly impact the correctness, accuracy, and/or completeness of the study data or that may significantly affect a subject's rights, safety, or well-being.

6. Data Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of treatment (visit 2). Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule of Assessment and eCRF. Data collected at unscheduled visits will be listed only, except for the following:

- Data from unscheduled visits will be included in the calculation of baseline laboratory values.
- Data from unscheduled visits will be included in the calculation of the worst CTCAE grade or abnormality used in the laboratory shift tables.
- For a nominal visit with a missing measurement, the measurements of the unscheduled visits occurring between this particular visit and the two adjacent visits will be used to assign the analysis value. The closest unscheduled visit value that is not assigned to previous visits will be assigned to this nominal visit.

6.2 Handling of Dropouts, Missing Data, and Outliers

Missing values on FVC, DL_{CO} and DL_{CO} corrected for hemoglobin, HRCT analysis variables, [REDACTED] at Visit 14 (Day 169) will not be imputed. In situations where the efficacy endpoints are missing, all available data will be analyzed with a mixed-effects model for repeated measures (MMRM). To evaluate robustness of results, sensitivity analyses will be performed by imputing missing data using statistical modelling of available data.

Incomplete dates (partial or missing dates) for start date of AEs will be imputed and used to determine treatment-emergent status as follows:

- If the start date of an AE is completely missing, the first dosing date (Day 1) and time will be used for the imputation and the AE will be considered treatment-emergent.
- If the start date of an AE is missing day and month:
 - If the year of the AE start date is the year of the first dosing date, the month and day will be imputed using the month and day of first dosing date;
 - Otherwise, the month and day will be imputed as January 1.
- If the start date of an AE is missing the day only:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- If the year and month of the AE start date is the same as the year and month of the first dosing date, the day will be imputed using the day of first dosing date;
- Otherwise, the day will be imputed as the first day of the month.
- If an imputed AE start date is later than the corresponding AE end date, the imputed AE start date will be replaced with the AE end date.

AEs with missing relationship (related or not related) to study treatment will be treated as related AEs in summaries of AEs by relationship to study treatment.

Partial dates with day or day and month missing for concomitant medications date will be imputed as follows:

- If the year and month are present and the day is missing, set the start date as the first day of the month, and set the end date as the last day of the month as applicable.
- If the year and day are present and the month is missing, set the month to January as the start date, and set month to December as the end month as applicable.
- If the year is present and the month and day are missing, set January 1 as the start date, and set December 31 as the end date as applicable.
- Completely missing dates will not be imputed.
- If the start date is completely missing and the end date is on or after the first dosing date, the medication will be classified as concomitant; if the end date is missing, the medication will be classified as ongoing. Medications for which both the start and end dates are missing will be classified as concomitant.

7. Statistical Methods

7.1 General Principles

Efficacy data will be summarized and analyzed on the ITT population and PP population. Safety and treatment compliance data will be summarized based on the SAF population. Demography and other baseline characteristics data will be summarized based on the SAF population.

Baseline is defined as the last scheduled or unscheduled value assessed on or before study day 1, prior to the first dose of study treatment, including pre-medication unless otherwise indicated. Assessments carried out on day of first dose administration are considered to have taken place before the dose administration, if

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

the corresponding times have not been recorded. Measurements that are obtained after the first date of study treatment will be considered post-baseline values. Change from baseline is defined as (post-baseline value – baseline value).

Time-to-event endpoints will be summarized using Kaplan-Meier (KM) method to estimate the median, and the 25th and 75th percentiles.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Treatment arm labels and order presented	1. Placebo 2. ND-L02-s0201 45 mg 3. ND-L02-s0201 90 mg 4. Total (if applicable)
Tables	Data in summary tables for safety will be presented by treatment arm, and Total, and visit (where applicable). Data in summary tables for efficacy will be presented by treatment arm.
Listings	All data collected presented by treatment arm, subject, and visit date (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects (n), mean, standard deviation, median, minimum, maximum
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	By-visit summaries: number of subjects with non-missing data at the visit assessed in the analysis population of each treatment arm; Other summaries: Number of subjects in the analysis population of each treatment arm, unless specified otherwise.
Include "Missing" as category	Included for demographics and other baseline characteristics when the number of missing is greater than zero for at least one treatment arm. Missing post-baseline values will not be summarized, unless otherwise specified.
Display for percentage	One decimal place, except for 100%
Display for 0 percentages	blank
Display to one more decimal place than collected value	Mean, Median

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Principle	Value
Display to two more decimal places than collected value	Standard Deviation Confidence interval
Display to p-value	P-values will be rounded to 3 decimal places. P-values less than 0.0005 (e.g. 0.0002) will not be rounded to 3 decimal places (e.g. 0.000) but instead be displayed as <0.001.
Date Format	DDMMYYYY
Statistical Analysis	All statistical tests will be conducted at the 2-sided, 0.05 level of significance. There will be no adjustment for multiplicity.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment arm and overall for all randomized subjects and will include the number and percentage of subjects:

- randomized;
- randomized by randomization stratification factor (i.e., standard of care at enrollment);
- included in each analysis population (SAF, ITT, PK1, PK2, and PP).
- completed the study
- discontinued treatment
- primary reason for discontinuation of treatment
- terminated early from the study (terminated before Visit 8 or after visit 8) including early termination due to COVID-19 pandemic.
- primary reason for early termination.

7.3 Protocol Deviations

All protocol deviations will be listed. Important protocol deviations leading to exclusion from the PP population will be listed and summarized by treatment arm for the ITT population. Protocol deviations due to COVID-19 will be listed separately.

The deviations leading to exclusion from the PP population will be identified before data are unblinded.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment arm and overall for the SAF population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) [as reported in the eCRF];

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- weight (kg);
- height (cm);
- body mass index (kg/m²) [calculated as (weight/height²) where weight is in kg and height is in m];
- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- body temperature (°C);
- pulse rate (beats/min);
- respiratory rate breaths (breaths/min);
- pulse oximetry (SPO₂) (%);
- forced vital capacity (FVC) in L;
- percent predicted FVC (%);
- forced expiratory volume in 1 second (FEV1) in L;
- percent predicted FEV1 (%);
- ratio of FEV1/FVC;
- diffusion capacity of the lung for carbon monoxide (DLco) ;
- percent predicted DLco (%);
- hemoglobin corrected DLco;
- hemoglobin corrected percent predicted DLco (%);

- duration of IPF since diagnosis to start of study treatment (months)
 - calculated as (first dose date-initial IPF diagnosis date+1)/30.4375
- GAP IPF Risk of Mortality: The risk of mortality (1-, 2-, and 3-year risk) will be derived based on baseline data at the start of the treatment period using the Gender, Age, and Physiology (GAP) methodology described in Ley et al, 2012 ([Appendix 1](#));

The total counts and percentages of subjects will be presented for the categorical variables of:

- gender;
- childbearing potential for females
- race;
- ethnicity;
- BMI group [Underweight (below 18.5); Normal (18.5 - 24.9); Overweight (25 - 29.9); Obese (30 and above)]
- smoking history(yes/no)
 - If smoking history is yes, active smoker(yes/no)
- background standard of care (nintedanib, pirfenidone, none);

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- GAP IPF Stage: The IPF stage will be derived based on baseline data at the start of the treatment period using the Gender, Age, and Physiology (GAP) methodology described in Ley et al, 2012 ([Appendix 1](#));

No formal tests of statistical significance will be performed on the demographic and baseline data.

7.4.1 Medical History

Medical history will be coded using the lasted version of Medical Dictionary for Regulatory Activities (MedDRA), per the Data Management Plan, throughout the study. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for the SAF population by system organ class (SOC) and preferred term (PT) for each treatment arm and overall.

7.4.2 Previous and Concomitant Medications

Medications including COVID-19 vaccination received prior to or concomitantly with study treatment will be coded using the lasted version of WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) Classification codes, per the Data Management Plan, throughout the study. Only medications taken within 14 days before Visit 1a through end of study will be included in summary table and listing.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken and ended within the interval from 14 days before Visit 1a up to the earliest of 24 hours before Visit 1a or date of informed consent.
- Concomitant medications are those taken on or after the earliest of 24 hours before Visit 1a or date of informed consent. Medication taken prior to but ongoing after the earliest of 24 hours before Visit 1a or date of informed consent will be considered concomitant medication.

If a medication cannot be classified as “prior” or “concomitant” for missing/incomplete dates, it will be classified as both prior and concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for SAF populations for each treatment arm and overall.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and preferred term. Tables will be sorted in descending overall frequency by ATC-Level 2, ATC-Level 4, and preferred term, and then alphabetically.

7.5 Efficacy

7.5.1 Primary Efficacy Analysis

No primary efficacy endpoint is identified in the study protocol. Analyses of secondary endpoints for biological activity are described in [Section 7.5.2](#).

7.5.2 Secondary Efficacy Analysis

7.5.2.1 Analyses of FVC

Values of FVC variables described in [Section 3.4.1](#) will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include FVC (or percent predicted FVC) values, the change and percentage change from baseline to each post-baseline visit for each parameter. Results from unscheduled visits will not be included in summary tables, but will be included in subject-level listings and statistical model.

A random coefficients model will be used to analyze the rate of decline in FVC (L) from baseline to Visit 14 (Day 169) as well as the absolute change from baseline in FVC at Visit 14 in the ITT Population.

Reporting of model results will include the estimated mean change from baseline, adjusted for baseline FVC and standard of care, at each timepoint with corresponding 95% CIs. In addition, mean slope (rates of change) of FVC from baseline to Visit 14 (Week 24) for each treatment arm will be estimated along with 95%CIs. Treatment differences between mean slopes and corresponding p-values will be presented. No adjustments for multiple comparisons will be made. Spaghetti plots of individual FVC (L) data over time will be produced for each treatment arm with estimated means from the random coefficient model and 95% CIs at each timepoint superimposed.

Similar analysis will be repeated for FVC (L) relative change from baseline, absolute and relative change from baseline for percent predicted FVC (%FVC).

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Study treatment response is defined as a decline in FVC (L and % of predicted) of no more than 10% in the relative change at Visit 14 that is calculated as:

$$\text{Change in FVC L (\%)} = \frac{(\text{FVC L at Visit 14} - \text{FVC L at Baseline})}{\text{FVC L at Baseline}} * 100\%$$

The change in FVC % of predicted (%) will be calculated as:

$$\text{Change in FVC \% of predicted (\%)} = \frac{(\text{FVC \% of predicted at Visit 14} - \text{FVC \% of predicted at Baseline})}{\text{FVC \% of predicted at Baseline}} * 100\%$$

A positive value indicates improvement. Number and percent of subjects responding to treatment will be summarized.

The number and percent of subjects within each treatment arm showing an improvement, and subjects showing a decline of 0% to ≤5%, >5% to ≤10%, and >10% at Visit 14 (day 169) will be summarized by treatment arm. Subjects with an FVC response is defined as improvement in FVC or a decline of ≤10% from baseline FVC value.

7.5.2.2 Analyses of DLco

Values of DLco variables described in [Section 3.4.2](#) will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include the absolute and percent change from baseline to each post-baseline visit for each parameter. Results from unscheduled visits will not be included in summary tables or statistical models, but will be included in subject-level listings.

DLco corrected for hemoglobin and DLco not corrected for hemoglobin will be analyzed similarly as FVC as described in section 7.5.2.1.

7.5.2.3 Analyses of HRCT

Values of HRCT variables described in [Section 3.4.3](#) will be summarized with descriptive statistics by treatment arm and visit for the ITT Population. The summary will include the change from baseline to Visit 14 (or ET) for each parameter. Results from unscheduled visits will not be included in summary tables or statistical models, but will be included in subject-level listings. In addition, subjects who have visit 14 assessment and subjects who withdraw from treatment before visit 14 and have only ET assessment will be summarized separately for each HRCT variable.

The qualitative overall change in ILD from baseline to Visit 14/ET will be analyzed using the Kruskal-Wallis (KW) test. The test statistic and p-value from the KW test will be reported along with the pairwise comparisons of each active treatment arm with placebo.

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

A random coefficients model will be used to analyze the rate of change in the quantitative QLF score from baseline to Visit 14 as well as the absolute change from baseline at Visit 14. The model will include QLF score as the dependent variable, background standard of care, treatment, time and the interaction of treatment*time and baseline QLF score as fixed effects, and subject and subject*time as random effects. Subjects with missing values at Visit 14 will not be imputed for the analysis. The unstructured covariance model (UN) will be used to estimate the variance and covariance of random slopes and intercepts. If the computational algorithm fails to converge, the variance components (VC) covariance structure will be used for the analysis.

Reporting of model results will include the estimated mean change from baseline, adjusted for baseline QLF and standard of care, at Visit 14 with corresponding 95% CIs for each treatment arm. In addition, mean slope (rate of change) of QLF from baseline to Visit 14 for each treatment arm will be estimated along with 95% CIs. Treatment differences between mean slope and corresponding p-values will be presented. No adjustments for multiple comparisons will be made. The analysis will be repeated for subjects who have visit 14 assessment and subjects who withdraw from treatment before visit 14 and have only ET assessment. Spaghetti plots of individual QLF data over time will be produced for each treatment arm with estimated means from the random coefficient model and 95% CIs at Visit 14 superimposed.

Similar analysis will be repeated for relative change of QLF from baseline (derived as $100 \times (\text{QLF score at Visit 14} / \text{ET-Baseline QLF score}) / \text{Baseline QLF score}$).

Other quantitative HRCT variables including ground glass opacity, reticulation, honeycombing, normal lung, and emphysema will be analyzed similarly as QLF score.

7.5.2.4 Analysis of Time to First IPF Exacerbation or Death

Time to first IPF exacerbation or death is defined as the time from start of study treatment to first acute exacerbation of IPF which is determined by the investigator (Adverse event CRF, AE preferred term equal to Idiopathic pulmonary fibrosis) or death for each subject. Subjects who do not experience acute exacerbation of IPF will be censored to the last known alive date.

The analysis of time to first IPF exacerbation or death of each active treatment arm versus placebo will be performed using a log-rank test stratified with standard of care to generate p-value for each comparison. Median time to first IPF exacerbation and corresponding 95% CI as well as proportion of subjects without the event at 8-week interval will be summarized for each treatment arm using the Kaplan-Meier (KM) analysis. KM plot of time to first IPF exacerbation will also be presented by treatment. In addition, the hazard ratio and 95% CI will be calculated from a stratified Cox proportional hazards model that includes standard of care as the strata.

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

The rate of acute IPF exacerbation, which is defined as the number of patients with any acute IPF exacerbation divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be summarized by treatment arm. Tests of differences in rates between treatment arms will be assessed using chi-squared tests (χ^2) at the 2-sided, 0.05 level of significance. Corresponding exact 95% CIs of study treatment proportions and respective active ND-L02-s0201 differences from placebo will be estimated.

7.5.2.5 Other Secondary Analyses

The rates of hospitalization for respiratory ailments, which is defined as the number of patients with any hospitalization for respiratory ailments divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be tabulated by treatment arm. Tests of differences in event rate will be assessed using chi-squared tests (χ^2) at the 2-sided, 0.05 level of significance. Corresponding exact 95% CIs of study treatment proportions and respective active ND-L02-s0201 differences from placebo will be estimated. Time to hospitalization for respiratory ailments or death is defined as the time from start of study treatment to hospitalization for respiratory ailments or death for each subject. Subjects who do not experience hospitalization for respiratory ailments and have not died will be censored to last known alive date. The analysis of time to hospitalization for respiratory ailments or death of each active treatment arm versus placebo will be performed using a log-rank test stratified with standard of care to generate p-value for each comparison. Median time to hospitalization for respiratory ailments or death and corresponding 95% CI as well as proportion of subjects without the event at the 8- week interval will be summarized for each treatment arm using the Kaplan-Meier (KM) analysis. KM plot of time to hospitalization for respiratory ailments or death will also be presented by treatment. The hazard ratio and 95% CI will be calculated from a stratified Cox proportional hazards model that including standard of care as the strata.

Rate of mortality due to any cause, which is defined as the number of patients who died due to any cause, divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be analyzed similarly as the rate of hospitalization for respiratory ailments. In addition, overall survival which is defined as the time from start of study treatment to death due to any cause will be analyzed similarly as time to hospitalization for respiratory ailments. Any patient not known to have died at the time of analysis will be censored to the last known alive date.

Rate of deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death, which is defined as the number of patients with

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

any deterioration of IPF resulting in lung transplantation divided by the total study duration (years) summed over patients in that treatment arm and then multiplied by 100 to present in terms of per 100 patient years, will be analyzed similarly as the rate of hospitalization for respiratory ailments. In addition, time to deterioration of IPF resulting in lung transplantation or death defined as the time from start of study treatment to deterioration of IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death will be analyzed similarly as time to hospitalization for respiratory ailments. Any patient not known to have IPF resulting in lung transplantation (up to 12 weeks after the end of study treatment) or death at the time of analysis will be censored to 12 weeks after the end of study treatment or the last known alive date, whichever is earlier.

7.5.3 Sensitivity Analysis

- **Multiple imputation assuming missing not at random (MNAR)**

Sensitivity analysis will be performed for secondary efficacy endpoints including change and percent change from baseline in FVC (L) and percent predicted FVC (%), change from baseline in DLco corrected for hemoglobin and DLco not corrected for hemoglobin, and change and percent change from baseline in quantitative HRCT variables using multiple imputations with missing data imputed prior to fitting the linear regression. An assumption of MNAR will be made based upon an approach using regression based multiple imputations with missing data for all subjects imputed from a regression model estimated from patients in the placebo arm who stay on until visit 14. SAS PROC MI and MIANALYZE will be used to generate 100 complete datasets and combine the results from each complete dataset analyzed using ANCOVA model with baseline value, treatment arm, and standard of care as covariates.

- **Excluding subjects with deviations**

All the secondary efficacy analysis described in section 7.5.2 will be repeated using the PP population.

7.5.4 Subgroup Analysis

Subgroup analysis will be conducted comparing both active treatment arms with placebo arm to assess consistency of treatment effects across potential prognostic factors.

The following subgroups of ITT population will be analyzed for the secondary efficacy endpoints:

- Standard of care (none vs. nintedanib vs. pirfenidone)
- Anti-fibrosis (none vs. nintedanib or pirfenidone)

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- BMI (<30 vs. ≥ 30)
- GAP IPF Stage (I vs. II vs. III)
- Duration of IPF since diagnosis to start of study treatment (≤ 1 vs. $1 < 2$ vs. $2 < 3$ vs. $3 < 4$ vs. ≥ 4 year)
- Subjects who adhere to the protocol schedule vs. subjects who missed at least one treatment but continued treatment after the interruption vs. early terminated subjects (subjects did not miss any treatment before early termination)
- COVID-19 vaccination (not vaccinated vs. vaccinated prior to treatment start vs. vaccinated while on treatment)

More subgroup analysis may be done ad-hoc given feasible data support.

No adjustment to the significance level for testing will be made. For each subgroup level, the analysis will be as described in 7.5.2 except for subgroup analysis of standard of care, the standard of care covariate will be removed from the analysis model.

If there are less than 10 subjects across both treatment arms in comparison in a subcategory then only descriptive summaries will be provided.

Forest plots will be provided for the secondary efficacy analysis. For rate of decline in FVC (L) or FVC (%FVC) from baseline to Visit 14, the estimated mean slope difference and 95% CI will be summarized and presented on the forest plot for each subgroup category as well as the overall ITT population. For change from baseline in FVC (L), percent predicted FVC (%FVC), DLco corrected for hemoglobin, DLco not corrected for hemoglobin, and quantitative HRCT variables (as described in 3.4.3), estimated means difference and 95% CI will be summarized and presented on the forest plot for each subgroup category as well as the overall ITT population. If the model does not converge then only descriptive summaries will be presented.

For time to event analysis described in section 7.5.2.4 and 7.5.2.5, for each subgroup level of a factor, the hazard ratio (HR) and 95% CI will be calculated from a Cox proportional hazards model that includes treatment and presented on a forest plot. If there are too few events available for a meaningful analysis of a particular subgroup (less than 10 events across both treatment arms in comparison in a subcategory), the HR and 95% CI will not be created for the subgroup and only descriptive summaries (number of event and proportion of subjects with events) will be provided.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

7.5.5.2 Other analyses

Analyses to compare treatment effect between the two active treatment arms may be conducted ad hoc if both low dose and high dose treatment arm shows significant results versus the placebo arm.

7.6 Safety

7.6.1 Extent of Exposure

Duration of exposure will be summarized descriptively as a continuous variable in days, and also in the following categories:

- 0 - <2 weeks (14 days);
- 2 - <4 weeks (28 days);
- 4 - <6 weeks (42 days);
- ...;
- 20 - ≤23 weeks (161 days)

The number and percent of subjects who received the premedication will be summarized by visit and overall and treatment arm. The volume and dosage for study treatment infusion will be summarized descriptively by visit or overall and treatment arm.

The number and percent of subjects who have at least 1 infusion interruption, and number and percent of subject who have at least 1 infusion interruption not resumed at any visit as documented in the eCRF will be summarized by visit or overall and treatment arm.

The number of infusion interruptions per subject will be summarized both as a continuous variable using descriptive statistics, and as a categorical variable (categories: 0, 1, and ≥2) by visit or overall and treatment arm. Reasons for the infusion interruptions will also be presented. A reason that was recorded multiple times at different visits for one subject will be counted once for this subject for overall summary. In addition, the number of subjects who have at least 1 infusion interruption resumed at any visit, and the duration of such interruptions will be summarized. A listing will be provided for subjects with any infusion interruptions.

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Treatment compliance will be summarized descriptively by treatment arm for the SAF population. The following percentage compliance categories will also be summarized:

- <60%
- 60 – 79%
- 80 – 100%
- >100%

Subjects who missed 1 or 2 doses of study treatment due to COVID-19 pandemic as permitted by protocol will be summarized separately for exposure duration, total number of doses, and treatment compliance. A swimmer plot will be created for all scheduled study treatment administration from Day 1 to end of study. Events of IP administration, skipping study treatment due to COVID-19 pandemic, or treatment termination will be included.

7.6.2 Adverse Events

All AE data will be listed. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs resulting in death, TEAEs leading to discontinuation of study treatment, and TEAEs of special interests will be produced.

An overview table will summarize the number of all TEAEs, the number and percentage of subjects with at least one of the following TEAEs, by standard of care (none, nintedanib, pirfenidone), treatment arm and overall, where subjects with more than one TEAE in a particular category are counted only once in that category:

- any TEAE;
- any TEAE by relationship (definite, probable, possible, unlikely, none);
- drug-related TEAE;
- any TEAE by severity (mild, moderate, severe, life-threatening consequences, death);
- TEAE leading to study treatment interrupted;
- TEAE leading to study treatment withdrawn;
- TEAE leading to discontinuation from the study;
- Treatment-emergent SAEs;
- drug-related SAE;
- AEOIs
- Each AEOIs
 - [REDACTED]
 - [REDACTED]
 - Respiratory adverse events
 - Acute exacerbation of idiopathic pulmonary fibrosis
- TEAE leading to death;

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

This summary table will be repeated for each of the following COVID-19 vaccination status:

- Subjects vaccinated prior to start of study treatment
- Subjects vaccinated while on treatment
- Subjects not vaccinated

The number and percentage of subjects reporting each TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment arm and overall for the SAF population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and PT;
- TEAEs by PT; this table will also be repeated for each COVID-19 vaccination status as described above;
- TEAEs with frequency >10% in one or more treatment arms by PT;
- TEAEs related to the study treatment, by SOC and PT;
- TEAEs related to the study treatment, by PT;
- TEAEs by relationship to the study treatment, by SOC and PT;
- TEAEs related to pre-medication, by SOC and PT;
- TEAEs by maximum severity and PT;
- TEAEs related to the study treatment by maximum severity and PT;
- TEAEs leading to the study treatment interruption, by SOC and PT;
- TEAEs leading to the study treatment withdrawn, by SOC and PT;
- TEAEs related to the study treatment leading to the study treatment withdrawn, by SOC and PT;
- Serious TEAEs, by SOC and PT;
- Serious TEAEs related to the study treatment, by SOC and PT;
- Serious TEAEs with frequency >5% in one or more treatment arm by PT;

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing severity will be included as severe in the overall count of subjects with AEs, but will not be included in the counts of subjects with AEs within a SOC or PT.

The number and percentage of subjects with at least 1 treatment-emergent AEOI, and each type of treatment-emergent AEOI will be summarized. The number and percentage of subjects reporting at least 1 treatment-emergent AEOI will be summarized by SOC and PT for the following in the SAF population:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- treatment-emergent AEOI by SOC and PT;
- serious treatment-emergent AEOI by SOC and PT;
- treatment-emergent AEOI leading to study treatment interruption by SOC and PT;
- treatment-emergent AEOI leading to study treatment withdrawn by SOC and PT.

- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]

No statistical comparisons of AEs between treatment arms will be performed.

7.6.3 Laboratory Evaluations

All laboratory data will be reported in conventional units. Reference range will be presented in the listing. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

Laboratory data will be summarized by treatment arm, overall, and visit using standard descriptive statistics for the SAF population. Changes from baseline will also be summarized.

For hematology and serum chemistry, shift tables presenting movement in and out of reference range from baseline to each scheduled post-baseline visit will be provided for each treatment arm.

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]

For subjects with abnormal baseline values, the following summary will also be created:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

- ALT or AST >2x Baseline or total bilirubin >1.5x Baseline
- ALT or AST >2x Baseline and a concomitant total bilirubin >2x Baseline
- If baseline measurements were <2.5x ULN: ALT or AST >5x baseline

For all subjects, number of subjects with elevated ALT or AST and Total Bilirubin following the Hy's Law (ALT or AST >3X ULN and Total Bilirubin >2X ULN) will be summarized. The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation. Additionally, Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plots will be generated for peak total bilirubin vs peak ALT and peak AST.

Box-plots of the absolute value of lab tests at each scheduled visit will be provided. All lab tests results will also be listed.

7.6.4 Vital Signs and Pulse Oximetry

Vital signs and SpO₂ data and changes from baseline in vital signs and SpO₂ will be summarized by visit using standard descriptive statistics for the SAF population. For visits that have vital sign data collected before, during, and after study treatment infusion, the pre-infusion vital sign will be included in the summary table. A table for change from pre-infusion will also be provided for the visits with multiple vital sign measurements before, during, and after study treatment infusion. Vital sign findings per subject will be detailed in a listing.

7.6.5 Electrocardiograms

The ECG measurements and changes from baseline in ECG will be listed and summarized by treatment arm and visit using standard descriptive statistics for the SAF population. For visits (visit 4 and visit 8) where both pre-infusion and post-infusion ECG are measured, the pre-infusion ECG will be included in the summary table of change from baseline. In addition, difference of ECG measurements between pre-infusion and post-infusion of study treatment for visit 4 and visit 8 will be listed and summarized.

The number and percent of subjects with the averaged QT interval (msec) and Fridericia's corrected QT (QTcF) interval (msec) meeting below criteria will be summarized by treatment arm for baseline and post-baseline visits:

- QT interval >450 msec;
- QT interval >480 msec;
- QT interval >500 msec;
- QTcF interval >450 msec;
- QTcF interval >480 msec;
- QTcF interval >500 msec.

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

In addition, the number and percentage of subjects with average QT or QTcF interval meeting the following criteria will be summarized by treatment arm for each post-baseline visit:

- change from baseline in QT interval >30 msec;
- change from baseline in QT interval >60 msec;
- change from baseline in QTcF interval >30 msec;
- change from baseline in QTcF interval >60 msec.

ECG overall interpretation (normal, abnormal not clinically significant and abnormal clinically significant) will be presented as a categorical summary by treatment arm and scheduled visit. The ECG measurements and changes from baseline in ECG Shifts from baseline (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) at each post-baseline visit will be presented.

7.6.6 Physical Examination

Physical examination results (normal/abnormal) will be summarized for each visit by treatment arm. Details of abnormalities will be listed for each subject.

7.6.7 Other Safety Analyses

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Serology tests of HIV, HIV-1 RNA, hepatitis B, and hepatitis C as well as SARS-COV-2 will be listed.

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

7.6.9 Impact of COVID-19 Pandemic

The impact of COVID-19 pandemic on subject participation in the study will be summarized by treatment arm (including a total column) and visit with the number and percentage of subjects whose planned study visit was not performed, partially performed, performed by telephone visit, or performed outside of the protocol-specified window. In addition, a summary of subjects who early terminated study treatment or the study due to COVID-19 also will be provided. The subject-level listing will be provided and it will include any alternative procedures used to collect data per the eCRF.

Listing of protocol deviations due to COVID-19 will also be provided.

7.7 Interim Analysis

No formal interim analyses are planned for this study.

8. Changes in Planned Analysis

The following changes from protocol specified statistical analyses are made in this SAP.

Section 3.2 and 7.5.2.4 The efficacy endpoint Time to first acute IPF exacerbation has been updated to Time to first acute IPF exacerbation and death to avoid dependent censoring.

Section 7.5.2.1, 7.5.2.2, 7.5.2.3, and 7.5.5 Analysis of change from baseline in FVC, DLco, HRCT QLF, [REDACTED] will be using random coefficient model instead of ANCOVA. The random coefficient model will handle missing data by making use of all available data include subjects with missing data and no missing value will be imputed.

Section 7.5.3 Sensitivity analysis of FVC will use multiple imputation instead of ANCOVA without missing value imputation.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation

Sponsor Protocol ID: ND-L02-s0201-005

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Appendices

Appendix 1: GAP Algorithm for IPF Stage and Predicted Mortality

GAP IPF stage for each subject will be derived by summing the points in each of the following categories for each randomized subject:

Gender	Points
Male	0
Female	1
Age	
≤60	0
61-65	1
>65	2
Baseline FVC, % Predicted	
>75	0
50-75	1
<50	2
Baseline DLco*, % Predicted	
>55	0
36-55	1
≤35	2
Not Performed	3

*Corrected for hemoglobin

IPF stage for each subject will be assigned based on the total points as follows:

Sum of Points	IPF Stage
0-3	I
4-5	II
6-8	II

Risk of mortality will be derived using the following algorithm:

Step 1: Calculate S

$$S = [0.337 (\text{GENDER}) - 0.015 (\text{FVC} - 68.464) + 0.092 (\text{AGE1} - 67.676) - 0.052 (\text{AGE2}) + 2.237 (\text{DLco1}) + 0.024 (\text{DLco2})] \times 0.909$$

Where:

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

1) GENDER =

- a. 0.293 if the patient is male
- b. -0.707 if the patient is female

2) FVC = FVC, % predicted at baseline

3) AGE1 = patient's age (years)

4) AGE2 = refer to the table below. Enter the value of AGE2 that corresponds to the patient's age.

AGE	AGE2	AGE	AGE2	AGE	AGE2	AGE	AGE2
≤50	0	60	0.236	70	6.345	80	22.043
51	0	61	0.408	71	7.625	81	23.739
52	0	62	0.648	72	9.009	82	25.435
53	0	63	0.968	73	10.481	83	27.130
54	0	64	1.378	74	12.027	84	28.826
55	0	65	1.890	75	13.632	85	30.522
56	0.002	66	2.516	76	15.280	86	32.217
57	0.015	67	3.266	77	16.959	87	33.913
58	0.051	68	4.153	78	18.652	88	35.609
59	0.121	69	5.183	79	20.348	89	37.304

5) DLco1 =

- a. 0.921 if the subject could not do the DLco test
- b. -0.079 if the subject could do the DLco test

6) DLco2 =

- a. -50.549 if the subject could not do the DLco test
- b. (49.451 – the subject's baseline DLco, % predicted) if the subject could do the test

Step 2: Calculate risk using S:

1-year risk = $100 \times [1 - \exp(-\exp(S) \times 0.225)]$

2-year risk = $100 \times [1 - \exp(-\exp(S) \times 0.486)]$

3-year risk = $100 \times [1 - \exp(-\exp(S) \times 0.768)]$

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Appendix 2: Schedule of visits

	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
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
Serology (HCV Ab, HBsAg, HIV 1/2)	X										
SARS-CoV-2 test ^f	X										
Randomization			X								

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

	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	

Premedication (optional) ^w			X		X	X	X	X			
Study treatment			X		X	X	X	X			

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

Note: Refer to Section 18.6 of the protocol 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 of the protocol) [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.

CONFIDENTIAL

Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

^h Vital signs and SpO₂ 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 SpO₂ will be measured thrice: once before the study treatment infusion (if premedication is administered, vital signs should be measured after premedication), midinfusion \pm 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 of the protocol for more information.

[REDACTED]

[REDACTED]

[REDACTED]

[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 of the protocol for guidance on SARS-CoV-2 testing.

[REDACTED]

[REDACTED]

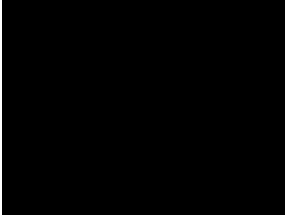
^w Subjects may be premedicated to mitigate the risk of infusion-related reactions at the discretion of the Investigator (see Section 18.5 of the protocol).

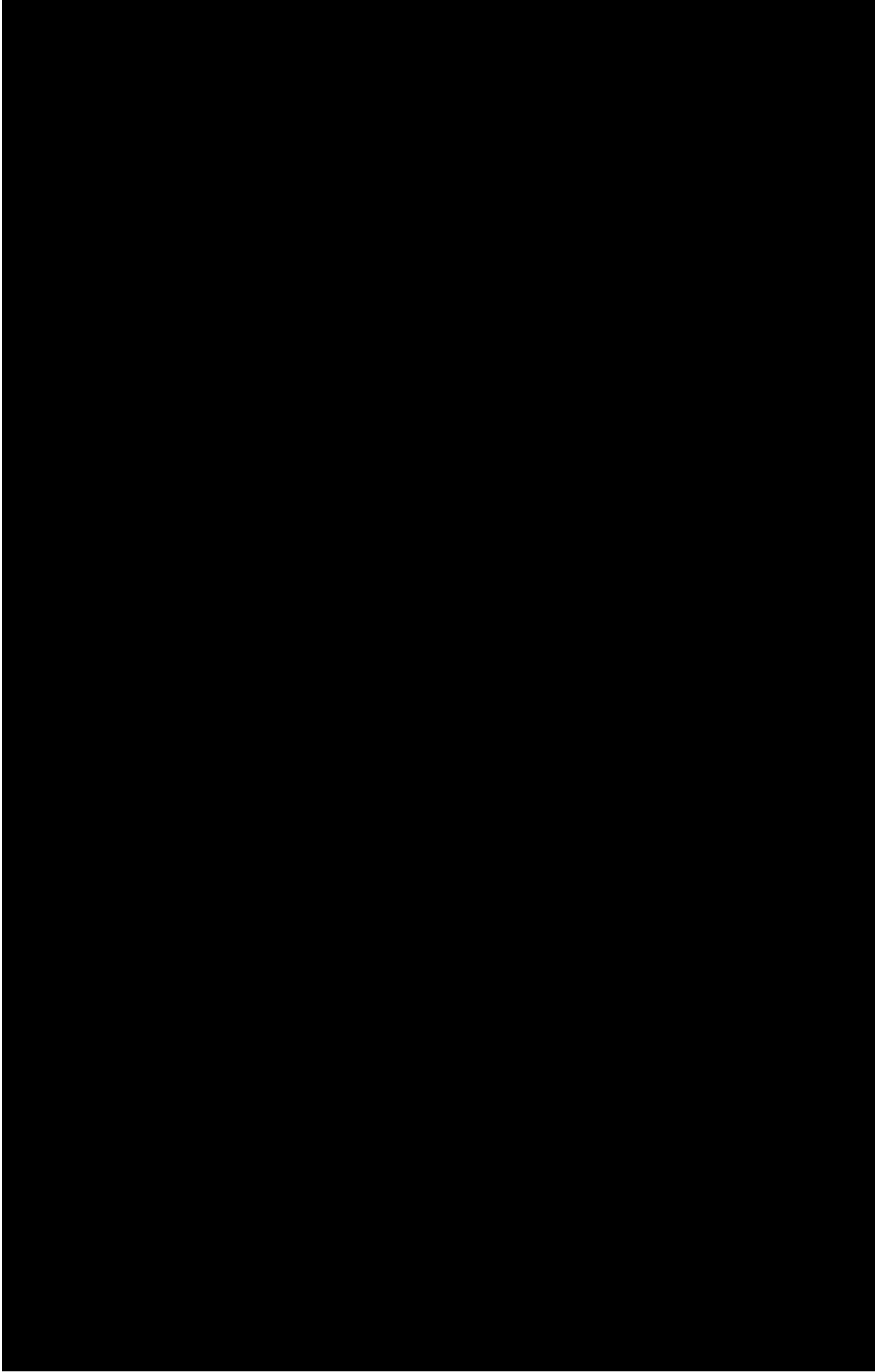
Statistical Analysis Plan

Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

Appendix 3: FVC and %FVC Baseline Determination

The baseline for FVC and %FVC will be determined as per the 
 Specification.





The first part of the paper discusses the importance of the research and the objectives of the study. It then presents a literature review of the existing research on the topic. The next section describes the methodology used in the study, including the data sources and the statistical techniques employed. The results of the study are then presented, followed by a discussion of the findings and their implications. The paper concludes with a summary of the main points and suggestions for further research.

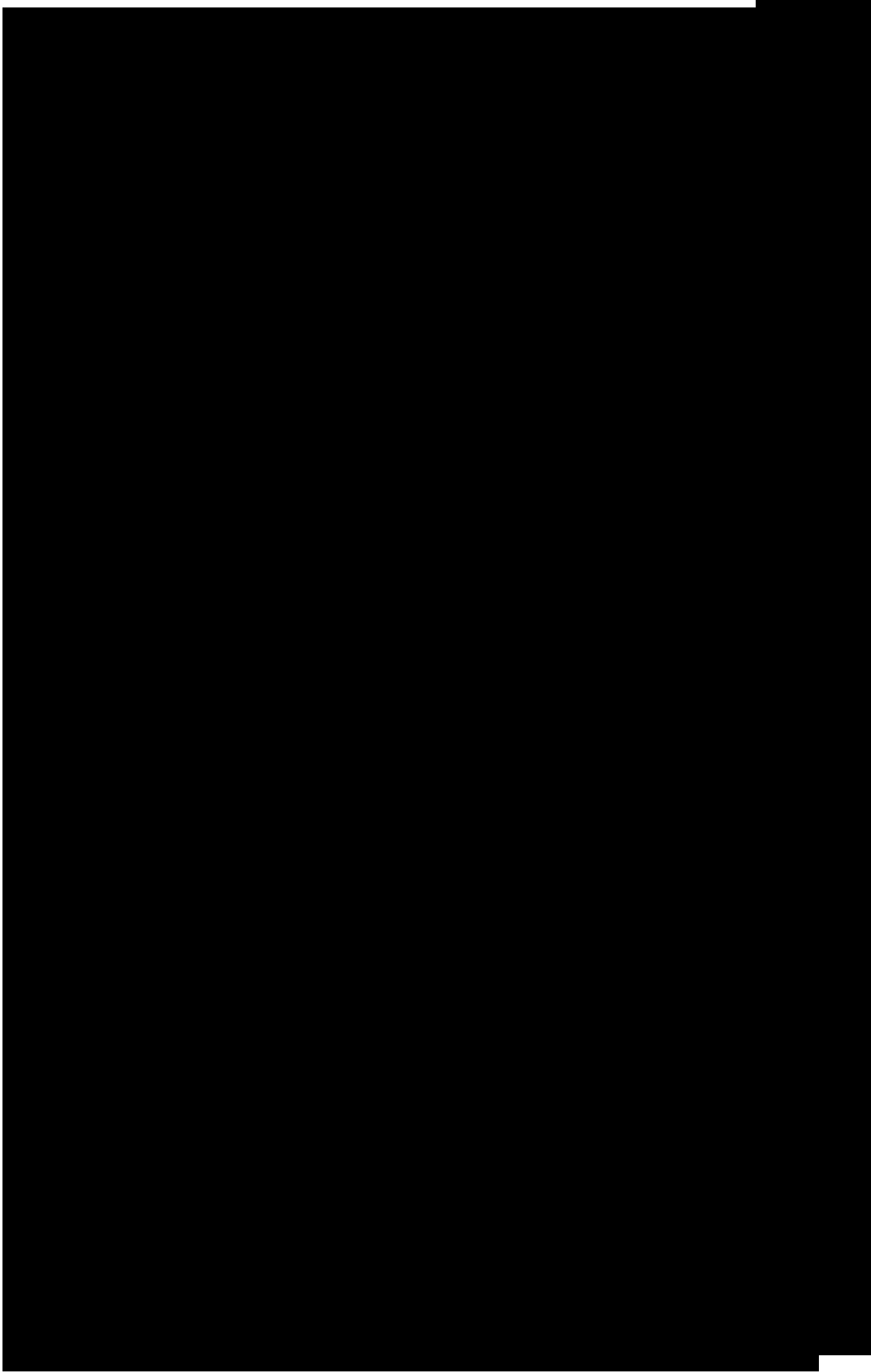
The study was conducted using a quantitative research design. Data was collected from a sample of 100 participants. The data was then analyzed using statistical software to determine the relationships between the variables. The results of the analysis are presented in the following table:

Variable	Mean	Standard Deviation	Minimum	Maximum
Age	35.2	12.5	20	50
Gender	50% Male	0	0	100
Education	12.5	1.5	10	15
Income	\$30,000	\$10,000	\$15,000	\$50,000

The results of the study indicate that there is a significant positive relationship between age and income. This suggests that as age increases, income also tends to increase. The study also found that there is a significant positive relationship between education and income. This suggests that as education increases, income also tends to increase. The study did not find a significant relationship between gender and income.

The implications of the study are that age and education are important factors in determining income. This suggests that individuals should focus on increasing their age and education to increase their income. The study also suggests that gender is not a significant factor in determining income.

Further research is needed to explore the relationships between these variables in more detail. The study was limited by its sample size and the use of self-reported data. Future studies should use larger samples and more objective measures of income.



The first of these is the fact that the system is not a simple one. It is a complex system, and as such, it is not possible to understand it by looking at its parts in isolation. The system is a whole, and its behavior is determined by the interactions between its parts. This is a fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The second of these is the fact that the system is dynamic. It is not a static system, and its behavior changes over time. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The third of these is the fact that the system is open. It is not a closed system, and it interacts with its environment. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The fourth of these is the fact that the system is self-organizing. It is not a system that is imposed from the outside, but one that emerges from the interactions between its parts. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The fifth of these is the fact that the system is resilient. It is not a system that is fragile and easily broken, but one that is able to withstand change and maintain its essential characteristics. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The sixth of these is the fact that the system is adaptable. It is not a system that is rigid and inflexible, but one that is able to change and evolve in response to its environment. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The seventh of these is the fact that the system is sustainable. It is not a system that is designed to last for a short time, but one that is designed to last for a long time. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The eighth of these is the fact that the system is equitable. It is not a system that is designed to benefit a few at the expense of many, but one that is designed to benefit all. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The ninth of these is the fact that the system is just. It is not a system that is designed to be unfair, but one that is designed to be fair. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

The tenth of these is the fact that the system is beautiful. It is not a system that is designed to be ugly, but one that is designed to be beautiful. This is another fundamental principle of systems thinking, and it is one that is often overlooked in traditional approaches to problem-solving.

the 1990s, the number of people in the world who are under 15 years of age has increased by 1.2 billion, from 1.1 billion in 1980 to 2.3 billion in 1999. The number of people aged 65 and over has increased by 0.5 billion, from 0.3 billion in 1980 to 0.8 billion in 1999.

There are a number of reasons why the world population is growing so rapidly. One of the main reasons is that the number of children born to each woman has increased. In 1980, the average woman in the world had 2.5 children. In 1999, the average woman had 2.7 children.

Another reason is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 52 years. In 1999, the average person lived for 72 years.

There are a number of factors that are contributing to the increase in the number of people who are surviving to old age. One of the main factors is that the number of people who are dying from infectious diseases has decreased. In 1980, there were 1.5 million deaths from infectious diseases in the world. In 1999, there were 0.5 million deaths from infectious diseases in the world.

Another factor is that the number of people who are dying from non-communicable diseases has decreased. In 1980, there were 1.5 million deaths from non-communicable diseases in the world. In 1999, there were 0.5 million deaths from non-communicable diseases in the world.

There are a number of factors that are contributing to the decrease in the number of people who are dying from infectious diseases. One of the main factors is that the number of people who are vaccinated against infectious diseases has increased. In 1980, only 10% of the world population was vaccinated against infectious diseases. In 1999, 50% of the world population was vaccinated against infectious diseases.

Another factor is that the number of people who are dying from infectious diseases has decreased because of the development of new drugs. In 1980, there were 1.5 million deaths from infectious diseases in the world. In 1999, there were 0.5 million deaths from infectious diseases in the world.

There are a number of factors that are contributing to the decrease in the number of people who are dying from non-communicable diseases. One of the main factors is that the number of people who are smoking has decreased. In 1980, there were 1.5 million deaths from non-communicable diseases in the world. In 1999, there were 0.5 million deaths from non-communicable diseases in the world.

Another factor is that the number of people who are dying from non-communicable diseases has decreased because of the development of new drugs. In 1980, there were 1.5 million deaths from non-communicable diseases in the world. In 1999, there were 0.5 million deaths from non-communicable diseases in the world.

There are a number of factors that are contributing to the increase in the number of people who are surviving to old age. One of the main factors is that the number of people who are dying from infectious diseases has decreased. In 1980, there were 1.5 million deaths from infectious diseases in the world. In 1999, there were 0.5 million deaths from infectious diseases in the world.

Another factor is that the number of people who are dying from non-communicable diseases has decreased. In 1980, there were 1.5 million deaths from non-communicable diseases in the world. In 1999, there were 0.5 million deaths from non-communicable diseases in the world.

There are a number of factors that are contributing to the decrease in the number of people who are dying from infectious diseases. One of the main factors is that the number of people who are vaccinated against infectious diseases has increased. In 1980, only 10% of the world population was vaccinated against infectious diseases. In 1999, 50% of the world population was vaccinated against infectious diseases.

Another factor is that the number of people who are dying from infectious diseases has decreased because of the development of new drugs. In 1980, there were 1.5 million deaths from infectious diseases in the world. In 1999, there were 0.5 million deaths from infectious diseases in the world.

The first of these is the fact that the system is not a simple one. It is a complex system, and as such, it is not possible to understand it by looking at its parts in isolation. The system is a whole, and it is only by looking at the whole that we can understand it. This is the first principle of systems thinking: the whole is greater than the sum of its parts.

The second principle is that the system is dynamic. It is not a static system, and it is not a system that can be understood by looking at a single point in time. The system is a process, and it is only by looking at the process that we can understand it. This is the second principle of systems thinking: the system is a process.

The third principle is that the system is interconnected. The parts of the system are not isolated, and they are not independent. They are interconnected, and they are interdependent. This is the third principle of systems thinking: the system is interconnected.

The fourth principle is that the system is self-organizing. The system is not a system that is imposed from the outside. It is a system that organizes itself from within. This is the fourth principle of systems thinking: the system is self-organizing.

The fifth principle is that the system is resilient. The system is not a system that is fragile. It is a system that is resilient, and it is only by looking at the system that we can understand it. This is the fifth principle of systems thinking: the system is resilient.

The sixth principle is that the system is adaptable. The system is not a system that is rigid. It is a system that is adaptable, and it is only by looking at the system that we can understand it. This is the sixth principle of systems thinking: the system is adaptable.

The seventh principle is that the system is sustainable. The system is not a system that is unsustainable. It is a system that is sustainable, and it is only by looking at the system that we can understand it. This is the seventh principle of systems thinking: the system is sustainable.

The eighth principle is that the system is equitable. The system is not a system that is inequitable. It is a system that is equitable, and it is only by looking at the system that we can understand it. This is the eighth principle of systems thinking: the system is equitable.

The ninth principle is that the system is just. The system is not a system that is unjust. It is a system that is just, and it is only by looking at the system that we can understand it. This is the ninth principle of systems thinking: the system is just.

The tenth principle is that the system is peaceful. The system is not a system that is violent. It is a system that is peaceful, and it is only by looking at the system that we can understand it. This is the tenth principle of systems thinking: the system is peaceful.

the 1990s, the number of people in the UK who are aged 65 and over has increased by 1.5 million, and the number of people aged 75 and over has increased by 1.2 million (Office of National Statistics 2000). The number of people aged 65 and over is projected to increase to 10.5 million by 2026, and the number of people aged 75 and over to 6.5 million (Office of National Statistics 2000).

There is a growing awareness of the need to develop strategies to meet the needs of the ageing population. The Department of Health (1999) has identified the need to develop a 'new paradigm' of care for the ageing population, which is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible. The 'new paradigm' of care for the ageing population is based on the principles of 'active ageing'. This paradigm is based on the idea that ageing is a process, and that people should be encouraged to remain active and engaged in their communities for as long as possible.

the 1990s, the number of people in the world who are under 15 years of age has increased from 1.1 billion to 1.5 billion. The number of people aged 65 and over has increased from 200 million to 350 million. The number of people aged 15–64 years has increased from 2.5 billion to 3.5 billion.

There are a number of factors which have contributed to the increase in the number of people in the world who are under 15 years of age. These factors include a decline in the death rate, a decline in the birth rate, and a decline in the rate of migration.

The decline in the death rate has been the most significant factor in the increase in the number of people in the world who are under 15 years of age. This decline has been due to a number of factors, including improvements in medical care, a decline in the incidence of infectious diseases, and a decline in the incidence of violence.

The decline in the birth rate has also contributed to the increase in the number of people in the world who are under 15 years of age. This decline has been due to a number of factors, including a decline in the number of children born to women, a decline in the number of children born to men, and a decline in the number of children born to couples.

The decline in the rate of migration has also contributed to the increase in the number of people in the world who are under 15 years of age. This decline has been due to a number of factors, including a decline in the number of people who are migrating from one country to another, a decline in the number of people who are migrating from one region to another, and a decline in the number of people who are migrating from one social class to another.

The increase in the number of people in the world who are under 15 years of age has a number of implications. These implications include a decline in the number of people who are in the workforce, a decline in the number of people who are paying taxes, and a decline in the number of people who are contributing to the economy.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the environment. These implications include a decline in the number of people who are using natural resources, a decline in the number of people who are polluting the environment, and a decline in the number of people who are contributing to climate change.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the future. These implications include a decline in the number of people who are living in poverty, a decline in the number of people who are living in slums, and a decline in the number of people who are living in the developing world.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the quality of life. These implications include a decline in the number of people who are healthy, a decline in the number of people who are educated, and a decline in the number of people who are employed.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the future of the world. These implications include a decline in the number of people who are living in peace, a decline in the number of people who are living in freedom, and a decline in the number of people who are living in a just and equitable world.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the future of the planet. These implications include a decline in the number of people who are living in a sustainable world, a decline in the number of people who are living in a world that is free from poverty, and a decline in the number of people who are living in a world that is free from violence.

The increase in the number of people in the world who are under 15 years of age also has a number of implications for the future of humanity. These implications include a decline in the number of people who are living in a world that is free from suffering, a decline in the number of people who are living in a world that is free from pain, and a decline in the number of people who are living in a world that is free from death.

the first of these is the fact that the majority of the population is now living in urban areas. This has led to a concentration of people in a few large cities, which has in turn led to a number of problems. One of the most serious is the problem of housing. In many of these large cities, the housing is of a very poor quality and is often overcrowded. This leads to a number of health problems, including the spread of disease. Another problem is the problem of pollution. The concentration of people in a few large cities has led to a concentration of factories and other sources of pollution. This has led to a number of health problems, including the spread of disease. A third problem is the problem of unemployment. In many of these large cities, the majority of the population is unemployed. This leads to a number of health problems, including the spread of disease.

The second of these is the fact that the majority of the population is now living in rural areas. This has led to a number of problems. One of the most serious is the problem of food. In many of these rural areas, the majority of the population is engaged in agriculture. This leads to a number of health problems, including the spread of disease. Another problem is the problem of education. In many of these rural areas, the majority of the population is illiterate. This leads to a number of health problems, including the spread of disease. A third problem is the problem of health care. In many of these rural areas, there is a lack of health care facilities. This leads to a number of health problems, including the spread of disease.

The third of these is the fact that the majority of the population is now living in a few large cities. This has led to a number of problems. One of the most serious is the problem of housing. In many of these large cities, the housing is of a very poor quality and is often overcrowded. This leads to a number of health problems, including the spread of disease. Another problem is the problem of pollution. The concentration of people in a few large cities has led to a concentration of factories and other sources of pollution. This has led to a number of health problems, including the spread of disease. A third problem is the problem of unemployment. In many of these large cities, the majority of the population is unemployed. This leads to a number of health problems, including the spread of disease.

The fourth of these is the fact that the majority of the population is now living in a few large cities. This has led to a number of problems. One of the most serious is the problem of housing. In many of these large cities, the housing is of a very poor quality and is often overcrowded. This leads to a number of health problems, including the spread of disease. Another problem is the problem of pollution. The concentration of people in a few large cities has led to a concentration of factories and other sources of pollution. This has led to a number of health problems, including the spread of disease. A third problem is the problem of unemployment. In many of these large cities, the majority of the population is unemployed. This leads to a number of health problems, including the spread of disease.

The fifth of these is the fact that the majority of the population is now living in a few large cities. This has led to a number of problems. One of the most serious is the problem of housing. In many of these large cities, the housing is of a very poor quality and is often overcrowded. This leads to a number of health problems, including the spread of disease. Another problem is the problem of pollution. The concentration of people in a few large cities has led to a concentration of factories and other sources of pollution. This has led to a number of health problems, including the spread of disease. A third problem is the problem of unemployment. In many of these large cities, the majority of the population is unemployed. This leads to a number of health problems, including the spread of disease.

The sixth of these is the fact that the majority of the population is now living in a few large cities. This has led to a number of problems. One of the most serious is the problem of housing. In many of these large cities, the housing is of a very poor quality and is often overcrowded. This leads to a number of health problems, including the spread of disease. Another problem is the problem of pollution. The concentration of people in a few large cities has led to a concentration of factories and other sources of pollution. This has led to a number of health problems, including the spread of disease. A third problem is the problem of unemployment. In many of these large cities, the majority of the population is unemployed. This leads to a number of health problems, including the spread of disease.

the 1990s, the number of people in the world who are under 15 years of age has increased by 1.2 billion, from 1.1 billion in 1980 to 2.3 billion in 1999. The number of people aged 15 years and over has increased by 1.1 billion, from 1.1 billion in 1980 to 2.2 billion in 1999.

There are a number of reasons why the world population is growing so rapidly. One of the main reasons is that the number of children born to each woman has increased. In 1980, the average woman in the world had 2.5 children. In 1999, the average woman in the world had 2.7 children.

Another reason why the world population is growing so rapidly is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

[The following text is a dense, continuous block of illegible characters and symbols, likely representing a corrupted or redacted document. It contains no discernible words or structure.]

100

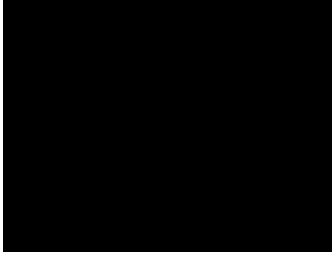
Statistical Analysis Plan

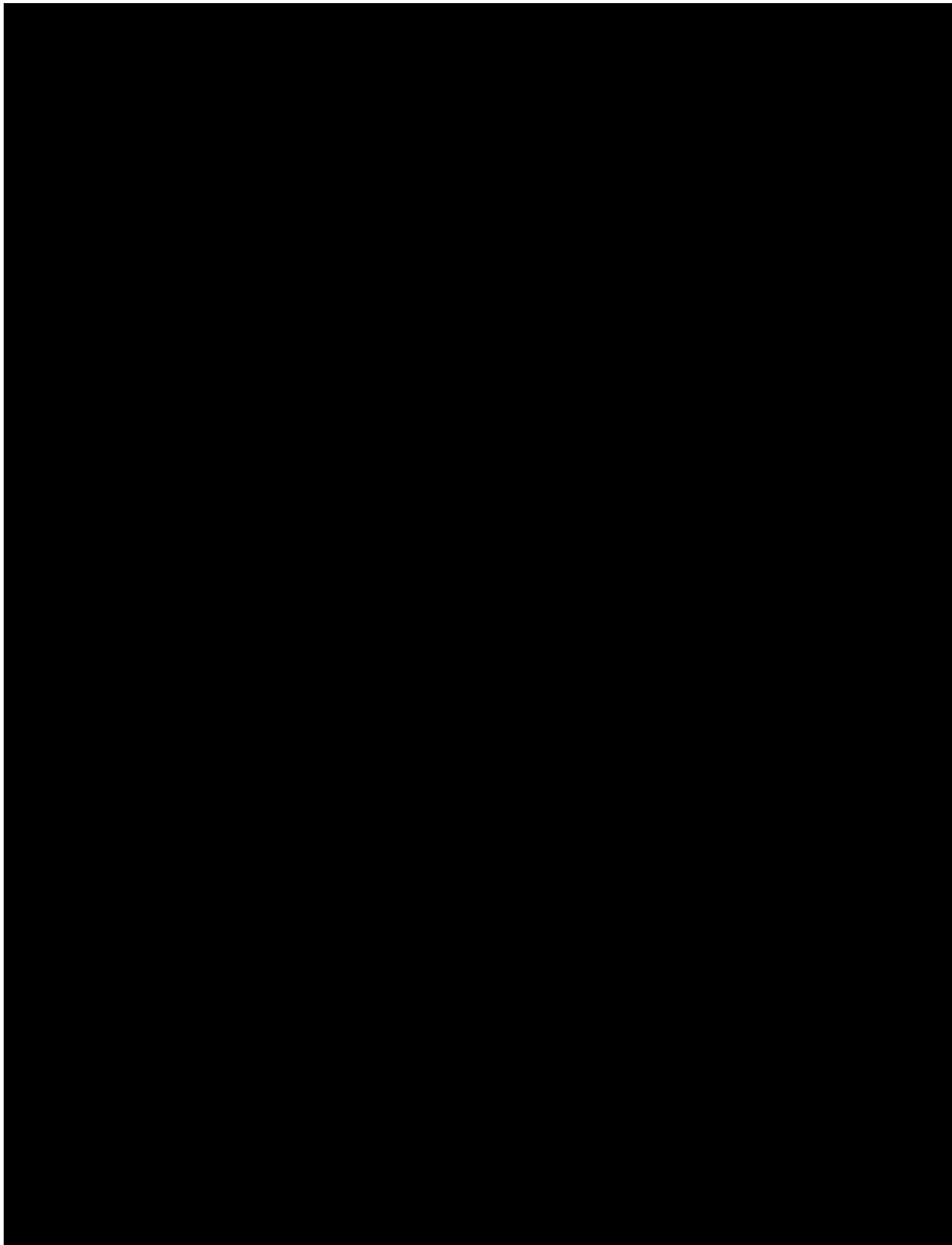
Sponsor Name: Nitto Denko Corporation
Sponsor Protocol ID: ND-L02-s0201-005

[REDACTED]

Appendix 4: HRCT Assessment

The qualitative and quantitative HRCT assessments are included in the [REDACTED]
Independent Review Charter V 3.0.





the 1990s, the number of people in the world who are under 15 years of age has increased from 1.1 billion to 1.5 billion, and the number of people aged 65 and over has increased from 0.2 billion to 0.5 billion (United Nations 1999).

There are a number of reasons why the world population is ageing. First, the number of people who are under 15 years of age has decreased from 1.1 billion in 1990 to 0.9 billion in 1999. This is due to a decline in the birth rate, which has been caused by a number of factors, including a decline in the number of children born to women, a decline in the number of children born to women who are under 15 years of age, and a decline in the number of children born to women who are over 35 years of age.

Second, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

Third, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

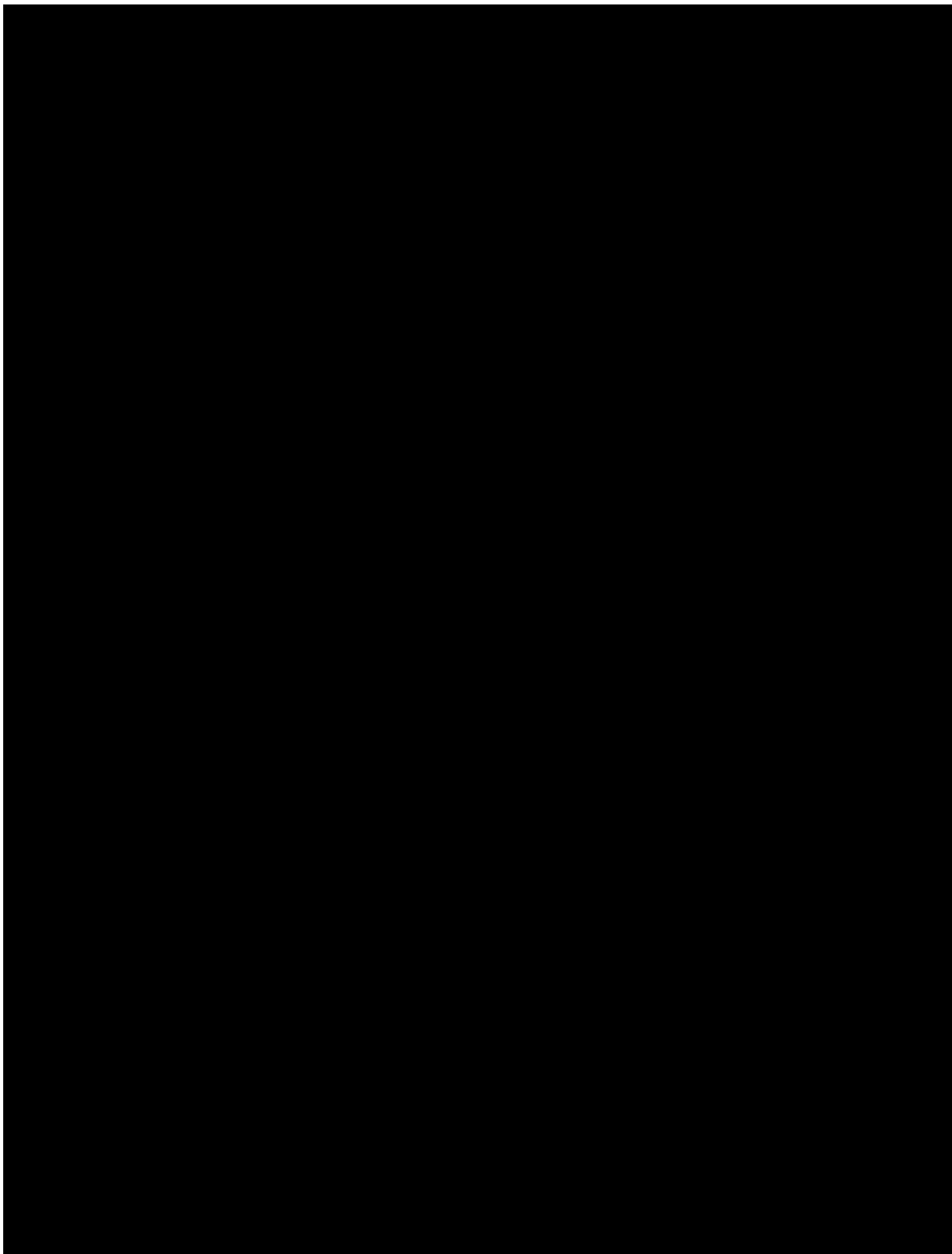
Fourth, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

Fifth, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

Sixth, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

Seventh, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.

Eighth, the number of people who are 65 years of age and over has increased from 0.2 billion in 1990 to 0.5 billion in 1999. This is due to a decline in the death rate, which has been caused by a number of factors, including a decline in the number of people who die from infectious diseases, a decline in the number of people who die from non-infectious diseases, and a decline in the number of people who die from accidents.



the 1990s, the number of people in the UK who are aged 65 and over has increased from 10.5 million to 12.5 million, and the number of people aged 75 and over has increased from 4.5 million to 6.5 million (Office for National Statistics 2000). The number of people aged 65 and over is projected to increase to 15.5 million by 2020, and the number of people aged 75 and over to 8.5 million (Office for National Statistics 2000).

There is a growing awareness of the need to develop strategies to meet the needs of older people, and to ensure that they are able to live independently and actively in their own homes for as long as possible. This has led to a number of initiatives, including the development of age-friendly communities, and the establishment of age-friendly networks.

Age-friendly communities are communities that are designed to be accessible and inclusive for older people. They are communities that offer a range of services and facilities that meet the needs of older people, and that encourage them to participate in community life.

Age-friendly networks are networks of organizations and individuals that work together to support older people. They provide a range of services and facilities, and they encourage older people to participate in community life.

There are a number of factors that can contribute to the development of age-friendly communities and age-friendly networks. These factors include the availability of services and facilities, the willingness of older people to participate in community life, and the support of local authorities and other organizations.

There are a number of challenges that need to be addressed in order to develop age-friendly communities and age-friendly networks. These challenges include the need to ensure that services and facilities are accessible to older people, the need to encourage older people to participate in community life, and the need to secure the support of local authorities and other organizations.

There are a number of strategies that can be used to address these challenges. These strategies include the development of age-friendly communities, the establishment of age-friendly networks, and the provision of services and facilities that meet the needs of older people.

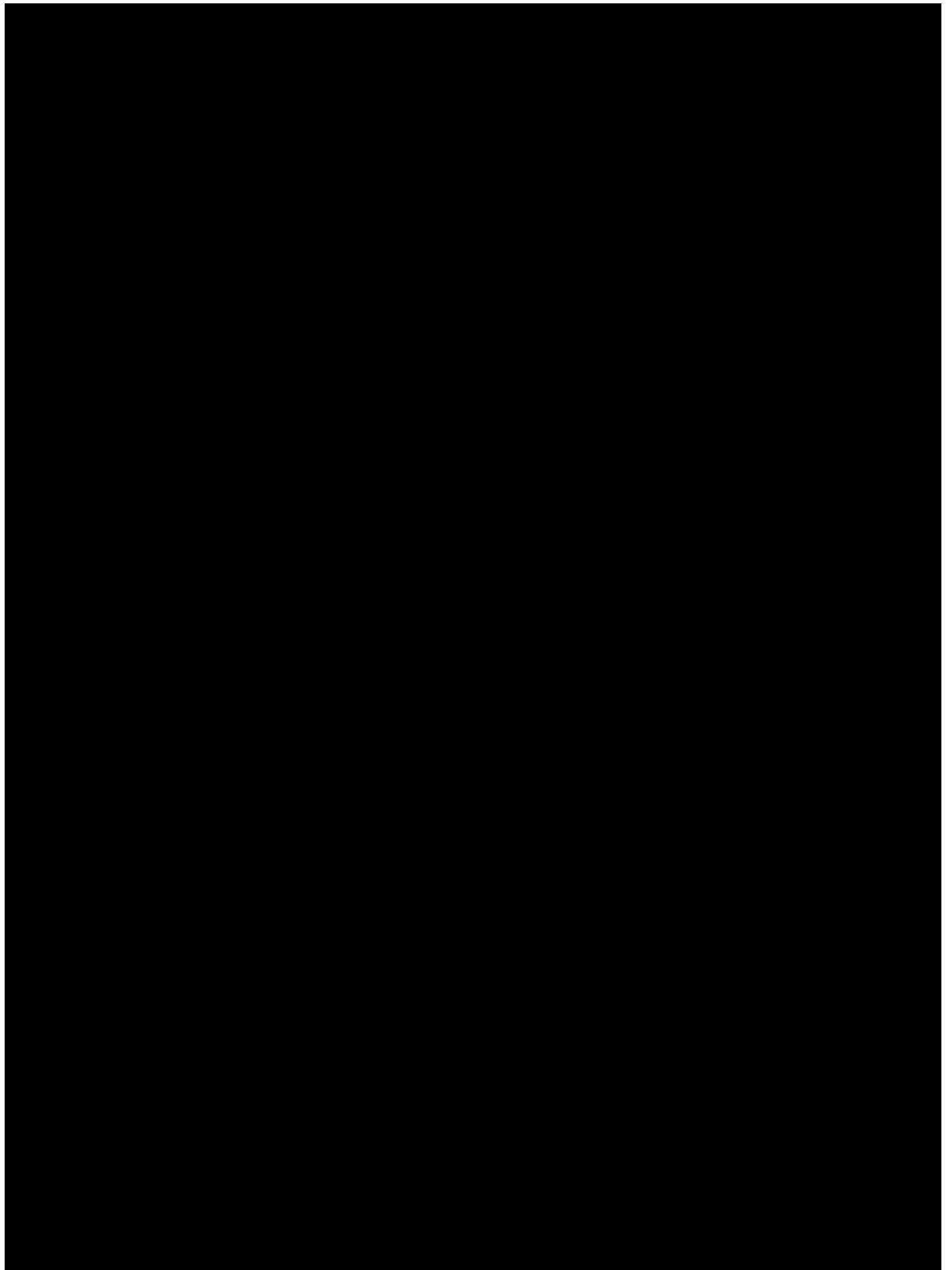
There are a number of benefits that can be realized from the development of age-friendly communities and age-friendly networks. These benefits include the ability to live independently and actively in one's own home for as long as possible, the ability to participate in community life, and the ability to receive the support and services that are needed.

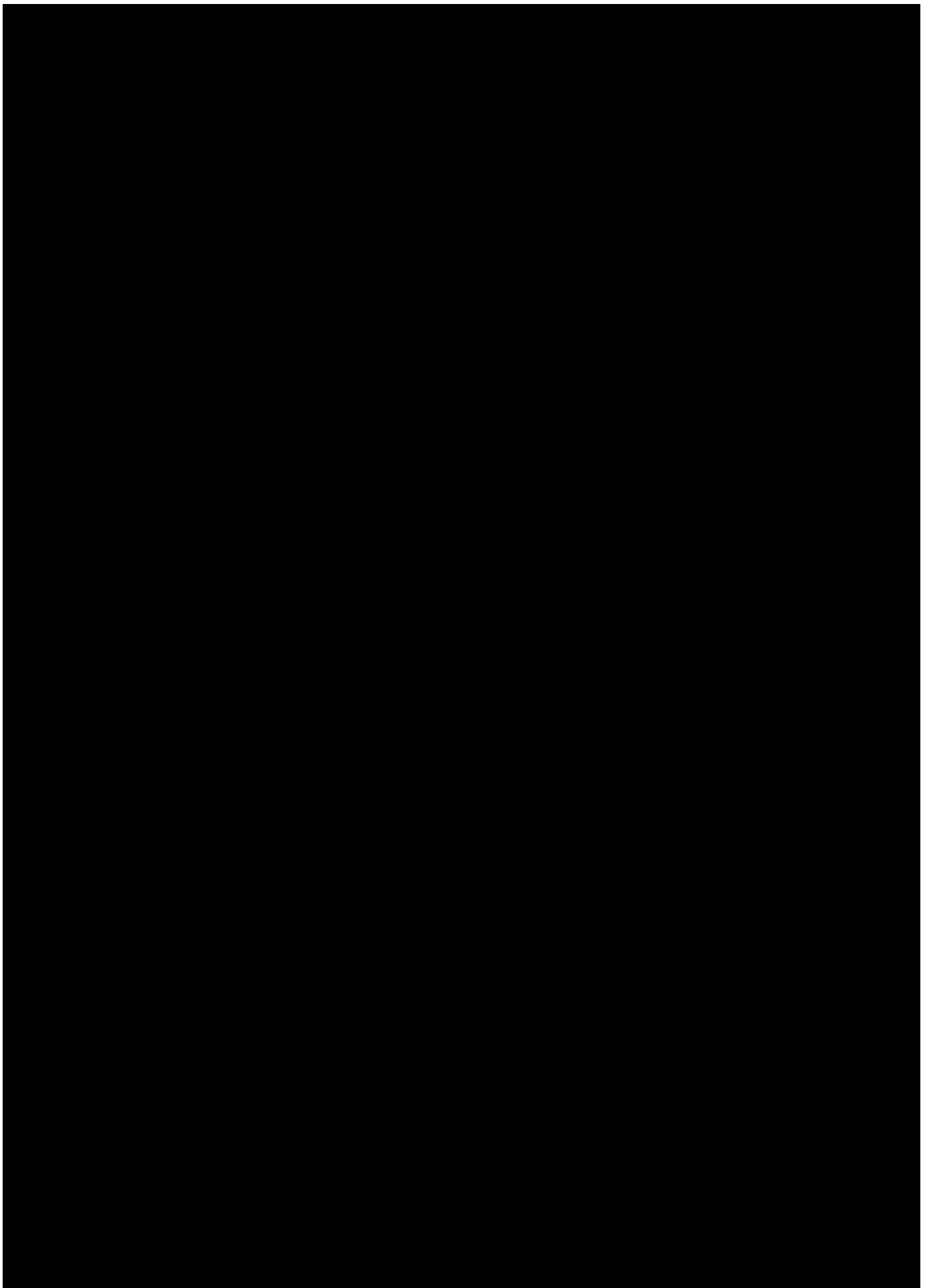
There are a number of organizations and individuals that are working to develop age-friendly communities and age-friendly networks. These organizations and individuals include local authorities, community organizations, and older people themselves.

The first part of the paper discusses the importance of the research and the objectives of the study. It then presents a literature review of the existing research on the topic. The second part of the paper describes the methodology used in the study, including the data collection and analysis techniques. The third part of the paper presents the results of the study, and the fourth part discusses the conclusions and implications of the findings.

The study was conducted in a laboratory setting, and the data was collected using a series of experiments. The results of the study show that there is a significant difference between the two groups, and this difference is statistically significant. The findings of the study have important implications for the field of research, and they provide a basis for further research in this area.

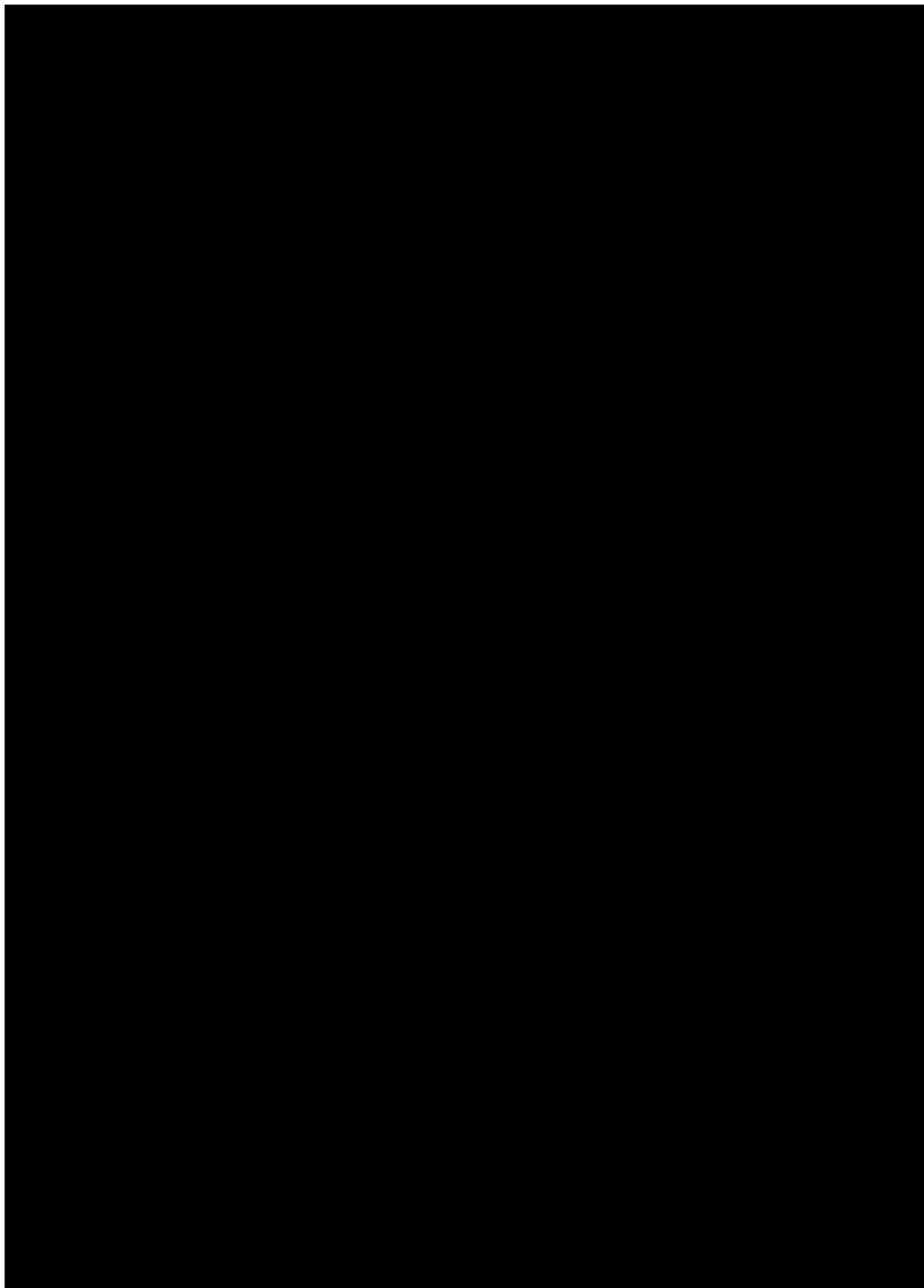
In conclusion, the study has shown that there is a significant difference between the two groups, and this difference is statistically significant. The findings of the study have important implications for the field of research, and they provide a basis for further research in this area.





[The following text is a dense, continuous block of characters and symbols, likely representing a corrupted or heavily redacted document. It contains no legible words or phrases.]

[The following text is a dense, continuous block of illegible characters and symbols, likely representing a corrupted or redacted document. It contains no discernible words or structure.]

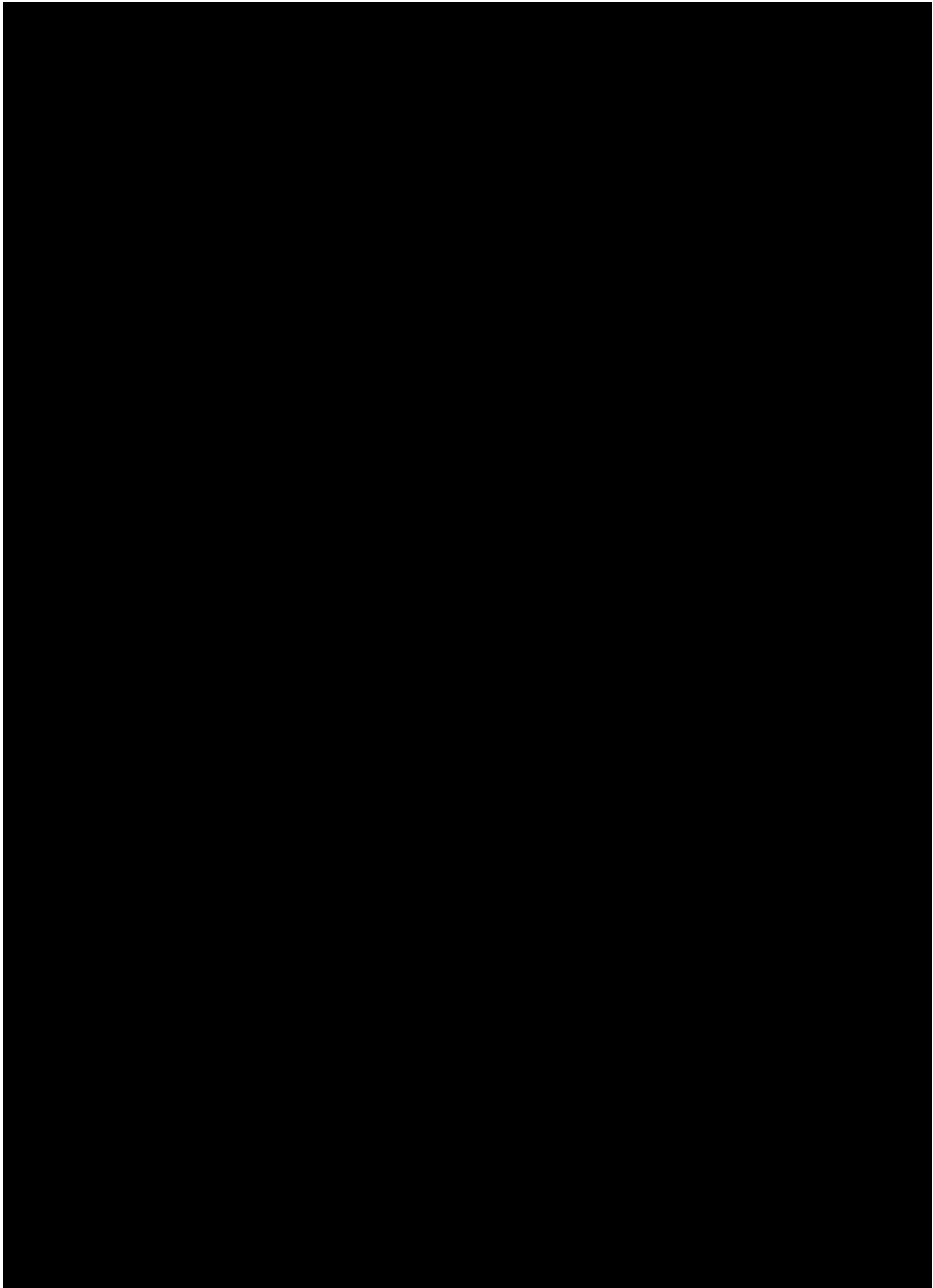


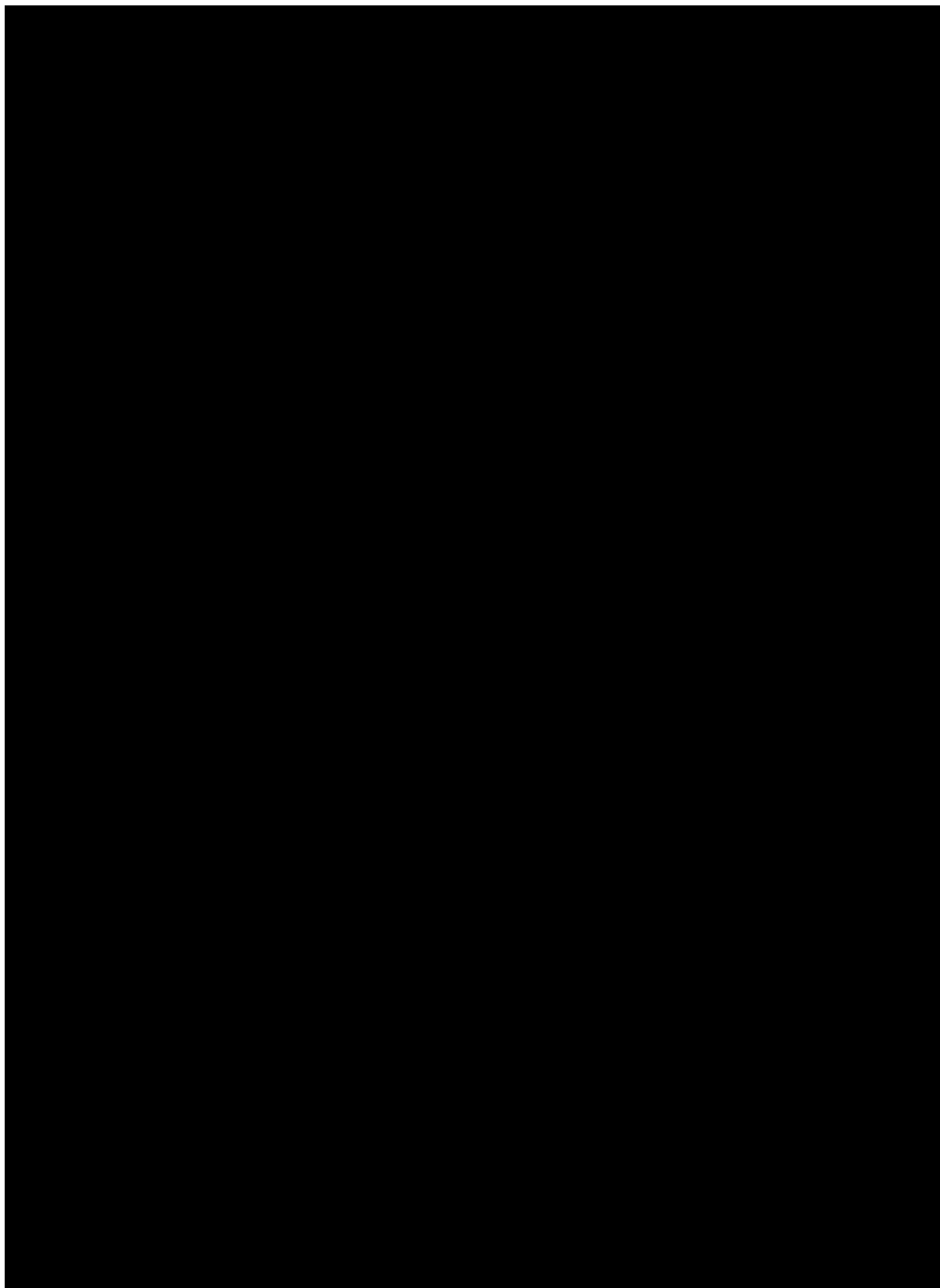
The first part of the paper discusses the importance of the research and the objectives of the study. It then presents a literature review of the existing research on the topic. The second part of the paper describes the methodology used in the study, including the data collection and analysis techniques. The third part of the paper presents the results of the study, and the fourth part discusses the conclusions and implications of the findings.

The study was conducted using a quantitative research design. Data was collected from a sample of 100 participants, and the results were analyzed using statistical software. The findings of the study indicate that there is a significant relationship between the variables being studied.

The results of the study suggest that the research objectives have been achieved. The findings provide valuable insights into the topic and have implications for future research.

In conclusion, the study has shown that the research objectives have been achieved and that the findings have implications for future research.





The first part of the paper discusses the importance of the research and the objectives of the study. It then presents a literature review of the existing research on the topic. The second part of the paper describes the methodology used in the study, including the data collection and analysis techniques. The third part of the paper presents the results of the study, and the fourth part discusses the conclusions and implications of the findings.

The research was conducted using a quantitative approach, and the data was collected from a sample of participants. The results of the study indicate that there is a significant relationship between the variables being studied. The findings suggest that the research has important implications for the field, and further research is needed to explore the topic in more detail.

In conclusion, the study has provided valuable insights into the research topic, and the findings have important implications for the field. The research was conducted using a rigorous methodology, and the results are reliable and valid. The findings suggest that the research has important implications for the field, and further research is needed to explore the topic in more detail.

