

Global Clinical Development - General Medicine

IDD001D Electronic Remote Patient Monitoring

Clinical Trial Protocol CIDD001D2402 / NCT03379233

A 24-week randomized, controlled, multicenter, open-label study to evaluate the effect of reminder notifications and motivational/adaptive messaging on treatment adherence of COPD subjects receiving Ultibro[®] Breezhaler[®] treatment using the Concept2 inhaler for dose administration and tracking

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Clinical Trial Protocol Template Version 3.4 (May 2017)



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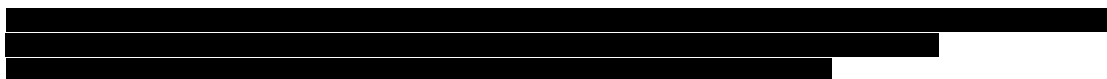
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List of abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ANCOVA	Analysis of Covariance Model
AVRF	Audiovisual Reminder Function
BIPQ	Brief Illness Perceptions Questionnaire
BPH	Benign Prostatic Hyperplasia
BMI	Body Mass Index
BMQ	Beliefs about Medicine Questionnaire
CDS	Core Data Sheet
CE	Conformité Européenne
CFR	US Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPO	Country Pharma Organization
CRO	Clinical Research Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form
CTFG	Clinical Trial Facilitation Group
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
ER	Emergency Room
EU	European Union
FAS	Full Analysis Set
FEV ₁	Forced expiratory volume in 1 second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GVP	Guideline on Good Pharmacovigilance Practices
hCG	human Chorionic Gonadotropin
β-hCG	Beta- human Chorionic Gonadotropin
IB	Investigator Brochure
ICH	International Council for Harmonization
ICF	Informed Consent Form
ICS	Inhaled corticosteroids



ID	Identification
IFU	Instructions for use
IEC	Independent Ethics Committee
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISM	Industrial, Scientific and Medical
IUD	Intrauterine device
IUS	Intrauterine system
LABA	Long-Acting Beta-Adrenoceptor agonists
LAMA	Long-Acting Muscarinic Agents
MARS	Medication Adherence Rating Scale
MEDDEV	Medical devices
MedDRA	Medical Dictionary for Regulatory Activities
nPI	National Prescribing Information
PIT	Preferred Inhalation Time
PPS	Per-Protocol Set
prn	pro re nata
PSW	Premature subject withdrawal
QM	Quality Management
QoL	Quality of Life
RAN	Randomized
SABA	Short-Acting β 2-Adrenergic agonist
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Specific Absorption Rate
SGRQ-C	St. George's Respiratory Questionnaire
SMS	Short Message Service
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
UK	United Kingdom
US	United States
USADE	Unanticipated serious adverse device effect
WIFI	Wireless Local Area Network



WHO World Health Organization



Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug/treatment	The drug or treatment whose properties are being tested in the study.
Investigational medical device	Medical device being assessed for safety or performance in a clinical investigation This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.
Medication number	A unique identifier on the label of each medication/inhaler kit
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could



	contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each subject upon signing the informed consent
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of the study drug intervention and/or assessments; at this time the intervention, and all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject.
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject. Per European Union (EU) Regulation 536/2014 the start of a clinical trial' means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol.
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the



	definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data



Amendment 1

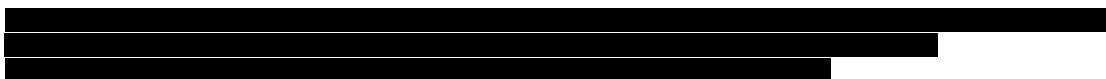
Amendment rationale

This amendment addresses comments received from the Ethics Committees and Health Authorities to clarify study procedures and includes editorial changes related to the new Novartis protocol template regarding data protection measures.

Recruitment for the study has not initiated as of the time of this protocol amendment finalization.

Changes to the protocol:

- The classification of this study has been changed to ‘an open label controlled trial’ instead of ‘single blind’ to match with the study procedures already planned for the trial.
- The trial phase has been changed from Proof of Concept to Phase III since the Investigational Medicinal Product is a registered/ approved product being investigated in this trial with unapproved Concept2 inhaler and the trial is intended to support registration of the Concept 2 inhaler with the DAS with potential inclusion in Summary of Product Characteristics (SmPC).
- The study design has been amended to use only a single written informed consent form (ICF) required to be signed by subjects at the start of the clinical trial, instead of two ICFs planned to be used in the earlier study design. The second ICF is therefore no longer required.
- Inclusion Criteria 4 has been altered to include subjects who have either (spirometric) post-bronchodilator OR pre-bronchodilator forced expiratory volume in 1 second (FEV₁) in the last year, if the Chronic Obstructive Pulmonary Disease (COPD) diagnosis was confirmed with (spirometric) post-bronchodilator FEV₁/forced vital capacity (FVC) <0.7 in the past. This is reflected in the protocol summary and Section 5.1. The reason to change this inclusion criteria is to also allow subjects with a historical COPD diagnosis (>1 year) to be included in the trial to reflect the routine medical practice in the participating countries.
- Exclusion criteria 2 has been updated to reflect the contraception requirements as defined in the Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials (Version Final 2014-09-15). The changes are reflected in the protocol summary and Section 5.2.
- The glossary of terms is updated to include the definition of personal data, and clarify the definition of withdrawal of consent - which is also updated in Section 9.1.2. Additional terms which are used in the protocol have been added for more clarity.
- Section 6.5 is updated to clarify that the Ultibro® Breezhaler® capsules used in the trial for treatment is a clinical trial formulation of the Ultibro® Breezhaler® capsules
- The definition of end of study is added to Section 9.2.
- The timelines for Serious Adverse Device Event (SADE) safety reporting have been updated to reflect Medical Devices (MEDDEV) 2.7/3 revision 3, May 2015 regulations. Changes are reflected in Section 10.2.2.2.
- Section 6.4 has been clarified and table 6.2 inserted to document the blinding procedures in the study.



- Sections 4, 7 and 9 have been introduced as per new Novartis protocol template. As a result section numbers for some of the other sections have changed.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through for deletions and underlining for insertions.

The described changes pertaining to the aforementioned amendment rationale are implemented throughout the protocol.

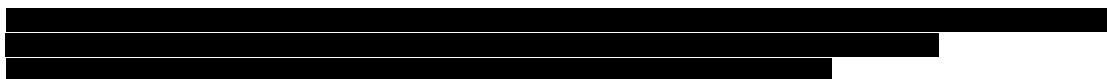


Protocol summary

Protocol number	CIDD001D2402
Title	A 24-week randomized, controlled, multicenter, open-label study to evaluate the effect of reminder notifications and motivational/adaptive messaging on treatment adherence of COPD subjects receiving Ultibro [®] Breezhaler [®] treatment using the Concept2 inhaler for dose administration and tracking
Brief title	A 24-week randomized, controlled study in subjects with Chronic Obstructive Pulmonary Disease (COPD) to evaluate the effect of reminders and motivational/adaptive messages on their treatment adherence tracked by the Concept2 inhaler
Sponsor and Clinical Phase	Novartis
Investigation type	Devices
Study type	Phase 3
Purpose and rationale	This study will evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages over 24 weeks on treatment adherence behavior in subjects with COPD. The dose tracking is done by the Concept2 inhaler and the reminder notifications, feedback on inhaler use and motivational/adaptive messages are sent by the patient application.
Primary Objective(s)	The two primary objectives of this trial are to evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks for (1) on-time treatment adherence (2) total treatment adherence
Secondary Objectives	The secondary objectives are to evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks for (1) on-time adherence over the last four weeks of the Interventional period (2) total adherence over the last four weeks of the Interventional period
Study design	This is a 24 weeks multicenter, randomized, controlled, open label parallel-group study.
Population	The study population will consist of approximately 146 male and female adults age 18 years and older, with a clinical diagnosis of COPD (spirometric grade 2 or 3 according to GOLD 2017 criteria), a smoking history of at least 10 pack years, receiving COPD



	<p>maintenance treatment with Ultibro® Breezhaler® for at least 3 months prior to screening and with a known poor treatment adherence.</p>
<p>Key Inclusion criteria</p>	<ol style="list-style-type: none"> 1. a Signed informed consent must be obtained prior to participation in the study 2. Male and female adults aged ≥ 18 years. 3. Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years). 4. a A historical diagnosis of COPD confirmed by a post-bronchodilator $FEV_1/FVC < 0.70$ in the past and a pre-bronchodilator or post bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of the predicted normal value within the last year. 5. Have been taking Ultibro® Breezhaler® for at least 3 months prior to Visit 1 (in accordance with the local product label). 6. Have a total adherence of more than 10% but less than or equal to 70% during Screening period. Total adherence is defined as percentage of days on which the subject inhaled a dose of Ultibro® Breezhaler®. 7. Have been in the Screening period ≥ 35 days.
<p>Key Exclusion criteria</p>	<ol style="list-style-type: none"> 1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin(hCG) laboratory test. 2. a Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during the study. 3. Subjects contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof: <ul style="list-style-type: none"> • anticholinergic agents • long and short acting beta-2 agonists • sympathomimetic amines 4. Subjects contraindicated for having a history of reactions/ hypersensitivity to lactose or any of the other excipients of trial medication. 5. Subjects with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. 6. Subjects with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. Benign Prostatic



	<p>Hyperplasia (BPH) subjects who are stable on treatment can be considered.</p> <ol style="list-style-type: none">7. Subjects who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in 6 weeks prior to Visit 1.8. Subjects who develop a COPD exacerbation between screening (Visit 1) and prior to intervention (Visit 110) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.9. Subjects who have had a respiratory tract infection within 3 weeks prior to Visit 1.10.a Subjects who develop a respiratory tract infection between screening (Visit 1) and prior to intervention (Visit 110) will not be eligible, but will be permitted to be re-screened after a minimum of 3 weeks after the resolution of the respiratory tract infection.11. Subjects with a current diagnosis of asthma.12. Subjects with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, and pulmonary tuberculosis).13. Use of investigational drugs or other investigational devices at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.14. Subjects with a preferred inhalation time (PIT) between 10.00 pm and 2.00 am.15. Subjects taken off Ultibro® Breezhaler® treatment/inhaler use by the investigator during the Screening period for more than 7 days.16. Subjects not returning all Concept2 inhalers received during the Screening period, for the calculation of total adherence before randomization at Visit 110.17. Subjects who have demonstrated inability or unwillingness to use the digital system or to fill in questionnaires.
Study intervention	<p>The intervention in this study consists solely of the use of an investigational digital system, consisting of the patient application and the Concept2 inhaler. The digital system will be used in half of the subjects while the other group (control) will receive Usual Care delivered by the Concept2 inhaler, with no patient application. The drug treatment in this trial is not under investigation. All subjects in this study will receive daily Ultibro® Breezhaler® treatment as prescribed by their physician prior to their inclusion in the study. In this study the clinical trial formulation of Ultibro® Breezhaler® (capsules 110/50 µg) medicinal product will be provided to the subjects.</p>



	<p>The Concept2 inhaler will track subjects' treatment adherence with the once daily dosing regimen for Ultibro[®] Breezhaler[®] capsules. The digital adherence system, in addition, enables the real-time, wireless transfer of inhaler use data recorded by the Concept2 inhaler, to the patient application. These inhaler data are then interpreted and specific appropriate feedback to the subject are provided. Such feedback may include reminders to inhale medication, motivational/adaptive messages to encourage adherence with the treatment regimen and reports on inhaler use (daily, weekly, monthly).</p>
Efficacy assessments	<ul style="list-style-type: none"> • On-time treatment adherence • Total treatment adherence <div style="background-color: black; width: 100%; height: 20px; margin-top: 5px;"></div>
Key safety assessments	<ul style="list-style-type: none"> • COPD exacerbations regardless of suspected causality to concomitant treatments will be recorded into the Case Report Form (CRF) page(s) capturing the AE/SAE. • Device deficiencies/Device Events • Drug administration error, inhaler overuse, incorrect dose administration notified by the subject • New findings/updates in relation to already reported events • Adverse Events (AEs) and Adverse Device Effects (ADEs) • Serious adverse events (SAEs) and Serious Adverse Device Effects (SADEs) • Physical Examination • Vital signs • Height and weight • Highly sensitive urine or serum pregnancy test (for females of childbearing potential), and in case of positive testing, serum pregnancy test (β-hCG)
Other assessments	None
Data analysis	<p>The primary objectives are to determine whether the use of dose tracking by the Concept2 inhaler in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application can improve on-time adherence or total adherence over 24 weeks of intervention.</p> <p>On-time adherence is defined as the percentage of days on which the subject inhaled at least one dose within (\pm) 2 hours of the agreed preferred daily inhalation time. The daily inhalation time must be defined by the subject at the start of the study and can only be modified at scheduled study visits by the study investigator at the request of the subject.</p>



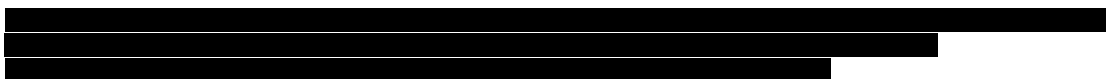
	<p>Total adherence is defined as the percentage of days on which the subject inhaled at least one dose (daily inhalation) and will be calculated as the sum of on-time adherence and off-time adherence. Off-time adherence is defined as percentage of days on which the subject did not inhale the daily dose within the (\pm) 2 hours of the predefined preferred inhalation time (PIT), but outside.</p> <p>Variable(s)</p> <p>The primary variables for the study are the change from baseline (Visit 110) in on-time adherence and change from baseline in total adherence during 24 weeks of Interventional period. The on-time adherence will be calculated as the number of days with at least one dose/inhaler use recorded via the Concept2 inhaler within (\pm) 2 hours of planned PIT, divided by the number of days the subject had the Concept2 inhaler over 24 weeks. Total adherence will be calculated as the sum of on-time adherence and off-time adherence. Off-time adherence will be calculated as the number of days the subject did not inhale the daily dose within the (\pm) 2 hours of the predefined PIT, but outside, divided by the number of days the subject had the Concept2 inhaler over 24 weeks.</p> <p>If more than one dose is inhaled within (\pm) 2 hours of the preferred inhalation time, it will be counted once for the purpose of on-time adherence (numerator) day calculation. The additional dose(s), if any, will be considered as overuse, if it meets the criteria outlined in Section 12.6.1.5.</p> <p>If the subject is inhaling one or more doses during one day, in addition to the dose administration within (\pm) 2 hours of preferred inhalation time, that will not be counted towards off-time adherence calculation, hence not in total adherence calculation.</p> <p>The dispensing period is 4 weeks, when one inhaler will be dispensed. In addition one Concept2 back-up inhaler will be dispensed at Visit 110 and Visit 140, each. In case the back-up inhaler is used before Visit 140 or end of Interventional period (Visit 170) the subject will receive a new one. Each inhaler is designed and validated for a maximum of 30 days delivery.</p> <p>In each 4-week dispensing period the number of days for the denominator will be defined as follows:</p> <ul style="list-style-type: none">- Date of the first inhaler use data recorded into the Concept2 inhaler or Pairing Time, whichever comes first, plus 27 days or last data recorded in Concept2 inhaler, whichever is later (from all used Concept2 inhalers, regular and back-up's). If the inhaler is lost then the corresponding visit day will be used as the first inhaler use date.- If a subject discontinues the study, the denominator for each of the remaining 4-week periods will be defined as 28. The missing data will be imputed as outlined in Section 12.4.3.
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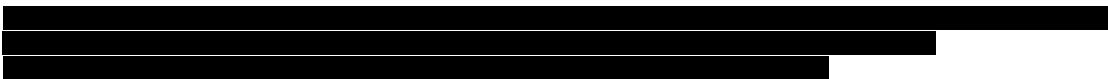
	<p>- The number of days from each of the six 4-week periods will be summed to be used as the overall denominator in calculations. Baseline on-time adherence and total adherence will be calculated from the 6 weeks Screening period (Visit 110 has a visit window of ± 7 days, that is days 35-49). The number of days in the denominator will be defined as:</p> <p>- Days between Visit 1 (exclusive) and Visit 110 (inclusive). A minimum of 35 days in the screening are expected for a subject to be eligible for having baseline adherence calculation performed. Subjects with a COPD exacerbation during Screening are considered screening failure.</p> <p>The period for which subject was taken off Ultibro[®] Breezhaler[®] treatment/inhaler use by investigator will be excluded from adherence calculation (for both Screening and Interventional period).</p> <p>Statistical model, hypothesis, and method of analysis</p> <p>The use of dose reminder notifications and motivational/adaptive messages will be evaluated by testing the following two null hypotheses H1 and H2 for on-time adherence and total adherence, respectively.</p> <p>H1: There is no difference in change from baseline in on-time adherence for subjects who received dose reminder and motivational/adaptive messages compared to subjects who received none.</p> <p>H2: There is no difference in change from baseline in total adherence for subjects who received dose reminder and motivational/adaptive messages compared to subjects who received none.</p> <p>The alternative hypothesis for each of H1 and H2 is that- there is a difference, respectively.</p> <p>Each of the primary variables will be analyzed using the analysis of covariance model (ANCOVA) for the FAS. The ANCOVA model will contain intervention (here defined as dose reminders and motivational/adaptive messages versus usual care), baseline total adherence group, country and baseline COPD severity as fixed effects with baseline on-time adherence/total adherence rate as covariate.</p> <p>The estimated adjusted difference of the intervention for the Telehealth group minus Usual Care group will be displayed along with the associated 95% (two-sided) confidence interval.</p> <p>Also the means of on-time adherence/total adherence will be presented graphically over 4-week time intervals by intervention group.</p>
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	<p>If at least one of the primary endpoints is significant the study will be considered positive.</p> <p>To control the overall type-1 error rate, multiplicity adjustment (for 2 endpoints) is described in Section 12.4.4.</p> <p>Handling of missing values/censoring/discontinuations</p> <p>Missing data for adherence will be imputed through a multiple imputation approach, under the assumption of missing data are missing at random. Utilizing this approach all subjects in the FAS will contribute in the analysis. For the primary analysis- data from inhalers (through investigator application) will be used. The supplemental data from patient application will not be used, to ensure a consistent imputation process for both groups.</p> <p>A sensitivity analysis will be done including the supplemental data from the patient application. That is, the missing data (from inhaler/investigator application) will first be imputed/updated with the patient application data, if available. Then the overall imputation will be done using the multiple imputation approach mentioned above.</p> <p>Further elaboration of the multiple imputations will be provided in the statistical analysis plan (SAP).</p> <p>Multiplicity adjustment</p> <p>To control the family-wise type-I error rate at the two-sided 5% significance level, the trimmed Simes test in Brannath et al (2009) is used. The family for the overall type-I error rate control contains 2 hypotheses- one for the on-time adherence primary endpoint and the other for the total adherence primary endpoint. Denote the two hypotheses for the two primary endpoints as H1 and H2, respectively. Below is a description of the testing procedure.</p> <p>Let p_1 and p_2 be the corresponding p-values (2-sided) of the two hypotheses of H1 and H2.</p> <p>Step 1: Retain both hypotheses and stop if ANY $p_i \leq 0.05$ (for $i=1$ or 2) AND the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. Usual Care group is better than intervention group); otherwise go to step 2.</p> <p>Step 2: Reject both hypotheses if $p_i < 0.05$ for BOTH $i=1, 2$, and stop here; otherwise go to step 3.</p> <p>Step 3: Perform the Bonferroni test and reject H1 if $p_1 < 0.025$ and reject H2 if $p_2 < 0.025$.</p> <p>For H1 and H2, their corresponding testing statistics follow jointly bivariate normal distribution. Therefore this testing procedure controls the overall type-I error rate at the 2-sided 0.05 level in the</p>
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	<p>strong sense regardless if the bivariate normal distributions have positive or negative correlations as shown in Brannath et al (2009). Other than the primary analysis, all other analyses will be performed at the nominal 2-sided 0.05 significance level without multiplicity adjustments.</p> <p>Sensitivity analyses</p> <p>As sensitivity analyses, the same ANCOVA used in the primary analysis will be also performed on the PPS to assess the robustness of the results from the primary analysis.</p> <p>The primary analysis model will be re-run including additional covariates, for example age and sex, to investigate the impact of these on any intervention effect. Details of these analyses will be pre-planned and described in the SAP.</p> <p>The secondary objectives on-time adherence and total adherence over the last four weeks of Interventional period (Week 21-24) will be summarized by intervention group.</p> <p>The change from baseline in on-time adherence/total adherence over the last 4 weeks of Interventional period will be analyzed using the same ANCOVA model specified for the primary analysis. The missing data imputation will be done using the same method used for the primary endpoints analysis</p>
Key words	Concept2, Ultibro [®] Breezhaler [®] , adherence, digital system



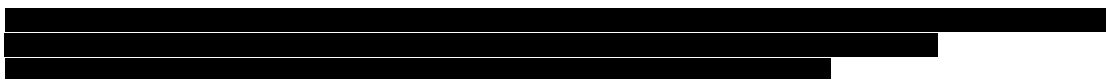
1 Introduction

1.1 Background

Poor adherence to drug therapy is a widespread issue affecting subjects irrespective of disease and treatment type. Treatment adherence is impacting the clinical benefit of the therapy influencing the results of clinical trials leading to erroneous conclusions, including underestimated efficacy, underestimated incidence of adverse effects, distorted pharmacoeconomic analyses and overestimated dosing requirements (Vrijens et al 2014). Poor adherence to medications therefore may account for many of the observed differences between the efficacy assessed in clinical trials and the real-world effectiveness of the drug treatment. Results from SUMMIT and TORCH (Vestbo et al 2009, Vestbo et al 2016) indicate that good adherence to inhaled medication was significantly associated with reduced risk of admission to hospital due to exacerbations in subjects with COPD (good adherence was associated with a 44% lower rate of severe exacerbations in the Torch trial; in the SUMMIT trial, the rate of adherence to treatment was high, only 3% of patients were taking less than 80% of prescribed study medication doses, with a reduction in COPD exacerbations of 18% to 27%).

Although adherence rates in clinical trials may be as high as 70% to 90%, in clinical practice adherence to treatment can be as low as 10% to 40% (Bourbeau and Bartlett 2008, Huetsch et al 2012) and decline with time. In the Lung Health Study, ~70% of participants reported satisfactory or better adherence to inhaled medication for COPD at the first 4-month follow-up visit; this decreased to ~60% over the next 18 months (Rand 2005). A similar observation was also reported by Chan et al (2015). In this study, the overall adherence in pediatric subject with asthma fell in both observed groups over time. Mean percentage adherence at 2, 4, and 6 months were 91%, 84%, and 79%, respectively, for the intervention group, compared with 40%, 33%, and 27%, respectively, for the control group. In Chronic Obstructive Pulmonary Disease (COPD) adherence to inhaled and oral medications has been reported to be between 41% and 57% (Bryant et al 2013, Cecere et al 2012), and up to 88% of subjects do not use their inhaler correctly (Thompson et al 1994, van Beerendonk et al 1998, van der Palen et al 1995, Serra-Batlles et al 2002, Molimard et al 2017). An increase of exacerbations frequency, number of hospitalizations and mortality rate are the consequences of the low adherence (Bourbeau and Bartlett 2008, Regueiro et al 1998, Plaza et al 2015). Adherence is often influenced by subject's perception of symptoms and beliefs about the necessity of medication. The most common self-reported reasons for poor adherence to inhaler use are forgetting (30% to 48%) (Osterberg and Blaschke 2005, Rand et al 1995) and consciously deciding not to use it when feeling good (31%; Dolce et al 1991, Bourbeau and Bartlett 2008). Other causes of non-adherence include concerns over the efficacy and safety of the drug and disagreement with the physician's diagnosis of the disease or its severity. To a lesser extent, non-adherence is also associated with the frequency of dosing and inhaler technique. If inhalers are used incorrectly, it remarkably reduces the efficacy of the drug and, consequently, the subject's adherence (Sanduzzi et al 2014).

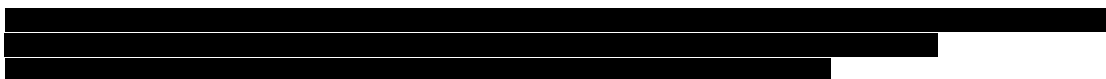
Adherence to treatment is difficult to monitor or evaluate without bias, as subjects tend to overestimate their adherence when using self-reporting questionnaires. Furthermore, most integral dose counters for inhaler devices and pill counters do not provide precise information about when the doses were taken. Rand et al (1992) showed that 14% of subjects with COPD, who were participating in a large multicenter clinical trial over the course of 1 year, were dumping



inhaled corticosteroid (ICS) medication (activation of canisters or removal of pills) immediately prior to a clinic visit presumably to make oneself appear adherent.

COPD is a progressive, debilitating and often fatal disease of the airways characterized by airflow limitation, which is not fully reversible and associated with an inflammatory response of the lung to noxious particles or gases. The aim of COPD treatment is to increase lung function, prevent disease progression, decrease symptoms and exacerbations, and improve Quality of life (QoL). Current treatment guidelines for COPD recommend the use of bronchodilators for all severities, either on an as-required (pro re nata: prn) basis, or on a regular basis ([GOLD guidelines 2017](#)) delivered by an appropriate inhaler. LABAs (Long-Acting Beta-Adrenoceptor agonists), such as formoterol, salmeterol and indacaterol, and LAMAs (Long-Acting Muscarinic Agents) achieve this goal as they provide long-term sustained bronchodilation. Published studies ([Mak and Barnes 1990](#), [Carstairs et al 1985](#), [Ikeda et al 1995](#)) have shown that the mechanisms of action of LABAs and LAMAs are complementary due to the differential density of β 2-adrenoceptors and M3-receptors in central versus smaller airways. Thus, LABAs work by relaxing small airways and LAMAs have a bronchodilatory effect in larger airways. There is also clinical evidence which suggests that combining bronchodilators from these two pharmacological classes results in significantly greater improvements in lung function (FEV₁) compared with individual components alone without increasing adverse effects ([Cazzola and Molimard 2010](#), [Wang et al 2011](#)). Subjects in this study will be treated with clinical trial formulation of the Ultibro[®] Breezhaler[®] (QVA149), a fixed combination of LABA and LAMA (a long acting β 2-agonist Indacaterol maleate (QAB149) and a long acting muscarinic antagonist Glycopyrronium bromide (NVA237)), which has been approved in Europe and Japan for once-daily maintenance treatment of COPD. Ultibro[®] Breezhaler[®] has been evaluated as safe and efficacious in a comprehensive Phase III development program comprising more than 12000 COPD subjects. Data from the studies have demonstrated improvement in lung function and health-related quality of life, decrease in COPD symptoms and decrease in use of short-acting β 2-adrenergic agonist (SABA) with a safety profile similar to placebo ([Bateman et al 2013](#)).

The intention of this study is to test whether subjects with COPD of spirometric grade 2 or 3 (according to GOLD 2017 criteria) on a regular once daily dosing regimen of Ultibro[®] Breezhaler[®] treatment using a patient adherence application in conjunction with the Concept2 inhaler, have improved adherence to treatment compared to subjects using the Concept2 inhaler alone. The Concept2 inhaler investigated in this study is a modification of the CE marked Ultibro[®] Breezhaler[®] inhaler (Concept1 inhaler), with the addition of electronics incorporated into the base of the device. The additional electronics do not alter the drug delivery characteristics of the inhaler itself, but produce a recording of each administered dose with a date and time stamp whenever the subject inhales a dose using the Concept2 device. Therefore, the Concept2 inhaler can be used to capture subjects' adherence with the approved once daily dosing regimen for Ultibro[®] Breezhaler[®] capsules. The digital adherence system enables in addition the real-time, wireless transfer of inhaler use data. These inhaler use data are then interpreted and specific appropriate feedback to the subject are provided. Such feedback may include reminders to inhale the medication and/or motivational/adaptive messages to encourage adherence with the treatment regimen.



The digital adherence system, being employed in this study, comprises the following components:

- (a) The Concept2 inhaler (also called eConcept1 Mark 1): The Concept2 inhaler is a device used by the subject to deliver the medication (Ultibro[®] Breezhaler[®]) from the capsule to the lungs and has electronic components in the base, [REDACTED]. The additional electronics do not alter the drug delivery characteristics of the inhaler itself, but produce a recording of each administered dose [REDACTED] based on the sound produced by the spinning capsule during inhalation. The recorded information [REDACTED] is then transmitted to the patient application.
- (b) A subject facing application (patient application or patient adherence application) running on a tablet device for home use and able to receive data from the Concept2 inhaler and transmit this data to the central data base (Concept2 portal). The intended use of the application is to monitor adherence to COPD maintenance therapy medication delivered through the Concept2 inhaler and to drive improvement in adherence by providing dose reminders, adaptive and motivational messages, and feedback on subject's level of adherence. The feedback comprises reports [REDACTED] for each individual subject.

Additional supportive components used for the conduct of the study are:

- (c) An investigator application (only used by the investigator) running on a tablet device and able to upload the data from the Concept2 inhaler(s) and to transmit this data to the Concept2 portal. An additional functionality of the application is to calculate the total adherence for each subject based on the uploaded screening data.
- (d) The Concept2 portal; a system made up of a central database for centrally storing inhaler usage data, answers/scores from questionnaires and study information.

1.2 Purpose

This study will evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages over 24 weeks on treatment adherence behavior in subjects with COPD. The dose tracking is done by the Concept2 inhaler and the reminder notifications, feedback on inhaler use and motivational/adaptive messages are sent by the patient application.

2 Study objectives and endpoints

2.1 Primary objectives

This study considers two primary endpoints:

- (1) the effect of the intervention on the on-time treatment adherence of the subjects
- (2) the effect of the intervention on the total treatment adherence of the subjects

[REDACTED]

2.1.1 On-time treatment adherence

This objective will evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's on-time treatment adherence.

On-time adherence is defined as percentage of days on which the subject inhaled at least one dose within (\pm) 2 hours of the agreed preferred daily inhalation time (PIT). The preferred daily inhalation time is defined by the subject at study start (Visit 1) and can only be modified on subject's request by the study investigator.

2.1.2 Total treatment adherence

This objective will evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's total treatment adherence.

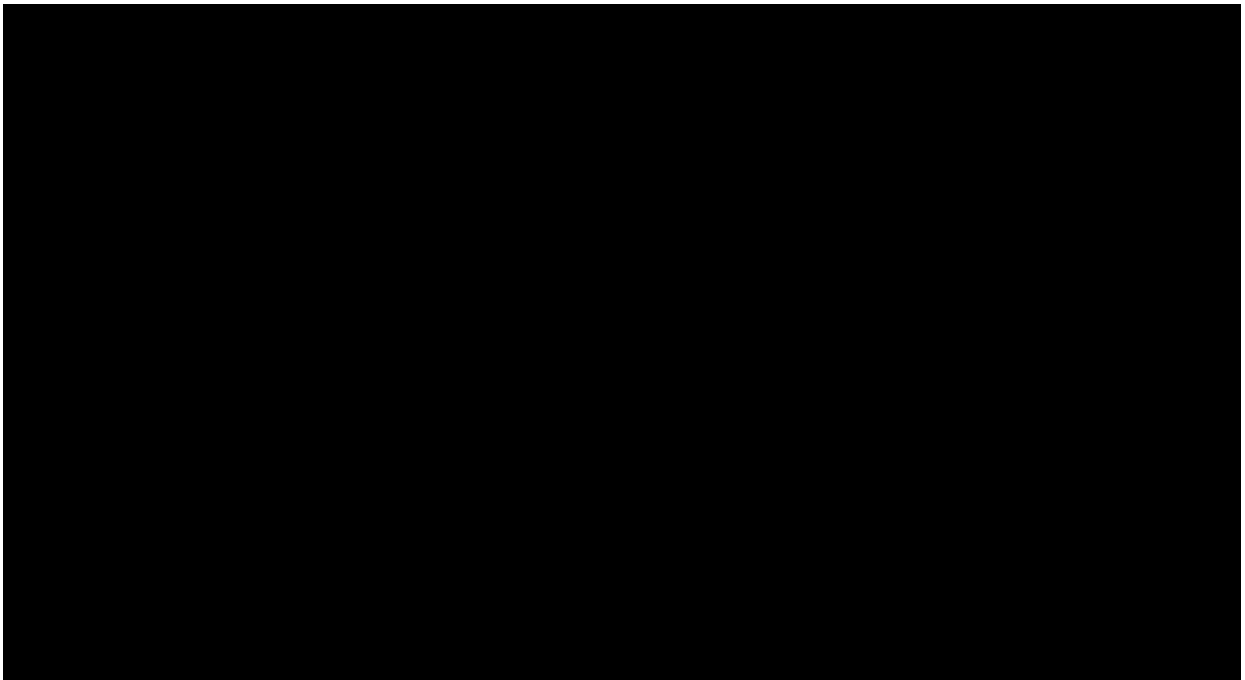
Total adherence is defined as percentage of days on which the subject inhaled at least one dose and represents the sum of on-time adherence and off-time adherence.

Off-time adherence is defined as percentage of days on which the subject inhaled a dose of medication, but did not do so within the target window (\pm) 2 hours of the agreed PIT.

2.2 Secondary objectives

To evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks for the subject's

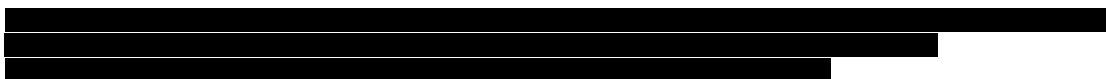
- On-time adherence over the last four weeks of the Interventional period
- Total adherence over the last four weeks of the Interventional period



2.4 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

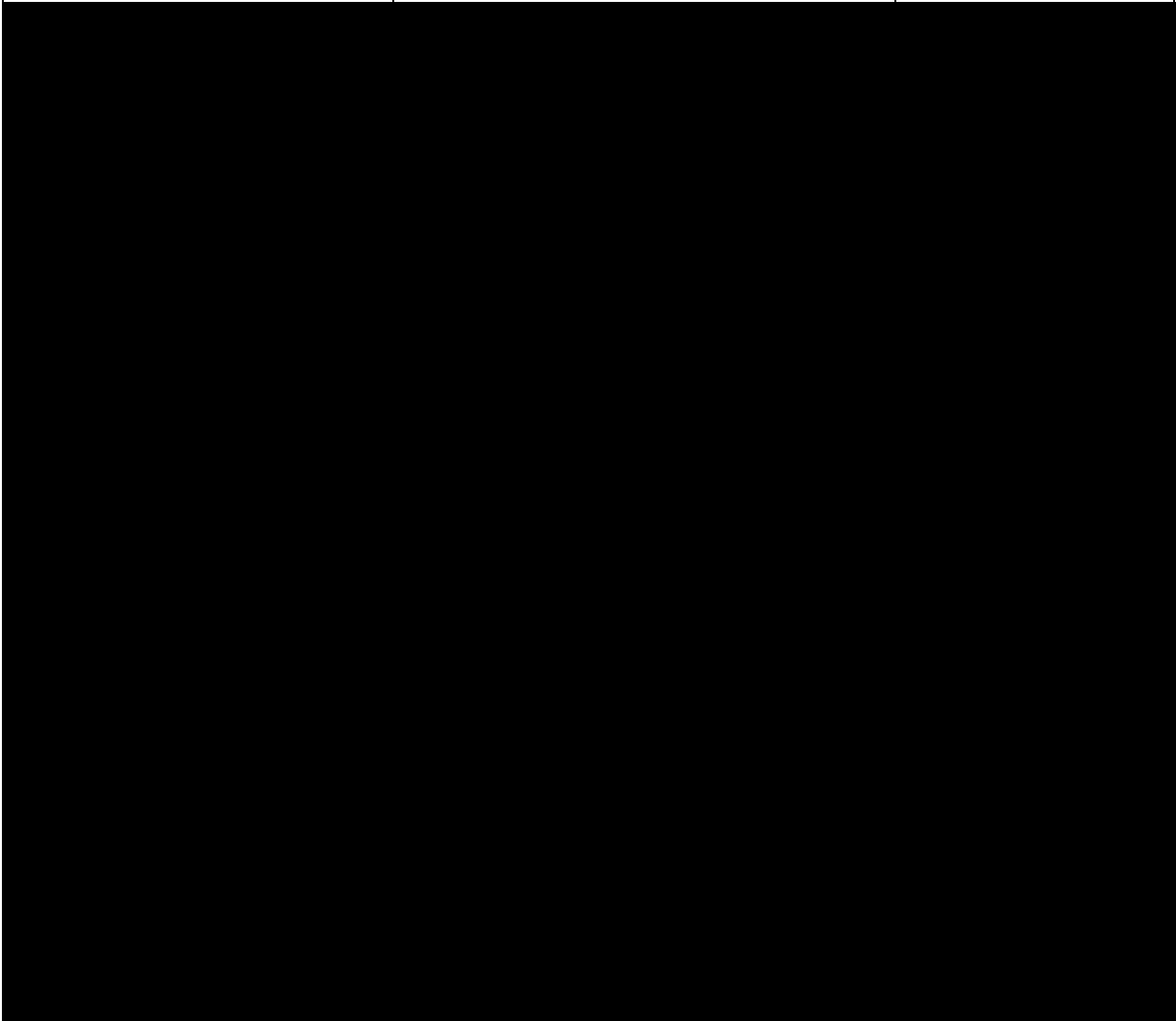
OBJECTIVE(s)	Endpoint(s)	Stat Analysis Section
Primary		
<p>To evaluate the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's on-time treatment adherence and therefore treatment behavior</p>	<p>Title: On-time adherence over 24 weeks</p> <p>On-time treatment adherence is defined as percentage of days on which the subject inhales at least one dose on-time. Dose inhaled on-time is a dose inhaled within (\pm) 2 hours of the agreed predefined preferred daily inhalation time (PIT).</p> <p>The number of days with an on-time treatment adherence will be calculated based on the recorded date and time for each inhaler use (inhalation) and the predefined PIT. The PIT is specific for each individual subject and defined by the subject. The first dose each day inhaled within the (\pm) 2 hours of the PIT will be considered for the on-time adherence calculation.</p> <p>Description: At screening subjects will be asked to use the Concept2 in the same way they were using the Ultibro[®] Breezhaler[®] inhaler prior to enrollment. Only at randomization subjects in the study will be instructed to inhale their daily Ultibro[®] Breezhaler[®] medication at the same time every day, using the Concept2 inhaler. During the study the Concept2 inhaler will track/record each time a subject uses the inhaler.</p> <p>Dose reminders and motivational/adaptive messages provided by the patient application for subjects in the Telehealth group will support the subject to inhale the dose at the same time every day.</p> <p>Unit of Measure: % of days</p> <p>Time Frame : 24 weeks</p>	<p>Section 12.4.</p>
<p>To determine the effect of dose tracking in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application over 24 weeks on the subject's</p>	<p>Title: Total adherence over 24 weeks</p> <p>Total adherence is defined as percentage of days on which the subject inhaled at least one dose and will be calculated for each subject as the sum of on-time adherence and off-time adherence.</p>	<p>Section 12.4.</p>

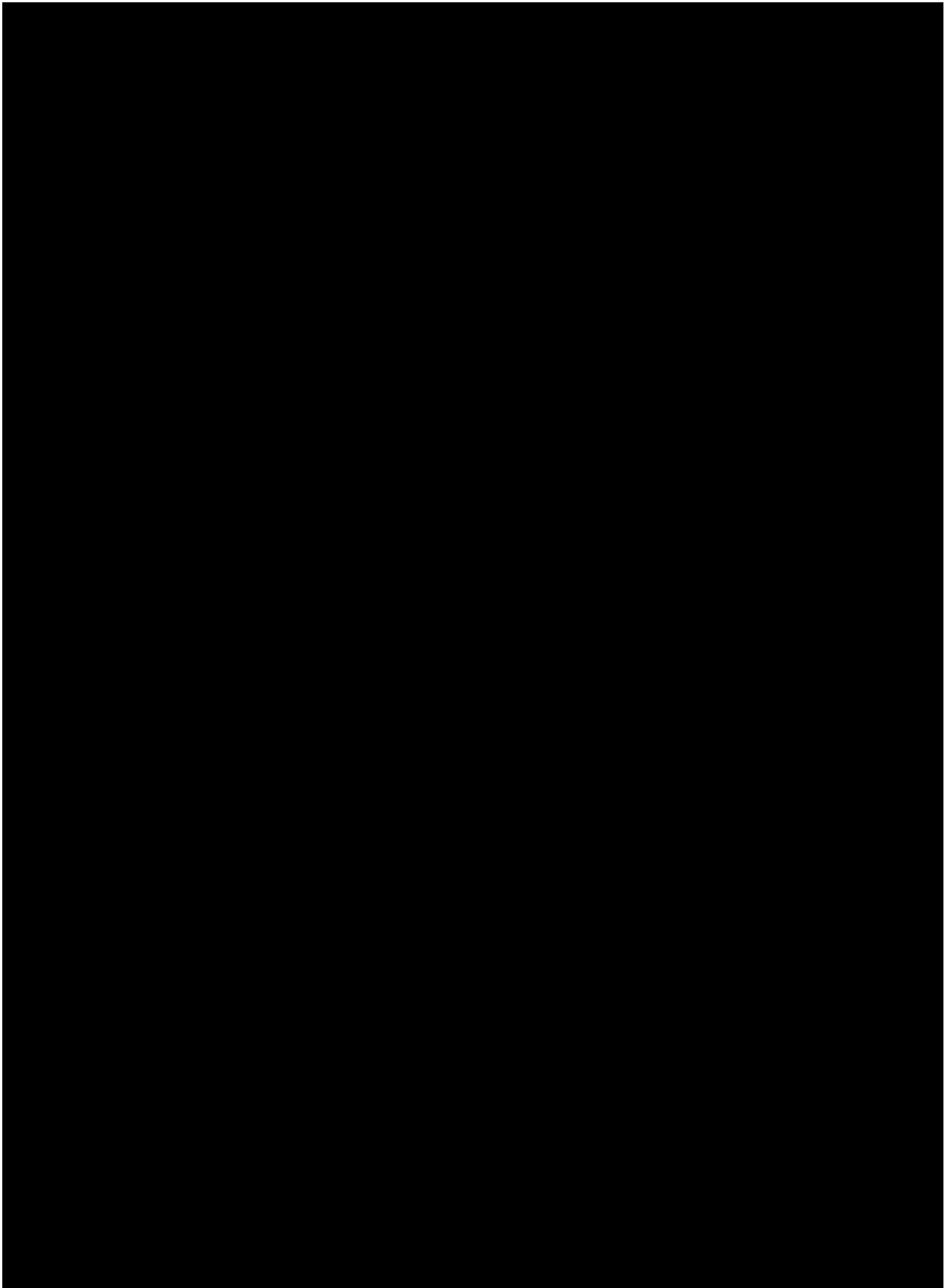


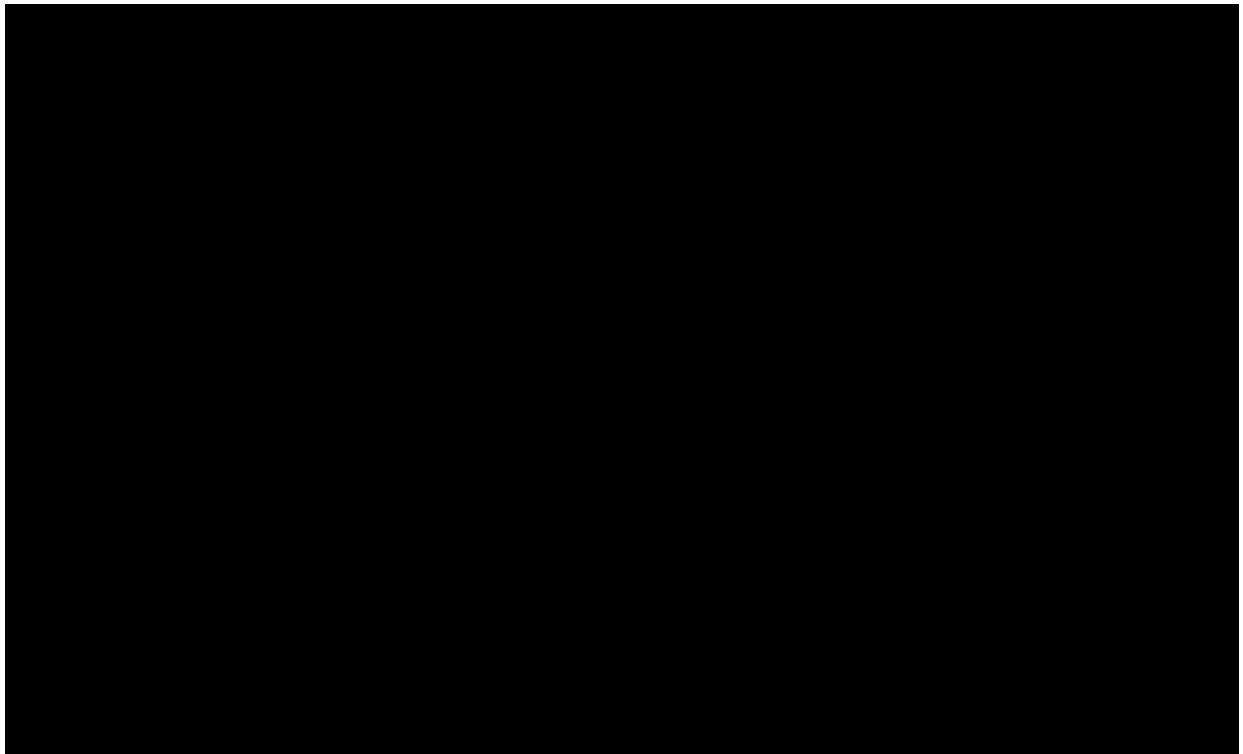
OBJECTIVE(s)	Endpoint(s)	Stat Analysis Section
<p>total treatment adherence and therefore treatment behavior</p>	<p>The definition of on-time adherence is explained in previous objective for on-time adherence. Off-time adherence is defined as percentage of days on which the subject did not inhale a dose within the (\pm) 2 hours of the predefined PIT, but outside.</p> <p>The number of days with a total adherence will be calculated based on the recorded date and time of each inhaler use (inhalation).</p> <p>Description: At screening subjects will be asked to use the Concept2 in the same way they were using the Ultibro[®] Breezhaler[®] inhaler prior to enrollment. Only at randomization subjects in the study will be instructed to inhale their daily Ultibro[®] Breezhaler[®] medication at the same time every day, using the Concept2 inhaler. During the study the Concept2 inhaler will track/record each time a subject uses the inhaler.</p> <p>Unit of Measure: % of days Time Frame : 24 weeks</p>	
Secondary		
<p>To explore the effect of dose reminders and motivational/adaptive messages sent by the patient application on the long term on-time adherence by comparing on-time adherence over the last four weeks of Intervention to the on-time adherence at baseline</p>	<p>Title: On-time adherence over the last 4 weeks of Intervention</p> <p>On-time adherence is defined as percentage of days on which the subject inhales at least one dose on-time. A dose inhaled on-time is a dose inhaled within (\pm) 2 hours of the agreed predefined preferred daily inhalation time.</p> <p>Description: The description is the same as for "on-time adherence over 24 weeks", only the time frame considered is changed. The relevant time frame for this secondary endpoint is the last 4 weeks of the Interventional period. This assessment will allow to explore the difference in long term on-time adherence between both groups (last 4 weeks of Intervention compared to baseline on-time adherence)</p> <p>Unit of Measure: % of days Time Frame : 4 weeks</p>	<p>Section 12.5.1.1</p>



OBJECTIVE(s)	Endpoint(s)	Stat Analysis Section
<p>To explore the effect of dose reminders and motivational/adaptive messages sent by the patient application on the long term total adherence by comparing total adherence over the last four weeks of Intervention to the total adherence at baseline</p>	<p>Title: Total adherence over the last 4 weeks of Intervention</p> <p>Description: The description is the same as for “total adherence over 24 weeks”, only the time frame considered is changing. The relevant time frame for this secondary endpoint is the last 4 weeks of the Interventional period. The assessment will allow to explore the difference in long term total adherence between both groups (last 4 weeks of Intervention compared to baseline total adherence)</p> <p>Unit of Measure: % of days</p> <p>Time Frame : 4 weeks</p>	<p>Section 12.6.1.1</p>







3 Study design

This is a multicenter, 1:1 randomized, controlled, parallel-group open label study to investigate whether COPD subjects on Ultibro[®] Breezhaler[®] once daily dosing regimen using a patient application in conjunction with the Concept2 inhaler have improved treatment adherence compared to subjects using the Concept2 inhaler alone.

It is planned to randomize approximately 146 subjects. These estimates are based on published literature used for sample size estimation ([Section 12.8](#)).

The total study duration is anticipated to be 34 weeks, which consists of a 6-week Screening period and a 24-week randomized Interventional period. A 4-week follow-up period will ensue to monitor subject's safety.

At Visit 1 all subjects eligible for the study will receive 3 Concept2 inhalers (two regular and one back-up inhaler), each one to be used for a maximum of 30 days, and clinical trial formulation of the Ultibro[®] Breezhaler[®] capsules for 6 weeks to use with the Concept2 inhaler. All subjects will continue to receive the Ultibro[®] Breezhaler[®] treatment they received prior to enrollment, as prescribed by their physician. At the end of the 6-week Screening period inhaler use data will be uploaded from the returned Concept2 inhalers and evaluated by the investigator application. [REDACTED]

Subjects, who during the Screening period have $> 10\%$ and $\leq 70\%$ total adherence (evaluated by the investigator application) and fulfill all other eligibility criteria, will be randomized via Interactive Response Technology (IRT) to one of the two study groups for 24 weeks. Total adherence results $> 70\%$ and $\leq 70.49\%$ will be rounded down to 70% total adherence.

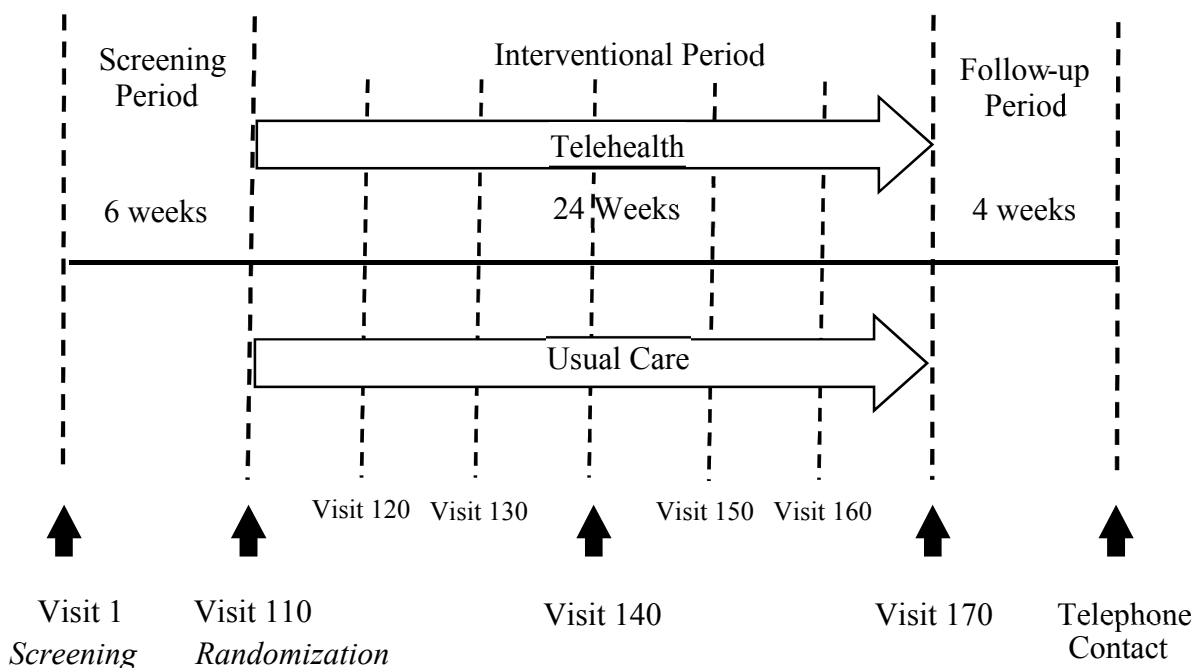


Subjects will be randomized 1:1 to either the Telehealth group or the Usual Care group. On the first day (Day 1, Visit 110) subjects randomized to the Telehealth group will receive Ultibro® Breezhaler® capsules (clinical trial formulation), the Concept2 inhaler and a tablet device with a pre-installed patient application to collect data and to receive dose reminder notifications and motivational/adaptive messages aimed at encouraging treatment adherence.

The other half of the randomized subjects assigned to the Usual Care group (control) will receive Ultibro® Breezhaler® capsules (clinical trial formulation) and the Concept2 inhaler only. They will continue to receive the usual care they received prior to study start.

The study design is illustrated in Figure 3-1.

Figure 3-1 Study design



The study consists of 8 planned study visits and a telephone contact. Investigators will be required to follow all procedures during the conduct of the study. Details of all efficacy and safety measurements made at each of the study visits are provided in Section 8.3 and Section 8.4 respectively and the timings of these measurements are detailed in Table 8-1.

The definitions of adherence in this study are as follows:

- A day, where at least one dose is inhaled within (\pm) 2 hours from preferred inhalation time is classified as an “on-time adherent” day



- A day, where no dose is inhaled within (\pm) 2 hours from preferred inhalation time, but one or more doses are inhaled outside of (\pm) 2 hours from preferred inhalation time, is classified as an “off-time adherent” day
- A day where no dose is inhaled is classified as a “non-adherent” day
- On-time adherence is the percentage of ‘on-time adherent’ days (with respect to time of consideration)
- Off-time adherence is the percentage of ‘off-time adherent’ days (with respect to time of consideration)
- Total adherence is defined as percentage of days on which the subject inhaled a dose and represents the sum of on-time adherence and off-time adherence
- Non-adherence is the percentage of ‘non-adherent’ days

Screening period

At the Screening visit (Visit 1) informed consent will be obtained before any study related assessments or procedures are performed and subject eligibility to take part in the study will be determined. Subjects will be asked to complete [REDACTED]

[REDACTED] a questionnaire aiming [REDACTED] Baseline demographic details and concomitant medications, including rescue medication use, will be reviewed and the subject’s medical history, history of cardiovascular risk factors, pulmonary disease history, COPD exacerbation history/events and smoking history will be recorded. All subjects will receive two Concept2 inhalers (each one to be used for a maximum of 30 days), one Concept2 back-up inhaler, the Instructions for Use (IFU) for the inhaler and clinical trial formulation of the Ultibro[®] Breezhaler[®] capsules to use with the Concept2 inhalers. Subjects will be instructed not to use the inhalers simultaneously and to only use the Concept2 back-up inhaler in case the regular Concept2 inhaler is damaged or lost. In the event, any of the Concept2 inhalers dispensed during this visit are not returned at Visit 110, the subject will be considered a screening failure and not permitted to be re-screened.

[REDACTED] However the subjects will be asked to follow the instructions for use (IFU) and to use the Concept2 in the same way they were using the Ultibro[®] Breezhaler[®] inhaler prior to enrollment. At this visit, participants should be instructed that for the inhalation of their medicinal product (Ultibro[®] Breezhaler[®] capsules) during the trial they should only use the Concept2 inhalers provided by the investigator.

Subjects will be asked about their preferred time of inhalation (PIT) during the day. The subjects PIT and the last 5 characters of the unique identification number of the dispensed inhalers (MAC Address; [Appendix 9](#)) will be noted in the investigator application page(s) capturing this information. In addition, every subject who enters the Screening period, will get a record in the Concept2 portal with the trial and subject number.

Interventional period

[REDACTED]

At Visit 110, (which will occur 6 weeks \pm 7 days after Visit 1) subjects will return all 3 Concept2 inhalers received at Visit 1 and the unused medication. [REDACTED]

[REDACTED] The investigator will download the data for the six weeks Screening period from the 3 returned inhaler(s) using the investigator application and subject's total adherence will be calculated by the investigator application. The calculation will consider the downloaded inhaler data from all 3 inhalers and the days the subject was taken off Ultibro® Breezhaler® treatment/inhaler use by the investigator. The period, for which a subject was taken off Ultibro® Breezhaler® treatment/inhaler use by the investigator, will be excluded from the adherence calculation and should not exceed 7 days. Subjects taken off the Ultibro® Breezhaler® treatment/inhaler use for more than 7 days will not be eligible and not permitted to be re-screened. In the event the downloaded data from all 3 inhalers comprises less than 35 days (lower bound of 42 days \pm 7 days' time window for Visit 110) the subject will be considered a screening failure and not be considered for a re-screening. All downloaded data from the inhalers will be transferred via wireless connection and stored in the Concept2 portal. All Concept2 inhalers dispensed during the Screening period are returned to Novartis at the end of the study.

The investigator will ask the subject about the rescue medication use in the past 6 weeks and enter the information in the CRF page capturing information about concomitant medication. Exacerbations that occurred during the Screening period will be recorded in the CRF as Adverse event (AE). Subjects who develop a COPD exacerbation after Screening (Visit 1) and prior to intervention (Visit 110) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.

Subjects who meet all eligibility criteria and who have a total adherence during Screening period $>10\%$ and less than or equal to 70% , will be considered for randomization (Day 1). All foreseen assessments for Visit 110 will be performed as listed in [Table 8-1](#). Subjects will also be asked to fill in a number of self-reported questionnaires and scales such as the "EuroQol EQ-5D-5L" questionnaire to assess the health status and the "St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease Patients" (SGRQ-C).

At each visit, subjects will be given an adequate supply of drug and Concept2 inhalers. Details on dispensing are described in [Section 6.5.1](#).

Half of the subjects will be randomized to the Telehealth group and the other half of subjects will be randomized to the Usual Care group (Day1). Subjects in both groups receive clinical trial formulation of the Ultibro® Breezhaler® capsules, a Concept2 inhaler to be used for a maximum of 30 days plus a Concept2 back-up inhaler and will be trained on how to use the inhalers and not to use them simultaneously. [REDACTED]

The Concept2 back-up inhaler should only be used in case the regular Concept2 inhaler is damaged and/or not functional, lost or if the next study visit scheduled is more than 30 days from the previous visit. The investigator will enter the last 5 characters of the unique identification number (MAC Address; [Appendix 9](#)) of all dispensed inhalers in the appropriated investigator application page(s) capturing the MAC Address. Subjects will be instructed to inhale Ultibro® Breezhaler® with the Concept2 inhaler at the same time every day, or as close

[REDACTED]

as possible. Subjects PIT will be recorded in the appropriated page(s) of the investigator application capturing the PIT; for subjects in the Telehealth group, the PIT will be entered/transferred to the patient application. The same PIT should be kept during the entire study but can, if requested by the subject, be changed by the study investigator at a scheduled visit. All changes to the PIT are recorded in the investigator application capturing the PIT.

Subjects who are randomized to the Telehealth group will receive, in addition, a tablet device with a pre-installed patient application. They will be trained on how to use the application in conjunction with the Concept2 inhaler and how to connect the Concept2 inhalers with the application.

Visits 120 and 130 will take place 4 weeks and 8 weeks respectively after Visit 110. A window of + 2 days will be allowed for the timing of these visits. At each of these two visits subjects will routinely bring all received Concept2 inhaler(s), the Concept2 back-up inhaler and unused medication back to the site or to any other agreed person/place. A download of data from all used Concept2 inhalers, using the investigator application, will be performed by the site for all subjects independent of the study group they have been randomized. Subjects will receive a new Concept2 inhaler to be used for a maximum of 30 days, medication for the next 4 weeks and, if necessary, also a new Concept2 back-up inhaler. The investigator will ensure that the last 5 characters of the unique inhaler identification number of dispensed inhaler(s) (MAC Address) are entered in the appropriated page(s) of the investigator application capturing the MAC Address ([Appendix 9](#)).

Visit 140 will take place 4 weeks after Visit 130. A window of + 2 days will be allowed for the timing of this visit based on the timing of Visit 130. At Visit 140 subjects will bring all received Concept2 inhaler(s), the Concept2 back-up inhaler and unused medication back to the site and download of data from used Concept2 inhalers, using the investigator application, will be performed for all subjects independent of the study group to which they have been randomized. Subjects will receive a new Concept2 inhaler to be used for a maximum of 30 days, medication for the next 4 weeks and a new Concept2 back-up inhaler. The subjects will be instructed not to use the inhalers simultaneously and will be re-trained on how to connect the Concept2 inhaler with the patient application, if required. The Concept2 back-up inhaler should only be used in case the regular Concept2 inhaler is damaged and/or nonfunctional, lost or if next study visit is scheduled more than 30 days from previous visit. The investigator will enter the last 5 characters of the unique inhaler identification number of the dispensed inhalers in the appropriated page(s) of the investigator application capturing the MAC Address ([Appendix 9](#)). The investigator will ask the subject about the rescue medication use during the past 12 weeks and enter the information in the CRF page capturing the concomitant medication. Exacerbations that occurred during the last 12 weeks will be recorded in the CRF as AEs.

The list of examinations to perform at this visit can be found in [Table 8-1](#).

Visits 150 and 160 will take place 4 weeks and 8 weeks respectively after Visit 140. A window of + 2 days will be allowed for the timing of these visits. At each of these two visits subjects will routinely bring all received Concept2 inhaler(s), the Concept2 back-up inhaler and unused

medication back to the site or to any other agreed person/place. A download of data from used Concept2 inhalers, using the investigator application, will be performed by the site. Subjects will receive a new Concept2 inhaler to be used for a maximum of 30 days, medication for 4 weeks and, if necessary, also a new Concept2 back-up inhaler. The investigator will ensure that the last 5 characters of the unique inhaler identification number (MAC Address) of the dispensed inhaler(s) are entered in the appropriated page(s) of the investigator application capturing the MAC Address ([Appendix 9](#)).

Visit 170 will take place 4 weeks after Visit 160. This is the final study visit of the Interventional period. A window of + 2 days will be allowed for the timing of this visit based on the timing of Visit 160.

The list of assessments to perform at this final study visit can be found in [Table 8-1](#).

During this visit, the investigator will ask the subject about the rescue medication use during the past 12 weeks and enter the information in the CRF page capturing the concomitant medication. Exacerbations that occurred during the past 12 weeks will be recorded in the CRF as AE. All subjects will return the Concept2 inhaler(s) received at Visit 160, the Concept2 back-up inhalers received and all study medication not used during the trial. Inhaler use data from the used Concept2 inhalers will be uploaded by the investigator using the investigator app and data transferred to the Concept2 portal. Subjects randomized in the “Telehealth” group will in addition also return the tablet device. The tablet device and the Concept2 inhalers from all subjects will be collected by the trial monitors at the conclusion of the study and returned to Novartis/vendors.

Follow-up period

All randomized subjects, regardless of whether they completed study through Week 24 or discontinued prior to Week 24, will be contacted (by telephone) 4 weeks after Visit 170 or study discontinuation for a Safety Follow-up. A window of ± 10 days will be allowed for the timing of this visit based on the timing of Visit 170 or study discontinuation visit.

The list of assessments to perform at the follow up study visit can be found in [Table 8-1](#).

If a subject refuses to return for any assessments or is unable/ unwilling to do so, every effort (preferable at least three documented efforts) should be made to contact the subject or a person pre-designated by the subject to ensure the safety of the subject. Attempts to contact the subject should be documented in the source records.

4 Rationale

4.1 Rationale for study design

The subject population will be described in more detail in [Section 5](#).

This is a randomized, controlled, parallel-group, open label study. The use of a parallel-group controlled study design enables a comparison between the subject groups during a 24 weeks Interventional period. The design of the study also intends to simulate the “real world” to the extent feasible within a controlled clinical trial, by minimizing the number of clinic visits and study interventions imposed.



A baseline total adherence will be established through the 6-week Screening period. The defined baseline treatment adherence (total adherence) of > 10% and less or equal to 70% has been chosen based on the published expected treatment adherence for COPD patients between 41% and 57% (Bryant et al 2013, Cecere et al 2012) and the anticipated treatment adherence for COPD patients in well-controlled clinical studies of 70-90% (Hawthorne effect; Bryant et al 2013). To study the relevant population, this study focuses on poorly adherent subjects, i.e. subjects with $\leq 70\%$ total adherence, in order to fully explore the adherence digital system's effectiveness. Subjects with a treatment adherence >70% during Screening period are therefore excluded from the participation in the study.

During the Screening period all subjects will receive the Concept2 inhaler without tablet device/application and no reminders or messages will be sent. As described earlier, the Concept2 inhaler looks similar to the commercially available Ultibro® Breezhaler® inhaler (Concept1 inhaler) and both are used in the same way. It is hence assumed, that the adherence behavior of the subjects during the Screening period, will not be different from the adherence behavior the subjects had prior to study enrollment.

Half of the subject population in this study will be assigned to the Telehealth group and on the first day of the Interventional period they will receive clinical trial formulation of the Ultibro® Breezhaler® capsules, a Concept2 inhaler and a tablet device with a pre-installed patient application (patient app).

The other half of subjects will be assigned to the Usual Care group and will receive clinical trial formulation of the Ultibro® Breezhaler® capsules and the Concept2 inhaler only, with the standard Instructions for use (IFU). After randomization both groups will receive training on how to use the Concept2 inhaler and will be reminded about the importance of treatment adherence.

Group	
Telehealth	<ul style="list-style-type: none">• Concept2 inhaler/ Ultibro® Breezhaler® capsules,• Patient application pre-installed on the tablet device for home use displaying dose-reminder notifications, feedback to the subject to encourage treatment adherence• Regular Medical visits
Usual Care	<ul style="list-style-type: none">• Concept2 inhaler/ Ultibro® Breezhaler® capsules,• IFU for the Concept2 inhaler (Instructions for use; paper)• Regular Medical visits

A 24-week Interventional period is considered to be a reasonable time frame to observe changes in subjects' treatment adherence behavior expecting that adherence will decline with time more in the control group. In the Lung Health Study, ~70% of participants reported satisfactory or

[Redacted footer text]

better adherence to inhaled medication for COPD at the first 4-month follow-up visit; this decreased to ~60% over the next 18 months (Rand 2005). A similar observation was also reported by Vrijens et al (2014) and Chan et al (2015). In the study conducted by Chan et al (2015) the overall adherence in pediatric subject with asthma fell in both observed groups over time. Mean percentage adherence at 2, 4, and 6 months were 91%, 84%, and 79%, respectively, for the intervention group, compared with 40%, 33%, and 27%, respectively, for the control group.

Self-reporting of adherence has moderate reliability (25%–67%) when compared against more objectives measures of adherence such as canister weight of pressurized Metered Dose Inhalers (Rand et al 1995, Rand et al 1992) or electronic monitoring (Gong et al 1988, Nides et al 1993, Bosley et al 1996).

Only a few studies have been carried out to improve adherence and most have concentrated on quantifying adherence, rather than exploring the factors which affect non-adherence, although need for motivational and cognitive ways to improve adherence has been pointed out (George et al 2005). The patient application along with the Concept2 inhaler, tracking the daily inhaler use, will remind the subjects randomized to Telehealth group every day to take their medication, if not done, on time;

The patient application will also provide feedback on inhaler use

4.2 Rationale for dose/regimen, route of administration and duration of treatment

The intervention in this study consists solely of the use of an investigational digital system consisting of the patient application and the Concept2 inhaler. All subjects in this study will continue to receive Ultibro® Breezhaler® treatment daily as prescribed by their physician prior to their enrollment in the study. Ultibro® Breezhaler® treatment is approved for the maintenance bronchodilator treatment of symptoms in subjects with COPD. In accordance with the EU product label, Ultibro® Breezhaler® (143 µg of indacaterol maleate equivalent to 110 µg of indacaterol and 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium) should be inhaled once daily on a regular basis. The treatment is delivered via the Ultibro® Breezhaler® inhaler (Concept1 inhaler).

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This study will recruit subjects who have been prescribed treatment with Ultibro[®] Breezhaler[®] (110/50 µg) for at least 3 months prior to Visit 1. The clinical trial formulation of Ultibro[®] Breezhaler[®] medicinal product will be used in this study. Subjects will be required to inhale the capsules via the Concept2 inhaler, instead of the Ultibro[®] Breezhaler[®] inhaler. Other than this, there will be no change to the subjects' prescribed dose and treatment.

The subjects are also permitted to use inhaled COPD rescue medication on 'as needed' basis as prescribed by their treating physician prior to enrollment in the trial according to the locally approved label. The use of rescue medication will be asked and recorded in study documents.

However, the subjects will not be supplied with inhaled COPD rescue medication. It has been demonstrated that the inhalation performance of the Concept2 inhaler is comparable to the approved Concept1 inhaler (the Breezhaler[®]), hence there are no additional anticipated risks by not providing the subjects with rescue medication. Further, a change in the type of COPD rescue medication supply may have the potential to bias subject's behavior towards their COPD treatment.

Changes to the subject's therapy and treatment interruptions are permitted at the discretion of the investigator. During the 6 weeks Screening period, treatment interruptions exceeding a total of 7 days will result in screening failure. Interruption of therapy or changes in treatment will be recorded on the appropriate CRF page. Treatment for COPD concomitant illnesses are at the discretion and choice of the managing physician at the study site.

The Concept2 inhaler used to deliver Ultibro[®] Breezhaler[®] treatment in this study has the same user steps, materials and equivalent dose delivery characteristics as the Ultibro[®] Breezhaler[®] inhaler (Concept1 inhaler) that the subjects were using prior to trial enrollment and therefore should not affect subjects' use of the inhaler device.

4.3 Rationale for choice of comparator

Adherence tracking is normally not performed in routine clinical practice. In this study the comparator will be the group assigned to use the Concept2 inhaler only. This group represents the usual care with Ultibro[®] Breezhaler[®], using the Breezhaler[®] inhaler to deliver the medication, and will be considered the Usual Care (control) group. The drug delivery with the Concept2 inhaler has been shown to be not altered with the addition of the electronic components and subjects can't download the inhaler use information recorded by the Concept2 inhaler. The primary reason for using the Concept2 inhaler in the Usual Care group is, that it will provide an actual measure of adherence similar to that provided for the Telehealth group. Thus, the only difference of intervention between the two study groups is the system of devices comprising of the patient app on the tablet device and its electronic connectivity to the Concept2 inhaler/s in the Telehealth group; which is not the case in the control group. The investigator in the study will be able to download the inhaler use data from all Concept2 inhalers by using the investigator app [REDACTED]. The data is wirelessly transmitted from the investigator app to the Concept2 portal [REDACTED].

4.4 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned.

[REDACTED]

4.5 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, study procedures and close clinical safety monitoring.

It has been demonstrated that the inhalational performance of the Concept2 inhaler is comparable to the approved Concept1 inhaler (the Breezhaler®), hence there are no additional risks associated with its use. Risks associated with the Concept2 inhaler are described in the Investigator Brochure (IB) Edition 1 for the Concept inhaler. Risks associated with the use of Ultibro® Breezhaler®, are those described in the Summary of Product Characteristics (SmPC)/National Prescribing Information (nPI) and the Investigator's Brochure for QVA149.

Women of child bearing potential and sexually active males will be informed during the first visit that taking Ultibro® Breezhaler® may involve unknown risks to the fetus if pregnancy were to occur during the study, and have to agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Improved total and on-time adherence to Ultibro® Breezhaler® prescribed for COPD is expected to result in subjects' benefit, by improvement in symptoms related to COPD.

It is possible that subjects in the Telehealth group may perceive the monitoring system to be invasive or intrusive on the subject's privacy. To mitigate this, the nature of the technology will be thoroughly explained at the randomization visit. The subject will be able to opt out of the study at any time and the study will be conducted in accordance with currently accepted ethical principles and International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

In case a subject in the Telehealth group may inhale more than one dose in a given day the subjects will receive a notification via the patient application that they have exceeded the recommended daily dosing. This information will also be noted on the subject's daily dosing record, which is located on the patient's application.

One potential benefit for the subject lies in a thorough medical evaluation of the subjects' disease and close clinical monitoring for the duration of the study. In addition, the inhaler training provided to all subjects will represent a tangible benefit.

The tablet device and the Concept2 devices are designed to emit electro-magnetic radiation in the Industrial, Scientific and Medical (ISM) and cellular radio frequency bands. Government and regulatory agencies have established SAR (Specific Absorption Rate) limits under which cellular devices have been determined to be safe and the devices being used in this study meets these limits. The technology chosen to enable the devices to communicate with the CDR (file format) is subject to regulation under European Radio Equipment Directive (RED) (i.e.: Directive 2014/53/EU of the European Parliament and of the Council of 16 April 2014 on the harmonization of the laws of the Member States relating to the making available on the market of radio equipment and repealing Directive 1999/5/EC) on radio equipment and telecommunications terminal equipment and complies with the essential requirements of both.



5 Population

The study population will consist of approximately 146 male and female adults age 18 years and older, with a clinical diagnosis of COPD (spirometric grade 2 or 3 according to GOLD 2017 criteria; [Appendix 10](#)), a smoking history of at least 10 pack years, receiving COPD maintenance treatment with Ultibro[®] Breezhaler[®] for at least 3 months prior to trial enrollment and with a known poor treatment adherence.

146 subjects are planned to be randomized into the study with the expectation that at least 120 subjects will complete the study. The study will be multicenter and drop-outs will not be replaced.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill all of the following criteria:

1. a Signed informed consent must be obtained prior to participation in the study.
2. Male and female adults aged ≥ 18 years.
3. Current or ex-smokers who have a smoking history of at least 10 pack years. (Ten pack- years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years).
4. a A historical diagnosis of COPD confirmed by a post-bronchodilator $FEV_1/FVC < 0.70$ in the past and a pre-bronchodilator or post-bronchodilator $FEV_1 \geq 30\%$ and $< 80\%$ of the predicted normal value within the last year.
5. Have been taking Ultibro[®] Breezhaler[®] for at least 3 months prior to Visit 1 (in accordance with the local product label).
6. Have a total adherence of more than 10% but less than or equal to 70% during Screening period. Total adherence is defined as percentage of days on which the subject inhaled a dose of Ultibro[®] Breezhaler[®].
7. Have been in the Screening period ≥ 35 days.

5.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG (human Chorionic Gonadotropin) laboratory test.
2. a Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception while taking Ultibro[®] Breezhaler[®] medication during the study. Basic contraception methods include:



- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/ vaginal suppository.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before entering the study.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

3. Subjects contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
 - anticholinergic agents
 - long and short acting beta-2 agonists
 - sympathomimetic amines
4. Subjects contraindicated for having a history of reactions/ hypersensitivity to lactose or any of the other excipients of trial medication.
5. Subjects with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
6. Subjects with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention. Benign Prostatic Hyperplasia (BPH) subjects who are stable on treatment can be considered.



7. Subjects who have had a COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in 6 weeks prior to Visit 1.
8. Subjects who develop a COPD exacerbation between screening (Visit 1) and prior to intervention (Visit 110) will not be eligible but will be permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
9. Subjects who have had a respiratory tract infection within 3 weeks prior to Visit 1.
- 10.a Subjects who develop a respiratory tract infection between screening (Visit 1) and prior to intervention (Visit 110) will not be eligible, but will be permitted to be re-screened after a minimum of 3 weeks after the resolution of the respiratory tract infection.
11. Subjects with a current diagnosis of asthma.
12. Subjects with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, and pulmonary tuberculosis).
13. Use of investigational drugs or other investigational devices at the time of enrollment, or within 30 days or 5 half-lives of Visit 1, whichever is longer.
14. Subjects with a preferred inhalation time between 10.00 pm and 2.00 am.
15. Subjects taken off Ultibro® Breezhaler® treatment/inhaler use by the investigator during the Screening period for more than 7 days.
16. Subjects not returning all Concept2 inhalers, received during the Screening period, for the calculation of total adherence at Visit 110.
17. Subjects who have demonstrated inability or unwillingness to use the digital system or to fill in questionnaires.

6 Intervention

The intervention in this study consists solely of the use of an investigational digital system, composed by the patient application and the Concept2 inhaler. The digital system will be used in half of the subjects while the other group (control) will receive Usual Care delivered by the Concept2 inhaler, with no patient application. The drug treatment in this trial is not under investigation. All subjects in this study will receive Ultibro® Breezhaler® capsules (110/50 µg) daily as prescribed by their physician prior to their enrollment in the study. The clinical trial formulation of Ultibro® Breezhaler® medicinal product will be provided to the subjects, required to be inhaled with the Concept2 inhaler instead of the Concept1 inhaler. (Section 4.2).

In this section, the details of the components of the digital system used in the study are described. The overview of the components and data flow is shown in Figure 6-1.

- (a) **Concept2 inhaler:** The Concept2 inhaler (or also called eConcept1 Mark1) is a modification of the currently marketed Ultibro® Breezhaler® inhaler (Concept1 inhaler), with the addition of electronic components in the base of the device: [REDACTED]
[REDACTED] The additional electronics do not alter the drug delivery characteristics of the inhaler itself, but produce a recording of each administered dose [REDACTED]
[REDACTED] and a date and time stamp whenever the

[REDACTED]

subject uses the inhaler with the intention to inhale a dose of drug [REDACTED] after pushing the buttons. [REDACTED]

(b) **Concept2 portal:** is a central data base for centrally storing of study relevant data, subject's ID numbers, [REDACTED] PIT, Mac-address of inhalers and inhaler use data. The data base will receive data from the tablet device running the patient and investigator application. All relevant clinical data in this data base will be sent to the clinical data base at Novartis on an ongoing basis and at the end of the study.

(c) **Applications:** the users of the applications are subjects and investigators. The applications will require a standard tablet device running an Android operating system. [REDACTED] Some of the described functionalities require an internet connection.

Application for the patient: the intended use of the patient application is to monitor adherence to COPD maintenance therapy medication delivered through the Concept2 inhaler and to drive improvement in adherence by providing dose reminders, motivational/adaptive messages and feedback on subject's level of adherence. The application will run on a customized tablet device for home use. The patient application also transmits the inhaler use data to the central data base (Concept2 portal). Functionalities:

- a.) Initial setup
- b.) Connect with the Concept2 inhalers
- c.) Receive data on inhaler use from a connected Concept2 inhaler
- d.) Display dose reminders or notifications [REDACTED]

- h.) Change of settings
- i.) Transfer data to the data base (Concept2 portal)

Application for the investigator: this application runs on a customized tablet device and has functionalities for the investigator such as:

- a.) Download of inhalers use data from the Concept2 inhalers returned by subjects' after use
- b.) Transmitting of Concept2 inhaler use data to the Concept2 portal
- c.) Calculation of screening total adherence

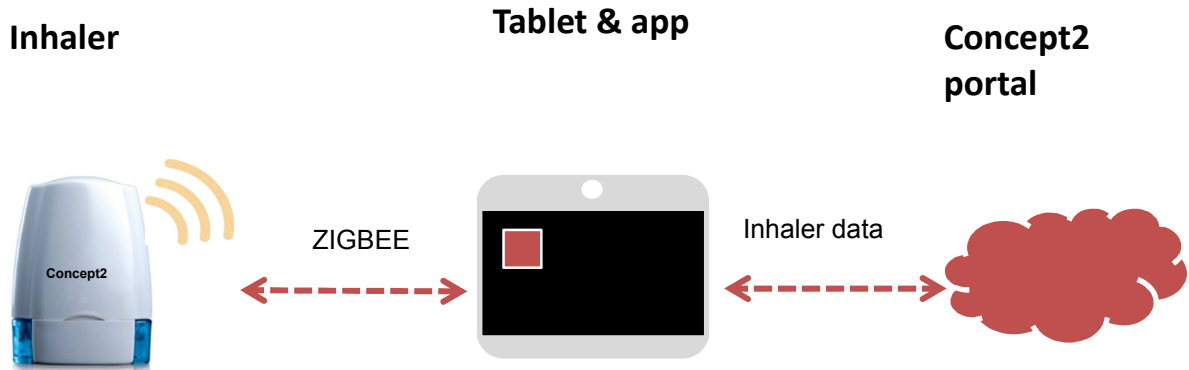
[REDACTED]

[REDACTED]

- e) Capturing of subjects preferred inhalation time and the Mac-Addresses of the dispensed inhaler for the individual subjects



Figure 6-1 Overview of the components of the digital adherence system and data flow



Concept2 Inhaler	Applications	Database (Concept2 portal)
<p>Delivers the medication from the capsule to the subject's lungs</p> <p>Records and stores inhaler use data (date and time stamp)</p> <p>Transmits wireless recorded inhaler use data to the patient application on the tablet device</p>	<p><i>Patient application:</i></p> <p>Receives inhaler use data from a connected Concept2 inhaler</p> <p>Reminds subjects to use their inhaler within their PIT</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Enables subjects to understand their adherence profile</p> <p>Transfers wireless inhaler use data to the Concept2 portal</p> <p><i>Investigator application:</i></p> <p>Downloads inhaler use data from the Concept2 inhalers</p> <p>Calculates screening total adherence data</p> <p>[REDACTED]</p> <p>Transfers wireless inhaler use data [REDACTED]</p> <p>[REDACTED]</p>	<p>Stores</p> <ul style="list-style-type: none"> - downloaded inhaler use data <p>[REDACTED]</p> <ul style="list-style-type: none"> - subject ID and study number - subject's PIT and Mac-Addresses of the dispensed inhaler(s) <p>Transfers relevant data to the Novartis Clinical Database</p>

The Concept2 inhaler will record the date and time at each occasion when the subject uses the Concept2 inhaler [REDACTED]. In the Telehealth group this information will be transmitted to the patient's application allowing subjects in this group to monitor their level of adherence. [REDACTED]

In the Usual Care group inhaler use information will be uploaded by the investigator via the investigator application.

If subjects in the Telehealth group do not use the inhaler once daily by their PIT, the application running on the tablet device will be pre-programmed to deliver reminders to the subjects to inhale their medication. Subjects who use the inhaler twice or more times within one day (overuse) with the intention to inhale the medication, will also be notified to only inhale one dose per day.

The application will in addition display regular motivational and adaptive messages to the subject to encourage adherence.

[Redacted]

[Redacted]

6.1 Control arm (Usual care group)

Subjects in the control arm will receive Usual Care (Ultibro[®] Breezhaler[®]) daily as prescribed by their physician prior to their enrollment in the study. The clinical trial formulation of Ultibro[®] Breezhaler[®] capsules (110/50 µg) will be provided) with the Concept2 inhaler, with no patient application and no tablet device.

6.2 Study arm (Telehealth group)

Subjects in the study arm (Telehealth group) will receive (Ultibro[®] Breezhaler[®]) treatment (110/50 µg) daily as prescribed by their physician prior to their enrollment in the study. The clinical trial formulation of Ultibro[®] Breezhaler[®] capsules (110/50 µg) will be provided to the subjects with the Concept2 inhaler and patient application (app) pre-installed on a tablet device.

6.3 Subject numbering, assignment of intervention and randomization

6.3.1 Subject numbering

Each subject is uniquely identified by a Subject Number assigned by Novartis. The subject number is composed of a site number and a sequential number. Once assigned to a subject, the Subject Number will not be reused. Upon signing the informed consent form, the subject is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site must select the CRF book with a matching Subject Number in the EDC system to enter data. Once assigned to a subject, the subject number will not be reused. If the subject fails to be randomized for any reason, the IRT must be notified within 2 days that the subject was not randomized.

6.3.2 Assignment of intervention and randomization

At Visit 110 all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the study arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria.

The randomization numbers will be generated using the following procedure to ensure that intervention assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different study arms, which in turn are linked to kit numbers.

[Redacted footer text]

[REDACTED] (Bryant et al 2013, Cecere et al 2012)).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Group.

6.4 Blinding

This is a randomized, controlled open label study in which investigators will have full knowledge of the allocation of the subjects. [REDACTED]

Sponsor Staff

With the exception of any unblinded sponsor staff identified below, Novartis staff will stay blinded to group allocation of the subjects until database lock. The following unblinded sponsor roles are required for this study:

- Unblinded clinical data review to review the safety reporting of devices
- Unblinded data manager to reconcile the serious adverse device events

The monitors will be unblinded through the review of the source documentation at site (source documentation will detail if the training for the patient application was done by the subject).

However, none of the unblinded roles will have access to subject’s treatment adherence data contributing to the co-primary endpoints analyses in the study

Table 6-2 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Intervention allocation	Safety event (single subject unblinded)	Adherence data (inhaler use)
Subjects	B	UI	NA	UI*
Site staff				
Pharmacy staff, nurse, investigator, site coordinator	B	UI	UI	B
Drug Supply and Randomization Office	UI	UI	B	B
Sponsor staff				
Trial monitors	B	UI	UI	B
Clinical data reviewer (safety review of device events)	B	UI	UI	B
Data manager (reconciliation of SADE)	B	UI	UI	B
Pharmacovigilance staff	B	UI	UI	B

[REDACTED]

Role	Time or Event			
	Randomization list generated	Intervention allocation	Safety event (single subject unblinded)	Adherence data (inhaler use)
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK ¹)	B	B	B	B
All other sponsor staff not identified above (e.g. trial team, other clinical data reviewers, other data managers, project team, management & decision boards, support functions)	B	B	B	B
Independent committees used for assessing interim results, if required (e.g. DMC ²)	NA	NA	NA	NA

UI: Allowed to be unblinded on individual subject level; B: Remains blinded; NA: Not applicable to this study

*: only for the subjects in the Telehealth group

¹: Pharmacokinetic

²: Data Monitoring Committee

6.5 Treating and monitoring the subject

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.











6.5.1 Dispensing the investigational digital(s) system and the medicinal product

The subjects assigned to the Telehealth group will receive upon randomization clinical trial formulation of the Ultibro® Breezhaler® capsules and the following devices: Concept2 inhalers and a tablet device with a pre-installed patient application. They will be training on how to use the inhaler and the application. The subjects assigned to the Usual Care group will receive, upon randomization, clinical trial formulation of the Ultibro® Breezhaler® capsules and the Concept2 inhalers only and be trained on how to use the inhaler. Each Concept2 inhaler has a label adhered to the Concept2 inhaler base including the 16 characters unique identification of the device (MAC Address). The Concept2 inhalers for the individual subjects will be assigned by IRT. At each visit subjects will bring all Concept2 inhalers received at the previous visit back to the site. Used inhalers will be replaced with new ones to use for a period of 30 days.

The medication will be dispensed at each visit as detailed in [Figure 6-2](#).



Figure 6-2 Dispensing of Concept2 inhalers and clinical trial formulation of Ultibro® Breezhaler® capsules

Screening	Intervention							Follow up
	Visit 1	Visit 110	Visit 120	Visit 130	Visit 140	Visit 150	Visit 160	
							-	-
								
back-up	back-up			back-up				
Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	Ultibro® Breezhaler® capsules	-	-

6.5.2 Handling of devices and medication

Concept2 inhalers, tablets running the app’s and Ultibro® Breezhaler® capsules provided by Novartis must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, medication and inhalers should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Complaints are to be reported to the trial monitor and respective Novartis CPO Quality Assurance.

Device and medication (clinical trial formulation of the Ultibro® Breezhaler® capsules) labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions. The Concept2 inhaler will in addition have a label adhered to the Concept2 inhaler base including a unique 16 characters MAC Address identification. The last 5 characters of this MAC Address will be entered by the investigator in the appropriate page(s) capturing the MAC Address when dispensing the inhaler(s) to the subject.

The investigator must maintain an accurate record of the shipment and dispensing of devices/tablets and medication in a device/drug accountability log. Monitoring of device accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return at each study visit the Concept2 inhalers received and the unused medication.

At the conclusion of the study, and as appropriate during the course of the study, used and unused Concept2 inhalers will be returned to Novartis. Subjects randomized in the Telehealth group will in addition also return the tablet device to the site after completing the intervention. At the conclusion of the study all tablets will be collected by the trial monitors and returned as appropriate. A copy of the completed device accountability log are collected at the site close out visit.



6.5.3 Instructions for using the devices and taking medication

All subjects will continue to receive Ultibro[®] Breezhaler[®] throughout the study as prescribed by their physician prior to their inclusion in the study. The clinical trial formulation of the Ultibro[®] Breezhaler[®] is required to be inhaled however with the Concept2 inhaler.

All subjects entering the study will be trained on how to complete the questionnaire(s) (Section 8.3.3) and will be encouraged to refer to the instructions for use (IFU) of the Concept2 inhaler. After randomization they will be trained in the use of the Concept2 inhaler (Appendix 2). Subjects randomized to the Telehealth group, will in addition, receive training on how to use the patient application and how to synchronize the patient application and the Concept2 inhaler.

The investigator should promote adherence by instructing the subject to inhale Ultibro[®] Breezhaler[®] exactly as prescribed and by stating that adherence is necessary for the subject's safety. The subject should be instructed to contact the investigator if he/she is unable, for any reason, to inhale the medication or use the Concept2 inhaler or the patient adherence application.

6.5.4 Permitted dose adjustments and interruptions of Ultibro[®] Breezhaler[®] treatment

The COPD treatment with Ultibro[®] Breezhaler[®] is not the investigational part of the study. All subjects will continue to receive Ultibro[®] Breezhaler[®] treatment throughout the study as prescribed by their physician prior to their inclusion in the study. The clinical trial formulation of the Ultibro[®] Breezhaler[®] will be provided to subjects in the study. Treatment interruptions are permitted at the discretion of the investigator. Treatment for COPD concomitant illnesses are at the discretion and choice of the managing physician at the study site. Changes in therapy will be recorded in the appropriated CRF page(s).

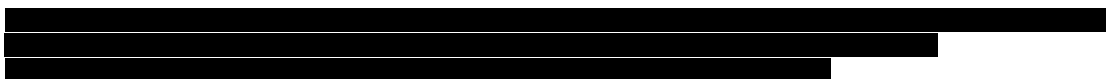
If at any point during the Interventional period the subject is taken off study drug by the investigator, this will be noted by the investigator in the CRF page(s) capturing interruptions of treatment, in order that the adherence calculation is based on the number of days the subject was scheduled to inhale Ultibro[®] Breezhaler[®]. For example, if the subject has an exacerbation of COPD and enters the hospital, any days off Ultibro[®] Breezhaler[®] will need to be recorded in the CRF. If the subject is discontinued from the study, this date will also be noted and entered in the CRF.

6.5.5 Treatment compliance and exposure

In addition to the tracking of treatment adherence by the Concept2 inhaler, the Investigator or designee will collect at each visit the used/unused medication and packaging from the subject (unused capsules, blister strips).

6.5.6 Rescue medication

There are no study specific requirements regarding the use of rescue medications. COPD rescue medication will not be provided to the subjects. The subjects are permitted to use their inhaled COPD rescue medication on 'as needed' basis as prescribed by their treating physician prior to enrollment in the trial and according to the locally approved label. Their use of rescue medication will be asked and recorded in study document at certain visits (Table 8-1). In the



event that a subject uses a dose of rescue medication, date of intake should be captured on the CRF page(s) capturing concomitant medications.

6.5.7 Concomitant medication

Treatment for COPD concomitant illnesses are at the discretion and choice of the managing physician at the study site. Each concomitant drug must be individually assessed against all exclusion criteria and the investigator should consult the section “Interaction with other medicinal products and other forms of interaction” of the SmPC for Ultibro[®] Breezhaler[®].

In addition, the investigator will instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the appropriate CRF.

6.5.8 Prohibited medication

There is no additional prohibited treatment in this trial. The investigator should consult the SmPC for Ultibro[®] Breezhaler[®].

6.5.9 Emergency breaking of assigned treatment code

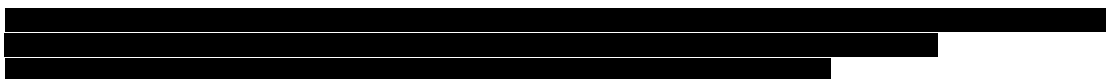
Not applicable.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent. If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis/sponsor before submission to the IRB/IEC.

Information about common side effects already known about the components of the investigational digital adherence system (the Concept2 inhaler and the Patient app) can be found in the respective Investigator's Brochure (IB); for the Ultibro[®] Breezhaler[®] treatment the information can be found in the Core Data Sheet (CDS). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational intervention that is identified between IB updates will be communicated as appropriate, for example, via an



investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the Ultibro® Breezhaler® treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

Table 8-1 lists all of the assessments and indicates with an “x” when the visits are performed.

Subjects should be seen for all visits on the designated day as close as possible within the time window. If this is not possible for any reason, the investigator must ensure the subject has received appropriate amount of Concept2 inhalers to not exceed the 30 days of use of each inhaler.



Missed or re-scheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for study discontinuation visit will be performed. At this final visit, all dispensed Concept2 inhalers, tablets and unused medication should be returned and the adverse events and concomitant medications reconciled on the CRF.

Subjects will be contacted for safety evaluations during the 30 days following study Visit 170 or last study visit, in case they discontinued earlier.



Table 8-1 Assessment schedule

Period	Screening	Intervention					Follow up
		110	120 130	140	150 160	170	
Visit Number	1						1999
Visit		Randomization				End of intervention PSW/Study Discontinuation	Study completion
Week	-6	1	4/8	12	16/20	24	28
Day	-42 ± 7 days	1	28/56 +2 days	84 +2 days	112/140 +2 days	168 + 2 days	196 ± 10 days
Obtain informed consent	X						
Demographics	X						
Medical history including COPD exacerbation history	X						
History of cardiovascular risk factors	X						
Pulmonary diseases history	X						
COPD exacerbation events ¹		X		X		X	
Smoking History	X						
Smoking Status		X				X	
Inclusion / exclusion criteria	X						
Pregnancy test (urine or serum)**	S	S				S	
Concomitant medication review, including rescue medication use	X	X		X		X	
Physical Examination		S		S		S	
Height and weight		X					
Vital signs		X				X	
Randomization via IRT		X					
Contact IRT in order to receive kit id # assignment	S	S	S	S	S		
Contact IRT to confirm discontinuation or end of intervention						S	
Dispensing of Concept2 inhalers and CT formulation of Ultibro [®] Breezhaler [®] capsules	S	S	S	S	S		
Entering Mac Address of dispensed inhalers	X	X	X	X	X		



Period	Screening	Intervention					Follow up
		110	120 130	140	150 160	170	
Visit Number	1						1999
Visit		Randomization				End of intervention PSW/Study Discontinuation	Study completion
Concept2 inhaler(s) return to site		S	S	S	S	S	
Dispensing of tablets*		S					
Tablets return* to site						S	
Concept2 inhaler training		S					
Application training*		S					
Subject setup into investigator application/ Concept2 portal	S						
Setting/re-setting of Preferred Inhalation Time (PIT)	X	X ²		X ²			
Download of Concept2 inhaler use data by the investigator		S	S	S	S	S	
Adverse Events/Serious Adverse event recording	X	X	X ⁵	X	X ⁵	X	X
Device Event/Device deficiency/Adverse Device Effects/Serious Adverse Device Effects recording	X	X	X ⁵	X	X ⁵	X	X
Medication return to site		S	S	S	S	S	
Concept2 inhaler and tablets recovery (device(s))						S	
Intervention completion status						X	
Study completion status							X
PSW = Premature subject withdrawal							
<p>X = assessment to be recorded on clinical data base S = assessment to be recorded on source documentation only * = only subjects randomized to Telehealth group **= only women of child-bearing potential 1. All exacerbations occurring during the study are to be recorded as AE/SAE in the CRF capturing AE/SAE, including the intervention/treatment and hospitalization and/ or emergency room visit 2. Only if during the visit the subject is asking to change the Preferred Inhalation Time</p>							
3. When exchanging the inhalers occurrence of AE/SAE/ADE/SADE should be sought and recorded							

Period	Screening	Intervention					Follow up
Visit Number	1	110	120 130	140	150 160	170	1999
Visit		Randomization				End of intervention PSW/Study Discontinuation	Study completion

8.1 Screening

In this trial re-screening of subjects is allowed if they were excluded due to exclusion criteria number 8 or 10 (see [Section 5.2](#)). Re-screening of subjects can only occur after they have been entered as screening failures in the IRT system. Re-screened subjects should be re-consented and a new subject ID should be assigned to them.

8.1.1 Information to be collected on screening failures

All subjects who have signed informed consent but not entered into the Interventional period will have the study completion page for the screening visit, subject ID, demographics, inclusion/exclusion, device event/device deficiencies, ADEs and SAEs/SADEs data collected. AEs that are not SAEs will be followed by the investigator and collected only in the source data.

8.2 Subject demographics/other baseline characteristics

The following demographics/baseline characteristics will be collected and recorded in the appropriate CRF page(s):

- Age
- Sex
- Race and ethnicity
- Smoking history
- Prior and concomitant medications
- Date of diagnosis of COPD
- Relevant medical history including COPD exacerbation history
- Height and Weight



Investigators will have the discretion to record abnormal test findings on the CRF pages capturing medical history whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

The Concept2 inhaler will track/record each time a subject uses the inhaler with the intention to inhale a dose of Ultibro[®] Breezhaler[®] [REDACTED]. For subjects that are randomized to the Telehealth group, this information will be sent to the tablet device and displayed on the patient application [REDACTED].

[REDACTED] For subjects in the Usual Care group without the patient application the dosing will be tracked by the Concept2 inhaler [REDACTED].

[REDACTED] The Concept2 inhaler data, for subjects in both study groups will be downloaded at the study visits by the investigator using the investigator application and transmitted to the Concept2 portal (central database).

8.3.1 On-time treatment adherence (Dose inhaled on-time)

Subjects will be instructed at the start of the Screening period (Visit 1) to inhale their daily Ultibro[®] Breezhaler[®] medication at the same time every day using the Concept2 inhaler. The PIT will be recorded in the investigator application.

On-time adherence is defined as percentage of days on which the subject inhales at least one dose within (\pm) 2 hours of the agreed PIT. The number of doses inhaled on-time will be recorded by the Concept2 inhaler. The dose reminders provided by the patient application will support the subject to inhale the dose at the same time every day.

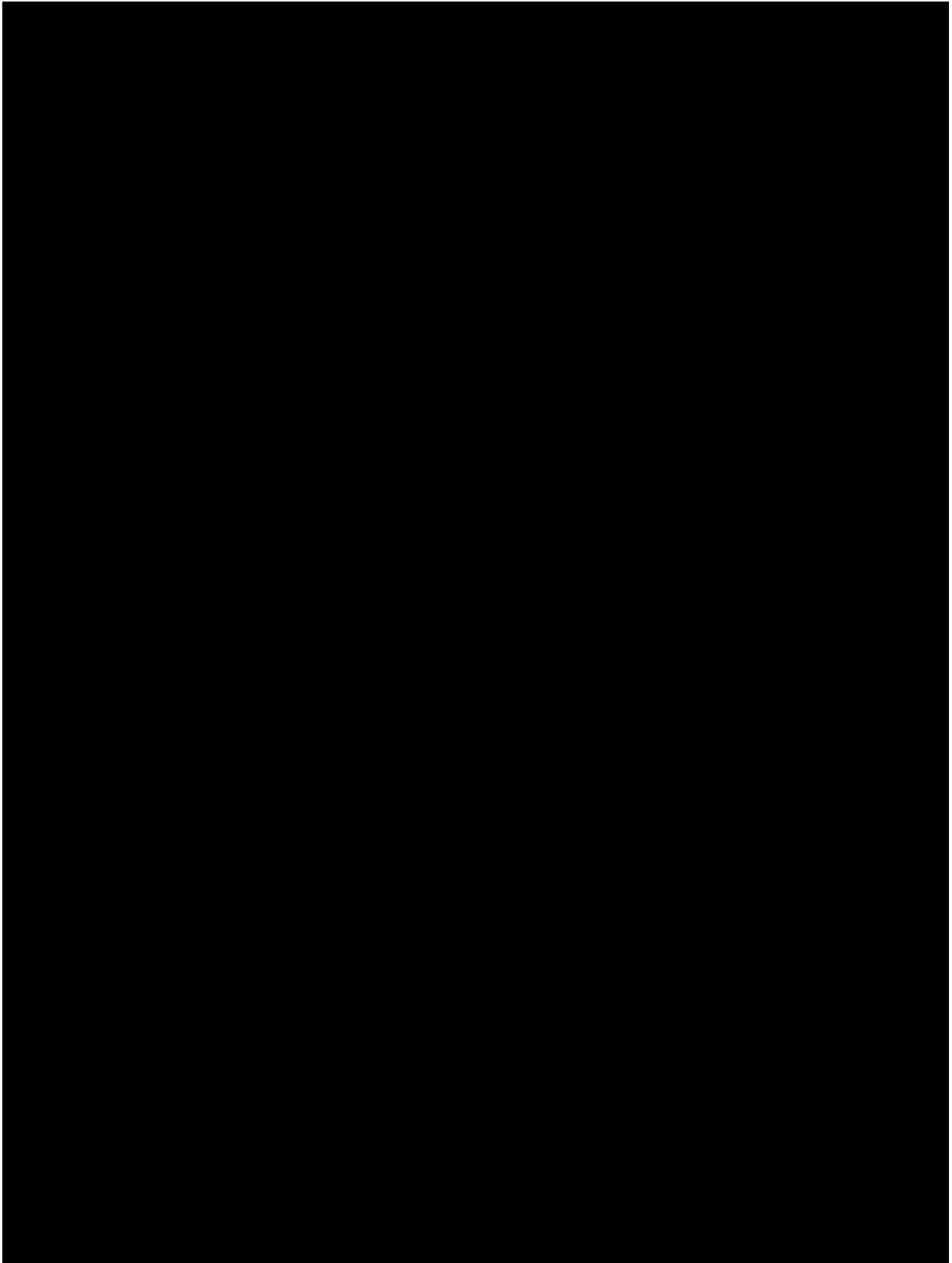
8.3.2 Total treatment adherence (Daily inhalation)

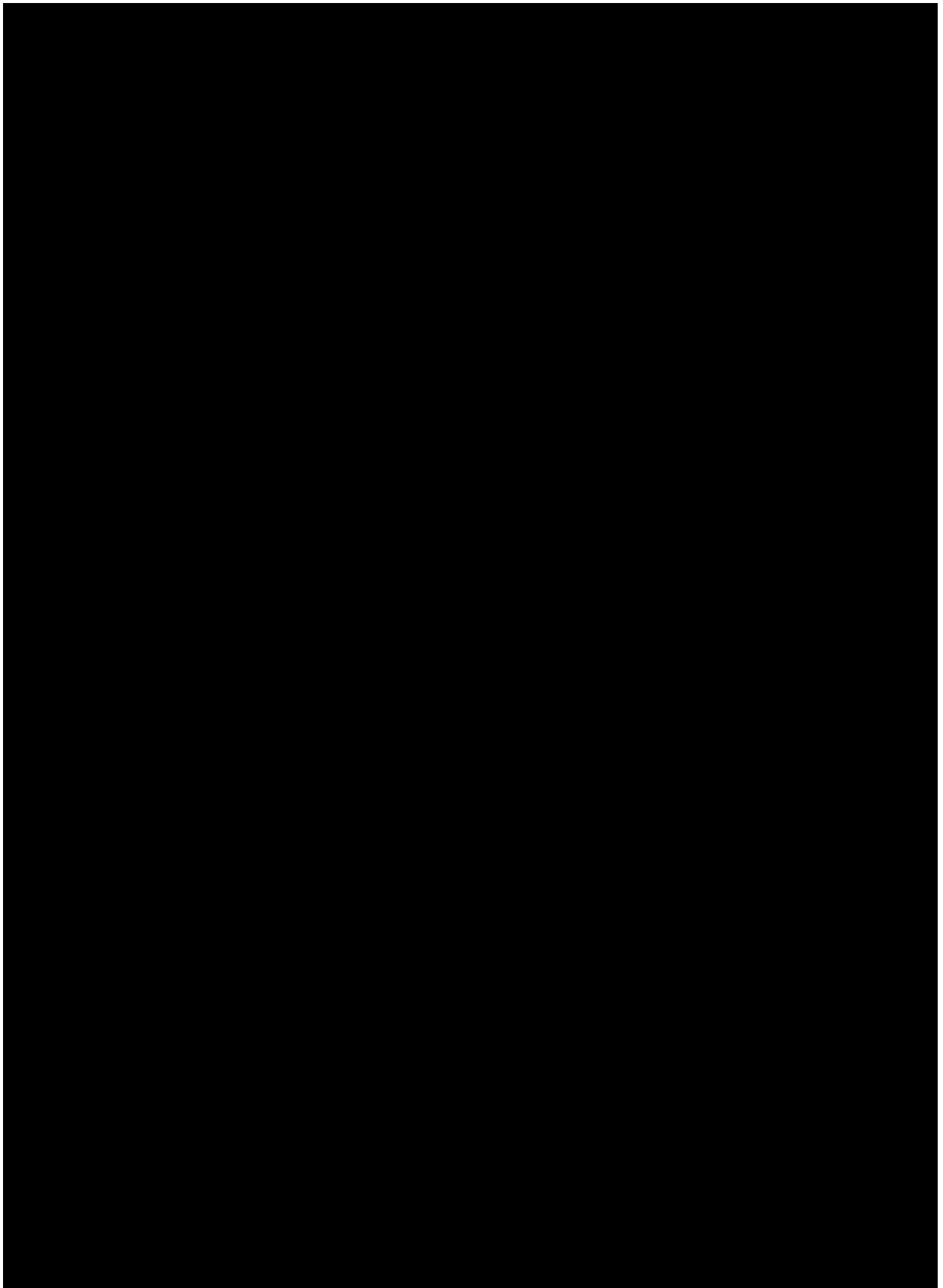
Total adherence is defined as percentage of days on which the subject inhales at least one dose and will be calculated for each subject as the sum of on-time adherence and off-time adherence.

The definition of on-time adherence is explained in [Section 8.3.1](#). Off-time adherence is defined as percentage of days on which the subject did not inhale the daily dose within the (\pm) 2 hours of the predefined PIT, but outside. The number of doses not inhaled on-time will be recorded by the Concept2 inhaler. [REDACTED]

[REDACTED]

[REDACTED]





8.3.4 Appropriateness of efficacy assessments

The efficacy assessments planned for this study are in line with the objectives and include change in adherence level, [REDACTED]

8.4 Safety

The intervention in this study consists solely in the use of an investigational digital adherence system, comprising the patient application and the Concept2 inhaler. The investigational investigator application is only used as a supportive component in the study to download the inhaler data from the Concept2 inhaler. The drug treatment in this trial is not under investigation. Subjects enrolled in this study continue to receive their prescribed Ultibro® Breezhaler® medication as part of the medical management of their COPD. The clinical trial formulation of Ultibro® Breezhaler® medicinal product will be provided to the subjects which is to be inhaled using the Concept2 inhaler, instead of the approved Ultibro® Breezhaler® inhaler. It has been demonstrated that the inhalation performance of the Concept2 inhaler is comparable to the approved Concept1 inhaler (the Breezhaler®), hence there are no additional anticipated risks to the subjects related to the medicinal product used in this trial.

Safety assessments will consist of monitoring and recording the following:

- COPD exacerbations regardless of suspected causality to concomitant treatments will be recorded into the CRF page(s) capturing AEs/SAEs (definition of a COPD exacerbation can be found in [Appendix 8](#)).
- Device deficiencies/Device Events
- Drug administration error, inhaler overuse, incorrect dose administration notified by the subject
- New findings/updates in relation to already reported events
- Adverse Events (AEs) and Adverse Device Effects (ADEs)
- Serious adverse events (SAEs) and Serious Adverse Device Effects (SADEs)
- Physical Examination

[REDACTED]

- Vital signs
- Height and weight
- Highly sensitive urine or serum pregnancy test (for females of childbearing potential), and in case of positive testing, serum pregnancy test (β -hCG)

8.4.1 Physical examination

A complete physical examination will be performed at study visits as described in [Table 8-1](#). It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to providing written informed consent for participation in the study by the subject must be included in the CRF capturing medical history. Significant findings made after the start of study, which meet the definition of an Adverse Event or Serious Adverse Event, must be recorded on the appropriate CRF page(s) capturing AEs.

8.4.2 Vital signs

Vital signs will include pulse rate (measured for 60 seconds) and systolic and diastolic blood pressure. Pulse rate and blood pressure will be assessed after the subject has rested in the supine/sitting position for at least 10 minutes.

Vital signs will be obtained at study visits as described in [Table 8-1](#). In the event of premature study withdrawal, vital signs will be collected at study discontinuation visit.

8.4.3 Laboratory evaluations

No laboratory evaluations are required by the study. Although formal laboratory evaluations are not included in the protocol per se, the study investigator should review the prescribing information for Ultibro[®] Breezhaler[®] and conduct any investigations as needed to provide appropriate care for the subject.

8.4.4 Electrocardiogram (ECG)

ECG evaluations are not required by the study. Although formal ECG evaluations are not included in the protocol, the study investigator should review the prescribing information for Ultibro[®] Breezhaler[®] and conduct any investigations as needed to provide appropriate care for the subject.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. The Investigator must establish at the start of the study whether a female subject is of childbearing potential. Female subjects of childbearing potential must practice safe contraception (see exclusion criteria for a definition of safe contraception [Section 5.2](#)). In these women, a highly sensitive urine or serum pregnancy test will be done at Visits 1, 110 and 170, respectively.



If the subject discovers that she is pregnant during the course of the study, she must inform the Investigator immediately. Where the pregnancy is confirmed (either through the laboratory β -hCG test or through the subject's primary care physician, etc.), the subject must be withdrawn from the study and followed up to determine outcome.

Assessment of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, (Follicle Stimulating Hormone) FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.6 Reporting of inhalation errors (overuse)

Inhalation errors refer to situations where the medicinal product is unintentionally/intentionally and inappropriately inhaled, not in accordance with the protocol.

Drug administration error, inhaler overuse, incorrect dose administration notified by the subject will be recorded into the CRF page(s) capturing Device Events. In addition, drug inhalation frequency (more than one inhalation per day; potential overuse) will be tracked and recorded by the Concept2 inhaler and data downloaded by the investigator using the investigator application. Evaluation of overuse (more than one inhalation per day) will be evaluated by study arm.

8.4.7 Device Event/Device deficiencies

A device event is any event suspected to be related to the device(s). Device deficiencies refer to the inadequacy of an investigational device related to its identity, quality, durability, reliability, safety or performance. This may include technical issues, device deteriorations in the characteristics or performance, device misuse, malfunctions, use error, device occlusion or inadequacy in the information supplied by the manufacturer.

Any device event or device deficiency will be recorded on the CRF page(s) capturing Device Event. A device event or device deficiency that might lead to an ADE or SADE will be reported as described in [Section 10.1](#) or [Section 10.2](#).

8.4.8 Appropriateness of safety measurements

The safety measurements being captured are those expected for this subject population.

8.5 Other assessments

No additional tests will be performed on subjects entered in the study.



9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of intervention

Discontinuation of study intervention for a subject occurs when the intervention is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

The investigator must discontinue study intervention for a given subject if, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study intervention must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the subject
- Inability of subject to use the device (Concept2 inhaler or the patient application)

If discontinuation of study intervention occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation from intervention and record this information.

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject. The investigator must also contact the IRT to register the subject's discontinuation from study intervention. After discontinuation of intervention, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse events/Serious Adverse Events/adverse device effect/Serious Adverse Device Effects

Subjects who discontinue study should undergo an end of study visit and then be discontinued from the trial.

9.1.1.1 Replacement policy

Subjects who are discontinued from the study will not be replaced by an equal number of newly enrolled subjects.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore

and



- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study intervention and Ultibro® Breezhaler® medication provided within the study must be discontinued and no further assessments conducted. The data that would have been collected at subsequent visits will be considered missing.

The investigator has to ensure that all dispensed Concept2 inhalers (used and unused), the Ultibro® Breezhaler® medication and the tablet device (if applicable) are returned to the study site.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in [Table 8-1](#).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law. All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Not applicable

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking treatment and use the intervention, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor



depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision

Subjects completing 24 weeks Interventional period will not be given further access to the digital adherence system.

The investigator must provide follow-up medical care for all subjects completing the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

For all subjects a safety follow-up visit (Visit 1999) is conducted (e.g. by telephone) 30 days after last visit (Visit 170) or after the subject has been prematurely withdrawn. The information to be collected at this follow up visit includes concomitant medications, adverse events, and survival status (Table 8-1).

10 Safety monitoring

In this trial, safety monitoring will be done for

- (1) the devices: the components of the investigational digital system (Concept2 inhaler and patient application) and the investigator application following the GVP Volume IX and MEDDEV regulations (MEDDEV 2.7/3 revision 3, May 2015) and
- (2) the medicinal product (clinical trial formulation of the Ultibro[®] Breezhaler[®]), despite not being an investigational treatment

by reporting:

- **Device related events:** Adverse device effects and serious adverse device effects, device deficiency that might lead to an SADE, and new findings/updates to already reported events for the devices
- **Not device related events:** Adverse events and serious adverse events (which may or may not be related to the medical product (Ultibro[®] Breezhaler[®]))

Device related cases (such as device malfunction, device deficiency, procedural errors, device deterioration, inaccurate instructions, degradation or destruction of the device) not meeting the definition of an adverse event are not considered ADE and are reported as Device Events.

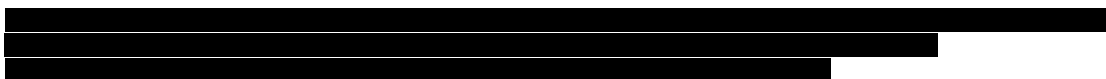
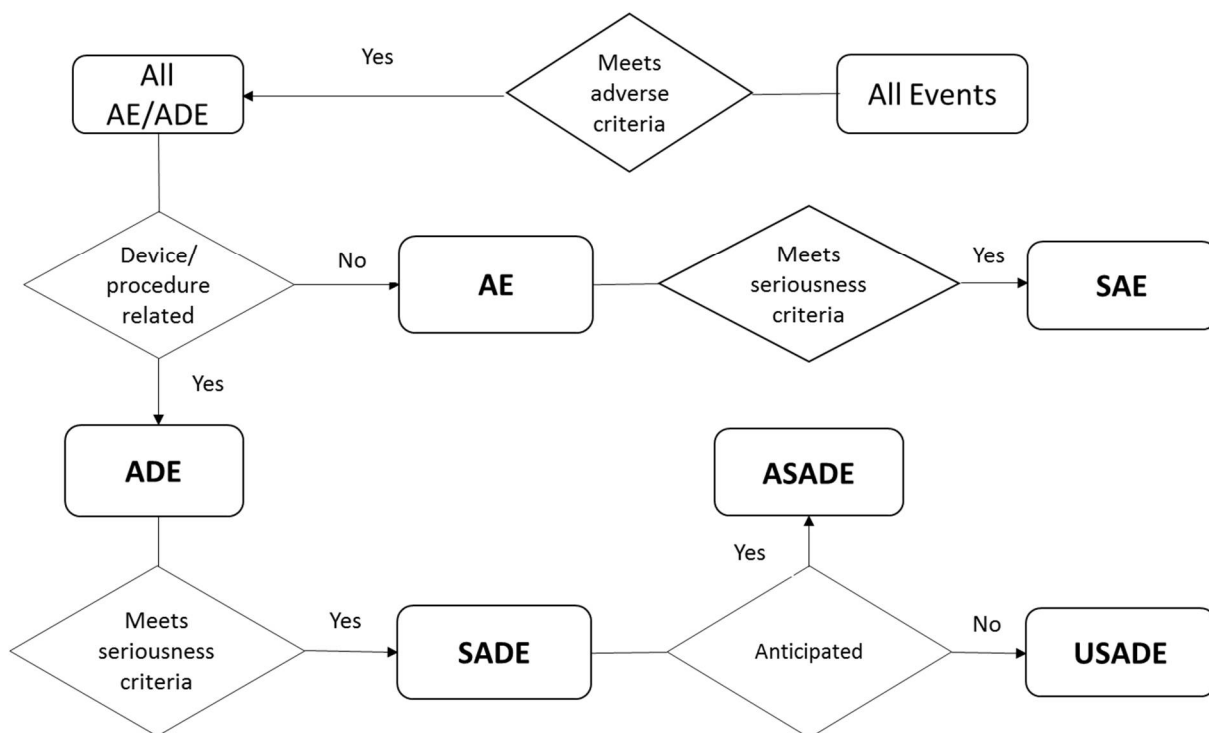


Figure 10-1 Safety monitoring



10.1 Adverse events and Adverse device effects definitions and reporting requirements

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal product or device. This definition includes also events related to the procedures involved. All reports of intentional misuse and abuse of the medicinal product are also considered an adverse event irrespective if a clinical event has occurred. AEs, which are related to the use of the device, are reported as adverse device effects as described hereafter.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from



baseline or the previous visit, or values which are considered to be non-typical in subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subjects and identifying adverse events.

An adverse device effect (ADE) is an adverse event related to the use of a device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the device(s). This includes also any event that is a result of a use error or intentional misuse.

The occurrence of adverse events or adverse device effects should be sought by non-directive questioning of the subject at each visit during the study. Adverse events or adverse device effects also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

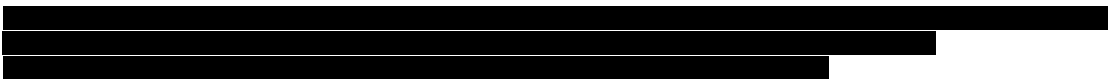
Adverse events and adverse device effects must be recorded on the appropriate CRF page(s) capturing AEs or ADEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

1. the severity grade:
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities
2. its relationship to the device(s) or medicinal product (No Relationship to medicinal product or device(s)/Relationship to medicinal product/Relationship to device(s))
3. its duration (start and end dates or if the event is ongoing an outcome of not recovered/not resolved must be reported)
4. whether it constitutes a serious adverse event (SAE) or serious adverse device effect (SADE) and which seriousness criteria have been met

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- treatment dosage not changed (i.e., no action taken, further observation only)
- treatment dosage increased/reduced
- treatment or inhaler use interrupted/withdrawn
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event or adverse device effect is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or



more frequently, if necessary) of any changes in severity, the suspected relationship to the medicinal product or device(s), the interventions required to treat it, and the outcome.

Information about known side effects of the device(s) can be found in the device specific Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject's informed consent and should be discussed with the subject during the study as needed. Known side effects of the drug can be found in the drug IB.

The investigator should also instruct each subject to report any new adverse event/adverse device effect (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to the medicinal product or device(s) used. This information should be recorded in the investigator's source documents; however, if the AE/ADE meets the criteria of an SAE/SADE, it must be reported to Novartis.

10.2 Serious adverse events and Serious adverse device effects definitions and reporting requirements

10.2.1 Serious adverse events

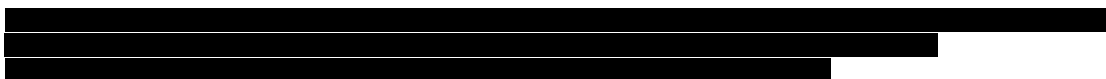
A serious adverse event (SAE) is an adverse event, related or not to the drug, that meets the criteria of seriousness as defined in [Section 10.2.1.1](#). Serious adverse events related to the use of a device are reported as serious adverse device effects as described in [Section 10.2.2](#).

10.2.1.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 1. routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
 2. elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 3. treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 4. social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.



Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe ([ICH-E2D Guideline](#)).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important device or medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse ([ICH-E2D Guideline](#)).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF page(s) capturing AEs, SAEs SAE reporting.

To ensure subjects safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and



reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.2.2 Serious adverse device effects

A serious adverse device effect (SADE) is an adverse event related to the use of a device, which meets the seriousness criteria defined in [Section 10.2.2.1](#).

10.2.2.1 Definition of SADE

An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event:

- led to a death, injury or permanent impairment to a body structure or a body function.
- led to a serious deterioration in health of the subject, that either resulted in:
 1. a life-threatening illness or injury, or
 2. a permanent impairment of a body structure or a body function, or
 3. in-patient hospitalization or prolongation of existing hospitalization, or
 4. in medical or surgical intervention to prevent life threatening illness
- led to foetal distress, foetal death or a congenital abnormality or birth defect

10.2.2.2 SADE reporting

The investigator must assess the relationship to each specific component of study intervention (Concept2 inhaler, patient application, investigator application) and complete and submit the SADE Report Form in English.

The investigators will distinguish between the serious adverse events related to the device(s) and those related to the procedures (any procedure specific to the clinical investigation).

Each SADE will be classified according to five different levels of causality. The investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational device or procedures.

1) **Not related**: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;



- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) **Unlikely**: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) **Possible**: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) **Probable**: the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5) **Causal relationship**: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
 - the investigational device or procedures are applied to;
 - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;



In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Events to be reported include:

- any SADE
- new finding/updates in relation to reported events
- any investigational Device deficiencies that might lead to a SAE if
 - suitable action had not been taken or
 - intervention had not been made or
 - if circumstances had been less fortunate

Once completed and signed the SADE form is sent by the investigator by fax immediately but not later than 3 calendar days after the site study personnel's awareness of the event to the local Novartis Patient Safety Department. If the SADE indicates an imminent risk of death, serious injury, serious illness or requires prompt remedial action for other subjects, users or other persons or a new finding to it, the SADE has to be reported immediately to the local Novartis Patient Safety Department. The telephone and fax number of the contact persons in the local department of Patient Safety, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SADE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SADE Report Form stating that this is a follow-up to a previously reported SADE.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SADE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study intervention a Patient Safety associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study intervention that this SADE has been reported. Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report is defined as an unanticipated serious adverse device effect. Unanticipated serious adverse device effect (USADE) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.3 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.



Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Ultibro® Breezhaler® treatment. Any SAE experienced during pregnancy must be reported.

10.4 Additional Safety monitoring

10.4.1 Liver safety monitoring

No liver safety monitoring is required by the study. Although formal evaluations are not included in the protocol, the study investigator should review the prescribing information for Ultibro® Breezhaler® and conduct any investigations as needed to provide appropriate care for the subject.

10.4.2 Renal safety monitoring

No renal safety monitoring is required by the study. Although formal evaluations are not included in the protocol per se, the study investigator should review the prescribing information for Ultibro® Breezhaler® and conduct any investigations as needed to provide appropriate care for the subject.

10.4.3 Prospective suicidality assessment

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 (US code of Federal Regulations) requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

This study will incorporate electronic technology to capture source data electronically (Concept2 inhaler(s) capturing subject inhaler use data over 4 weeks and electronic questionnaires running on a site tablet or investigator application). The data will be downloaded and transmitted or directly transmitted to the Concept2 portal system or vendor's data base and then sent electronically to Novartis. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.



All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Questionnaire data will be entered into an electronic tablet by the subject. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis.

The data collected in the Concept2 portal system will be sent electronically to Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource or CRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subjects records, the accuracy of data capture / data entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that medication and Concept2 inhalers are stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA (Clinical Research Associate) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent forms signed by the subject (a signed copy is given to the subject).



The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends. The primary analysis will be performed after all randomized subjects have completed the study or have withdrawn early from the study. A detailed Statistical Analysis Plan (SAP) will contain further explanation about the analysis plans. It will include details on the methodology used in the statistical analyses as well as details about reporting and data derivations.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The following analysis sets are defined for data analysis:

The randomized (RAN) set will consist of all subjects who were assigned a randomization number. The RAN set will be used for a summary of subject disposition, demographics and baseline characteristics.

The Full Analysis Set (FAS) will include all randomized subjects who inhaled at least one dose with the Concept2 inhaler and have one time and date stamp on the chip. Following the intent-to-treat principle, subjects will be analyzed according to the intervention group (either Concept2 with “application” or Concept2 alone) they were assigned to at randomization. Analysis of all efficacy variables will be done on the FAS.

The Per-Protocol Set (PPS) will include all subjects in the FAS without any major protocol deviations. Major protocol deviations will be defined in the statistical analysis plan prior to database lock and the un-blinding of the study. Subjects will be analyzed according to the intervention they received (either Concept2 with “application” or Concept2 alone). The PPS will be used for the supportive analysis of the primary variable.

The Safety Set will include all subjects who inhaled at least one dose with the Concept2 inhaler and have one time and date record. Subjects will be analyzed according to the intervention they received (either Concept2 with “application” or Concept2 alone). The safety set will be used in the analysis of all safety variables.

12.2 Subject demographics and other baseline characteristics

Demographic and baseline characteristics including age, gender, race, ethnicity, height, weight, body mass index (BMI), duration of COPD (as time span between date of diagnosis of COPD to date of enrollment), relevant medical history, COPD exacerbation history, smoking history, prior and concomitant medications, vital signs (Sitting systolic and diastolic blood pressure,



pulse rate), baseline adherence, [REDACTED] will be summarized by intervention group.

Continuous variables will be summarized using descriptive statistics (mean, median, standard deviation, minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of subjects in each category.

Baseline is defined as the last measurement before the first inhalation of Ultibro® Breezhaler® medication with the Concept2 inhaler during the interventional period, if available.

12.3 Intervention

The number of subjects and the length of time (in days) in the study will be summarized by intervention group for the safety set.

Concomitant medications will be summarized by intervention group for the safety set. Concomitant medications will be summarized by route of administration and preferred term”

12.4 Analysis of the primary variable(s)

The primary objectives are to determine whether the use of dose tracking by the inhaler in conjunction with reminder notifications and motivational/adaptive messages sent by the patient application can improve on-time adherence or total adherence over 24 weeks of intervention.

On-time adherence is defined as the percentage of days on which the subject inhaled at least one dose within (\pm) 2 hours of the agreed preferred daily inhalation time. The daily preferred inhalation time (PIT) must be defined by the subject at the start of the study and can only be modified at scheduled study visits by the study investigator at the request of the subject.

Total adherence is defined as the percentage of days on which the subject inhaled at least one dose and will be calculated as the sum of on-time adherence and off-time adherence. Off-time adherence is defined as percentage of days on which the subject did not inhale the daily dose within the (\pm) 2 hours of the PIT, but outside.

12.4.1 Variable(s)

The primary variables for the study are the change from baseline (Visit 110) in on-time adherence and change from baseline in total adherence during 24 weeks of Interventional period. The on-time adherence will be calculated as the number of days with at least one dose/inhaler use recorded via the Concept2 inhaler within (\pm) 2 hours of planned PIT, divided by the number of days the subject had the Concept2 inhaler over 24 weeks. Total adherence will be calculated as the sum of on-time adherence and off-time adherence. Off-time adherence will be calculated as the number of days the subject did not inhale the daily dose within the (\pm) 2 hours of the predefined PIT, but outside, divided by the number of days the subject had the Concept2 inhaler over 24 weeks.

If more than one dose is inhaled within (\pm) 2 hours of preferred inhalation time, it will be counted once for the purpose of on-time adherence (numerator) day calculation. The additional dose(s), if any, will be considered as overuse, if it meets the criteria outlined in [Section 12.6.1.5](#).

[REDACTED]

If the subject is inhaling one or more doses during one day, in addition to the dose administration within (\pm) 2 hours of PIT, that will not be counted towards off-time adherence calculation, hence not in total adherence calculation.

The dispensing period is 4 weeks, when one inhaler will be dispensed. In addition one Concept2 back-up inhaler will be dispensed at Visit 110 and Visit 140, each. In case the back-up inhaler is used before Visit 140 or end of Interventional period (Visit 170) the subject will receive a new one. Each inhaler is designed and validated for a maximum of 30 days delivery.

In each 4-week dispensing period the number of days for the denominator will be defined as follows:

- Date of the first inhaler use data recorded into the Concept2 inhaler or Pairing Time, whichever comes first, plus 27 days or last data recorded in Concept 2 inhaler, whichever is later (from all used Concept2 inhalers, regular and back-up's). If the inhaler is lost then the corresponding visit day will be used as the first inhaler use date.
- If a subject discontinues the study, the denominator for each of the remaining 4-week periods will be defined as 28. The missing data will be imputed as outlined in [Section 12.4.3](#).
- The number of days from each of the six 4-week periods will be summed to be used as the overall denominator in calculations.

Baseline on-time adherence and total adherence will be calculated from the 6 weeks Screening period (Visit 110 has a visit window of \pm 7 days, that is days 35-49). The number of days in the denominator will be defined as:

- Days between Visit 1 (exclusive) and Visit 110 (inclusive). A minimum of 35 days in the screening are expected for a subject to be eligible for having baseline adherence calculation performed. Subjects with a COPD exacerbation during Screening are considered screening failure.

The period for which subject was taken off Ultibro[®] Breezhaler[®] treatment/inhaler use by investigator will be excluded from adherence calculation (for both Screening and Interventional period)

12.4.2 Statistical model, hypothesis, and method of analysis

The use of dose reminder notifications and motivational/adaptive messages will be evaluated by testing the following two null hypotheses H_1 and H_2 for on-time adherence and total adherence, respectively.

H_1 : There is no difference in change from baseline in on-time adherence for subjects who received dose reminder and motivational/adaptive messages compared to subjects who received none.

H_2 : There is no difference in change from baseline in total adherence for subjects who received dose reminder and motivational/adaptive messages compared to subjects who received none.

The alternative hypothesis for each of H_1 and H_2 is that- there is a difference, respectively.

Each of the primary variables will be analyzed using the analysis of covariance model (ANCOVA) for the FAS. The ANCOVA model will contain intervention (here defined as dose



reminders and motivational/adaptive messages versus usual care), baseline total adherence group, country and baseline COPD severity as fixed effects with baseline on-time adherence/total adherence rate as covariate.

The estimated adjusted difference of the intervention for the Telehealth group minus Usual Care group will be displayed along with the associated 95% (two-sided) confidence interval.

Also the means of on-time adherence/total adherence will be presented graphically over 4-week time intervals by intervention group.

If at least one of the primary endpoints is significant the study will be considered positive.

To control the overall type-1 error rate, multiplicity adjustment (for 2 endpoints) is described in [Section 12.4.4](#).

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for adherence will be imputed through a multiple imputation approach, under the assumption of missing data are missing at random. Utilizing this approach all subjects in the FAS will contribute in the analysis. For the primary analysis- data from inhalers (through investigator application) will be used. The supplemental data from patient application will not be used, to ensure a consistent imputation process for both groups.

A sensitivity analysis will be done including the supplemental data from the patient application. That is, the missing data (from inhaler/investigator application) will first be imputed/updated with the patient application data, if available. Then the overall imputation will be done using the multiple imputation approach mentioned above.

Further elaboration of the multiple imputations will be provided in the statistical analysis plan (SAP).

12.4.4 Multiplicity adjustment

To control the family-wise type-I error rate at the two-sided 5% significance level, the trimmed Simes test in [Brannath et al \(2009\)](#) is used. The family for the overall type-I error rate control contains 2 hypotheses- one for the on-time adherence primary endpoint and the other for the total adherence primary endpoint. Denote the two hypotheses for the two primary endpoints as H_1 and H_2 , respectively. Below is a description of the testing procedure. Let p_1 and p_2 be the corresponding p-values (2-sided) of the two hypotheses of H_1 and H_2 .

Step 1: Retain both hypotheses and stop if ANY $p_i \leq 0.05$ (for $i=1$ or 2) AND the observed treatment difference for the corresponding p_i is in the wrong direction (i.e. Usual Care group is better than Intervention group); otherwise go to step 2.

Step 2: Reject both hypotheses if $p_i < 0.05$ for BOTH $i=1, 2$, and stop here; otherwise go to step 3.

Step 3: Perform the Bonferroni test and reject H_1 if $p_1 < 0.025$ and reject H_2 if $p_2 < 0.025$.

For H_1 and H_2 , their corresponding testing statistics follow jointly bivariate normal distribution. Therefore this testing procedure controls the overall type-I error rate at the 2-sided 0.05 level



in the strong sense regardless if the bivariate normal distributions have positive or negative correlations as shown in [Brannath et al \(2009\)](#).

Other than the primary analysis, all other analyses will be performed at the nominal 2-sided 0.05 significance level without multiplicity adjustments.

12.4.5 Sensitivity analyses

As sensitivity analyses, the same ANCOVA used in the primary analysis will be also performed on the PPS to assess the robustness of the results from the primary analysis.

The primary analysis model will be re-run including additional covariates, for example age and sex, to investigate the impact of these on any intervention effect. Details of these analyses will be pre-planned and described in the SAP.

12.5 Analysis of secondary variables

12.5.1 Efficacy variables

12.5.1.1 On-time adherence and total adherence over the last four weeks

The on-time adherence and total adherence over the last four weeks of Interventional period (Week 21-24) will be summarized by intervention group.

The change from baseline in on-time adherence/total adherence over the last 4 weeks of Interventional period will be analyzed using the same ANCOVA model specified for the primary analysis. The missing data imputation will be done using the same method used for the primary endpoints analysis.

12.5.2 Safety variables

12.5.2.1 Adverse events

All device related ADE/SADE and non-device related AE/SAE will be summarized by intervention group and by screening and Interventional period separately. Also COPD exacerbations during the Interventional period will be summarized by intervention group. Subjects having a COPD exacerbation during the Screening period are considered screening failures.

The following adverse event summaries will be produced: overall by system organ class and preferred term; overall by system organ class; preferred term and maximum severity; serious adverse events by system organ class and preferred term; and adverse events leading to permanent discontinuation of study by system organ class and preferred term.

12.5.3 Resource utilization

Data relating to resource utilization may be used for the purpose of economic evaluation, which will be carried out and reported as a separate activity.

12.5.4 Pharmacokinetics

Not applicable.



12.5.5 Pharmacogenetics/pharmacogenomics

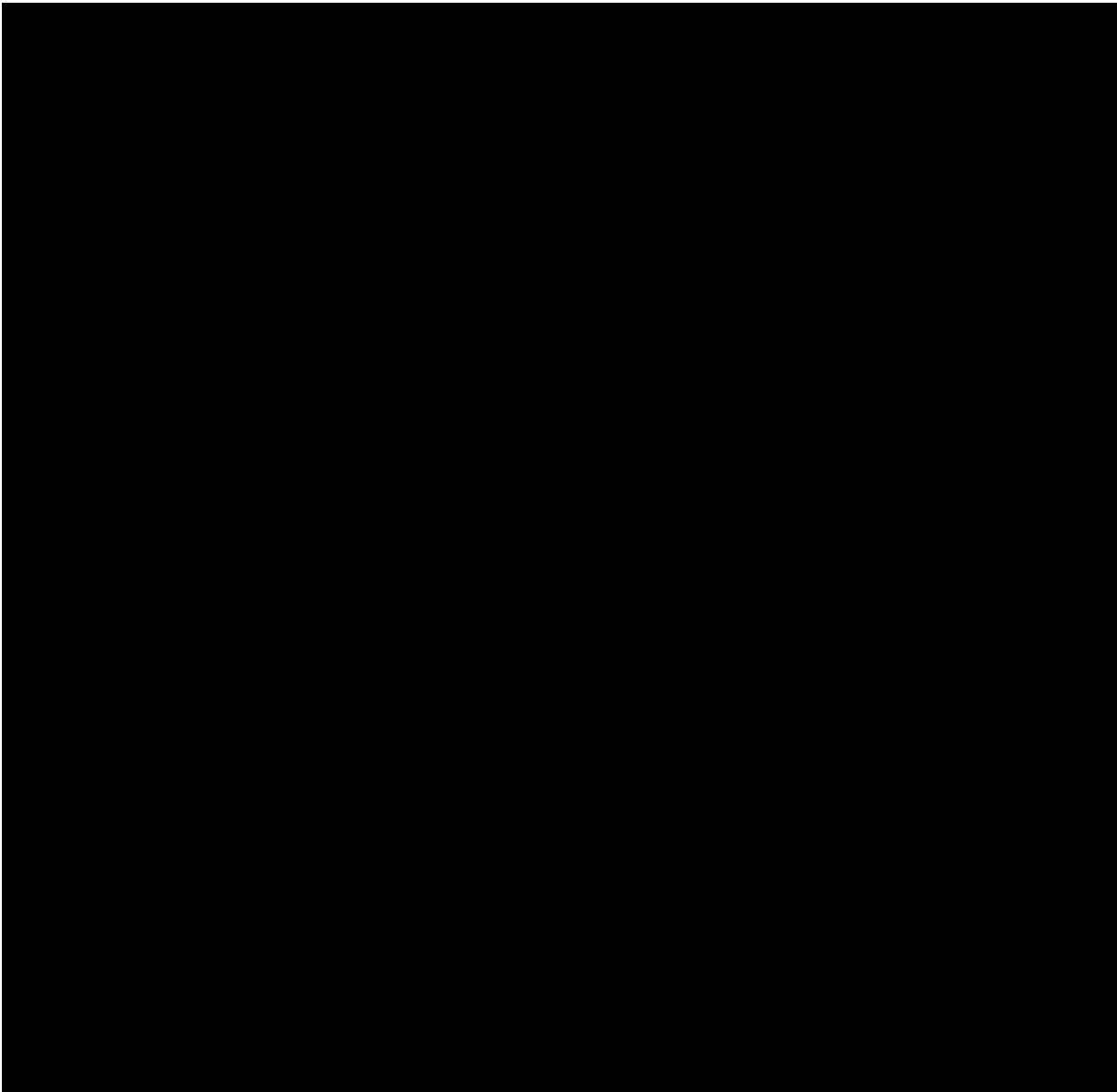
Not Applicable. The drug treatment in this trial is not under investigation.

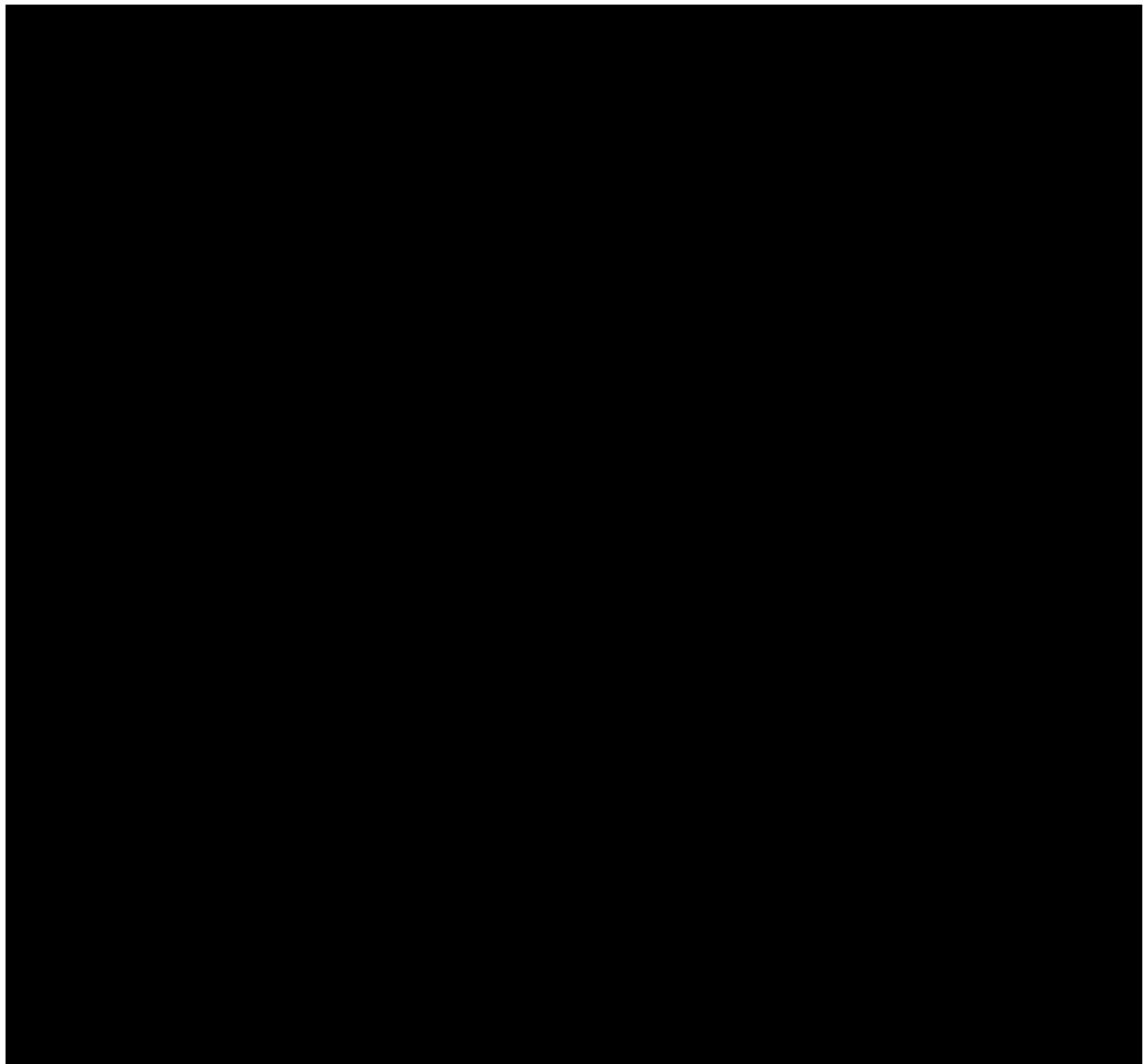
12.5.6 Biomarkers

Not applicable.

12.5.7 PK/PD

Not applicable.





12.7 Interim analyses

No interim analyses is planned.

12.8 Sample size calculation

Sample size calculation takes into account the following considerations:

1. To achieve 90% power (with multiplicity adjustment) for primary endpoint on-time adherence with a group difference of 15% between intervention group vs. Usual Care group (i.e. change from baseline in mean on-time adherence in intervention group – (minus) change from baseline in mean on-time adherence in Usual Care group), assuming a common standard deviation of 25%, based on reference below.



2. To achieve 90% power (with multiplicity adjustment) for primary endpoint total adherence with a group difference of 15% between intervention group vs. Usual Care group (i.e. change from baseline in mean total adherence in intervention group – (minus) change from baseline in mean total adherence in Usual Care group), assuming a common standard deviation of 25%, based on reference below.

In absence of any available assessment of the correlation between the two primary endpoints, a relatively conservative measurement (of 0.8) has been chosen for the simulation. Considering a 15% dropout, the simulation (under the testing scheme in [Section 12.4.4.](#)) shows that the sample size of 146 (73 per arm) will provide 90% power for on-time adherence and 90% power for total adherence, with multiplicity adjustment. With zero (0) correlation the power for on-time adherence will be above 90% and the power for total adherence will be above 90%.

The sample size and power calculations are performed in R 3.3.0.

(Reference: [Charles et al \(2007\)](#) an audiovisual reminder function (AVRF) study reported a difference in median adherence between the two groups (AVRF group vs. control group) as 18% (95% CI, 10% to 26%, $P < 0.0001$); [Strandbygaard et al \(2009\)](#), a daily SMS reminder study reported a difference in change from baseline in mean adherence between two groups, one received daily SMS and one did not, as 17.8%, 95% CI (3.2 – 32.3%), $p = 0.019$; common standard deviation for mean changes in adherence = 19%, (calculated)).

13 Ethical considerations

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US 21 CFR part 11 and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as [clinicaltrials.gov](#) and as required in EudraCT. In addition, after study completion (defined as last patient last visit)



and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines..

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs or devices under the protocol other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.



In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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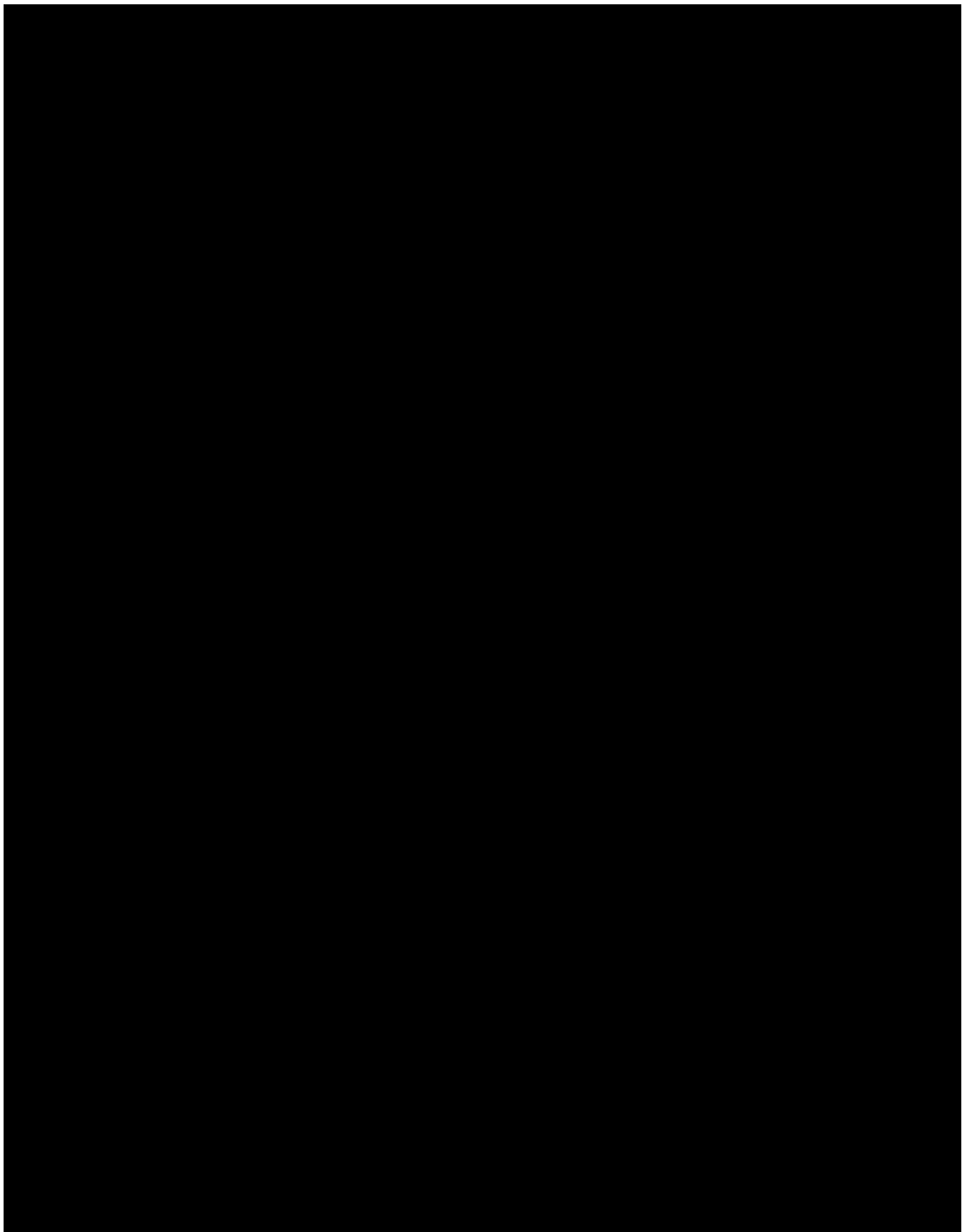
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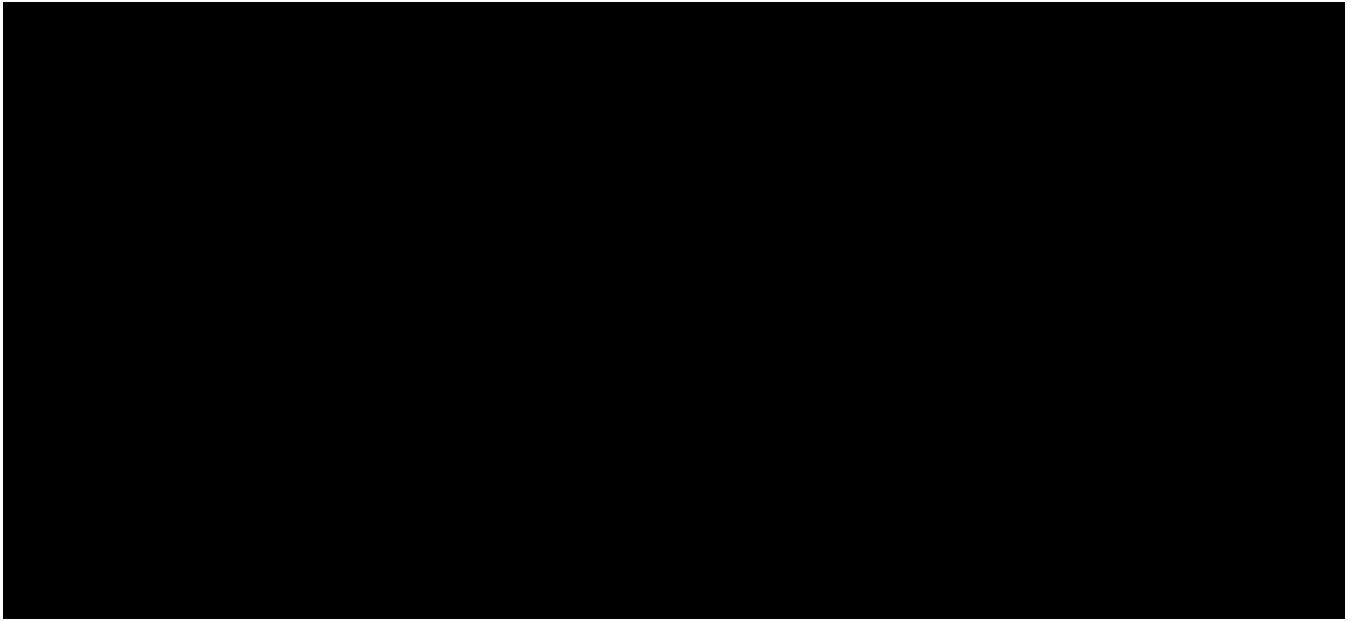
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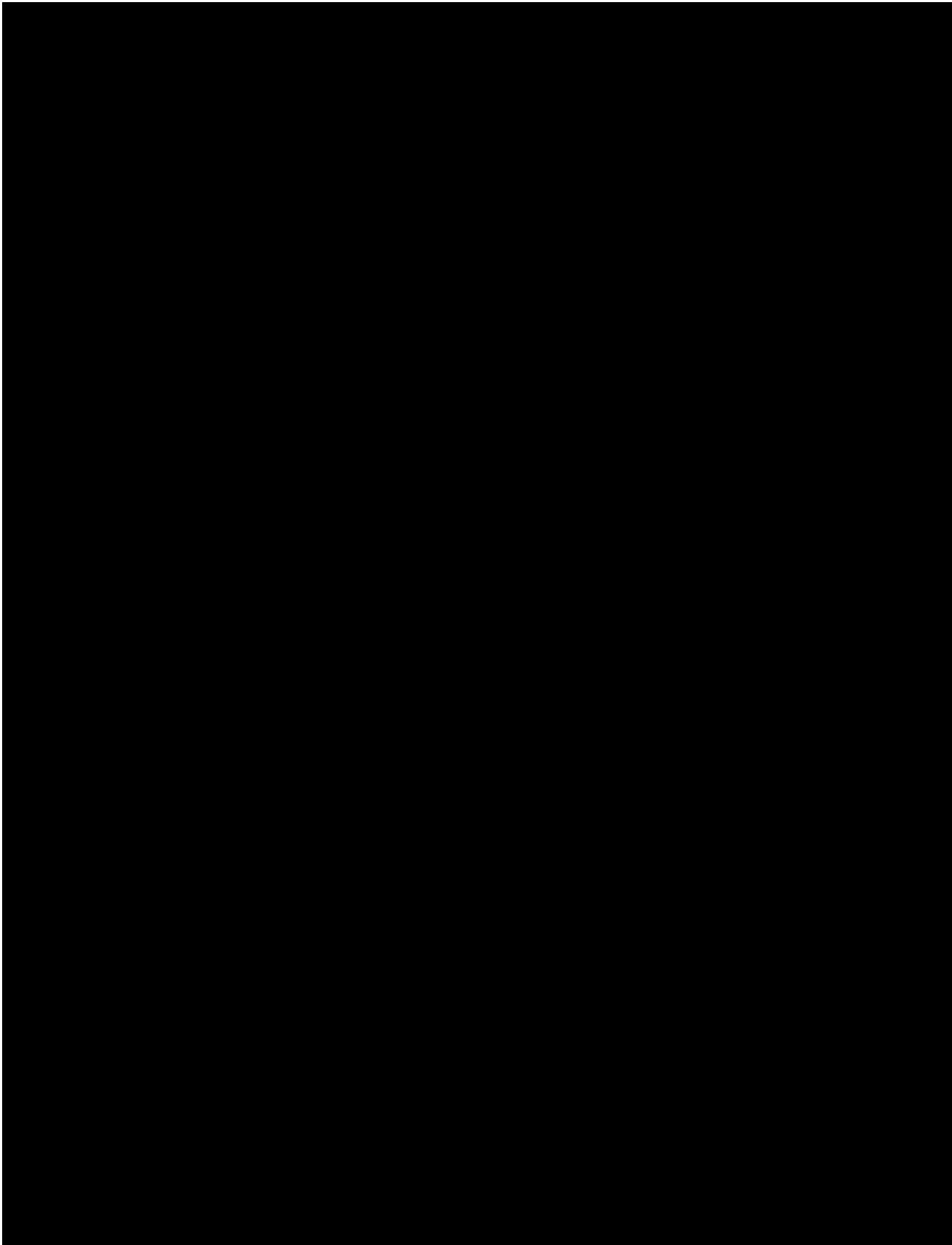
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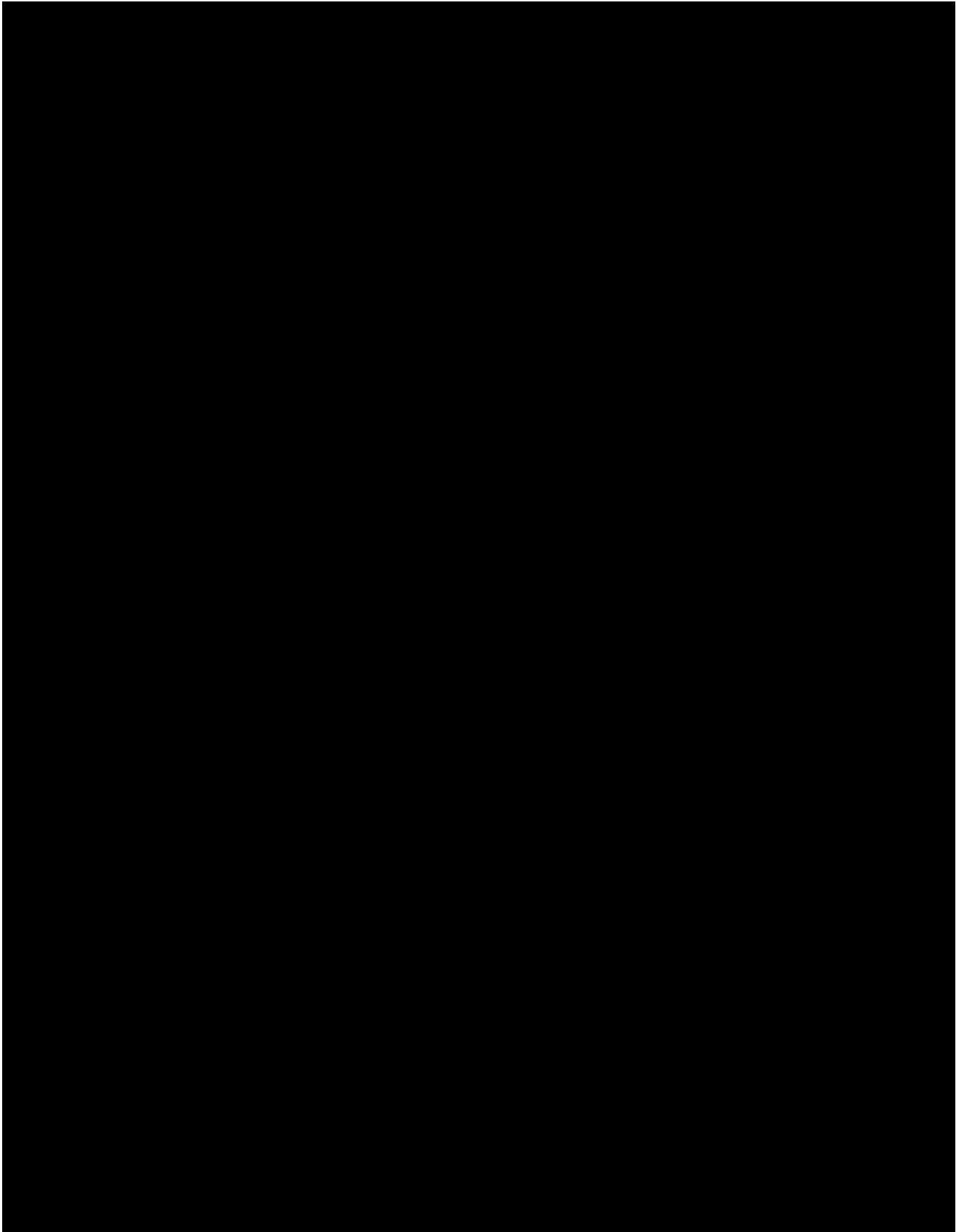


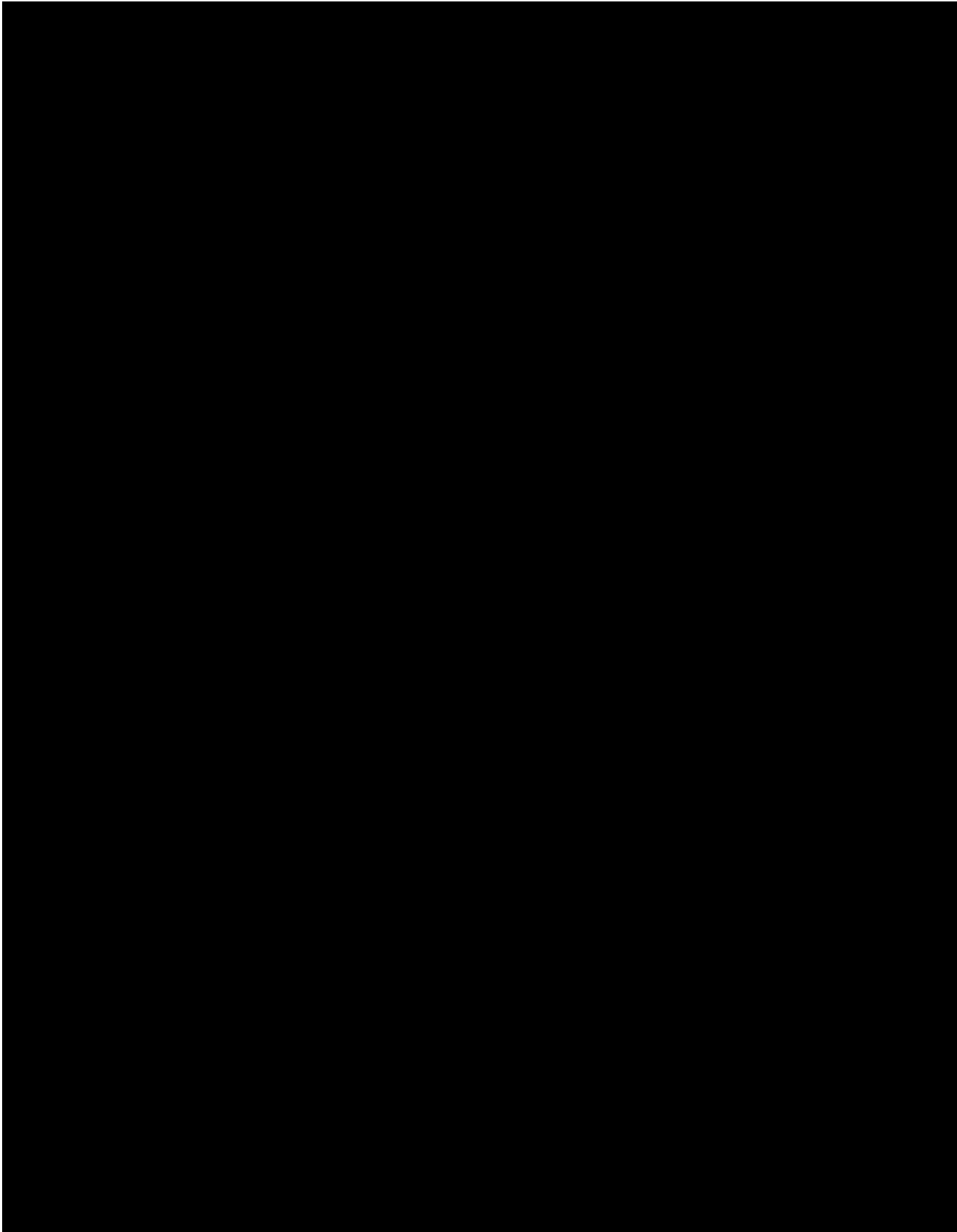


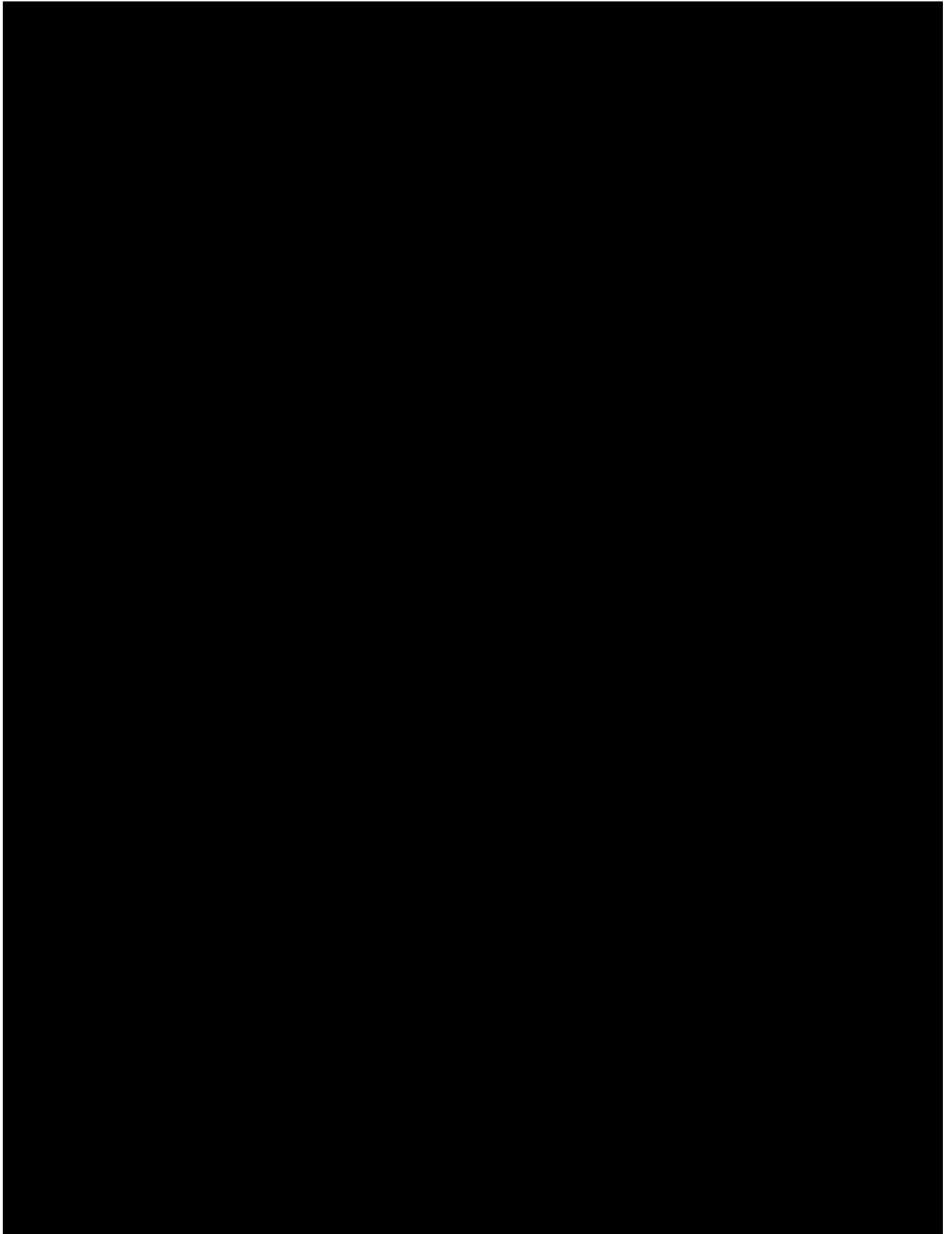
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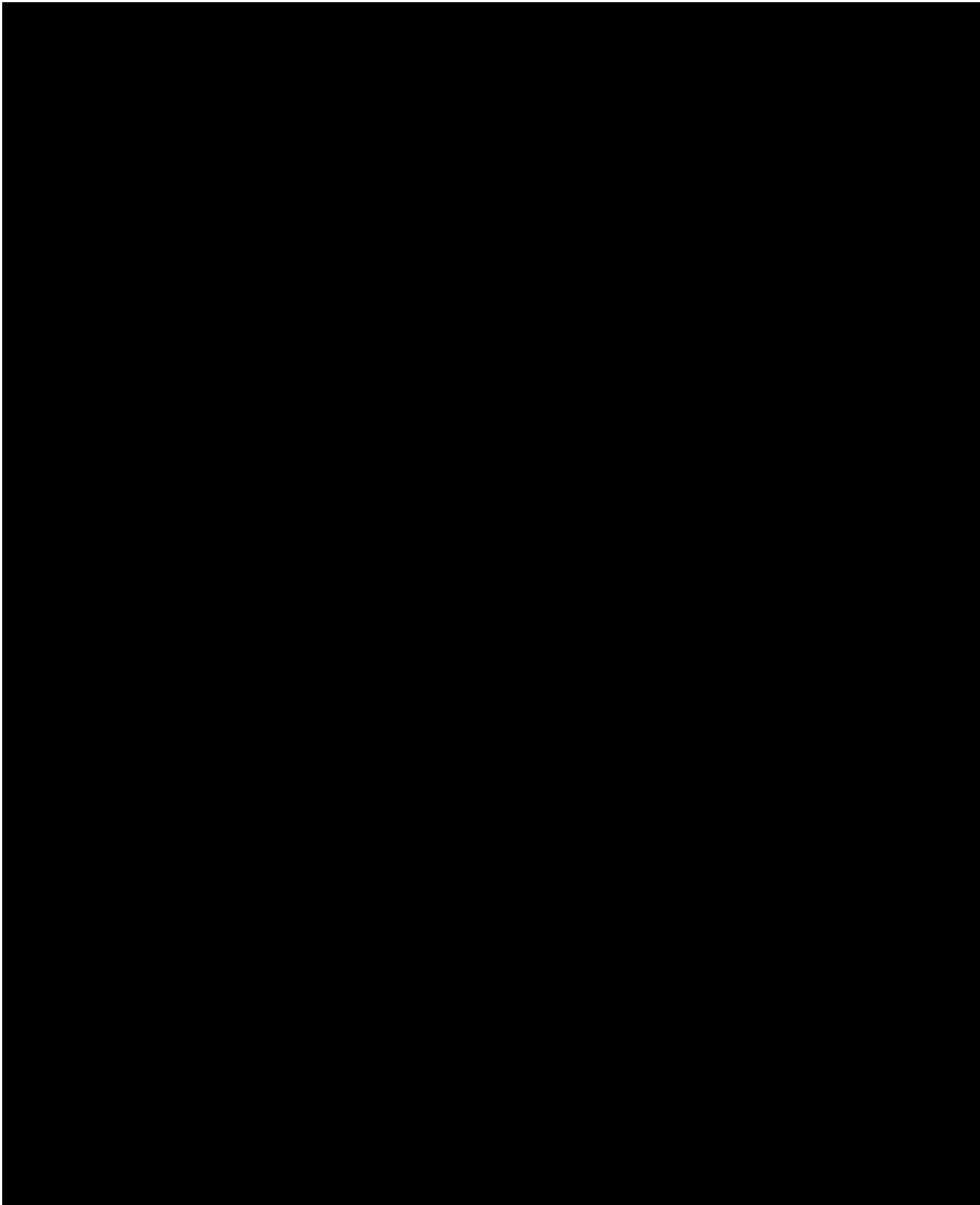


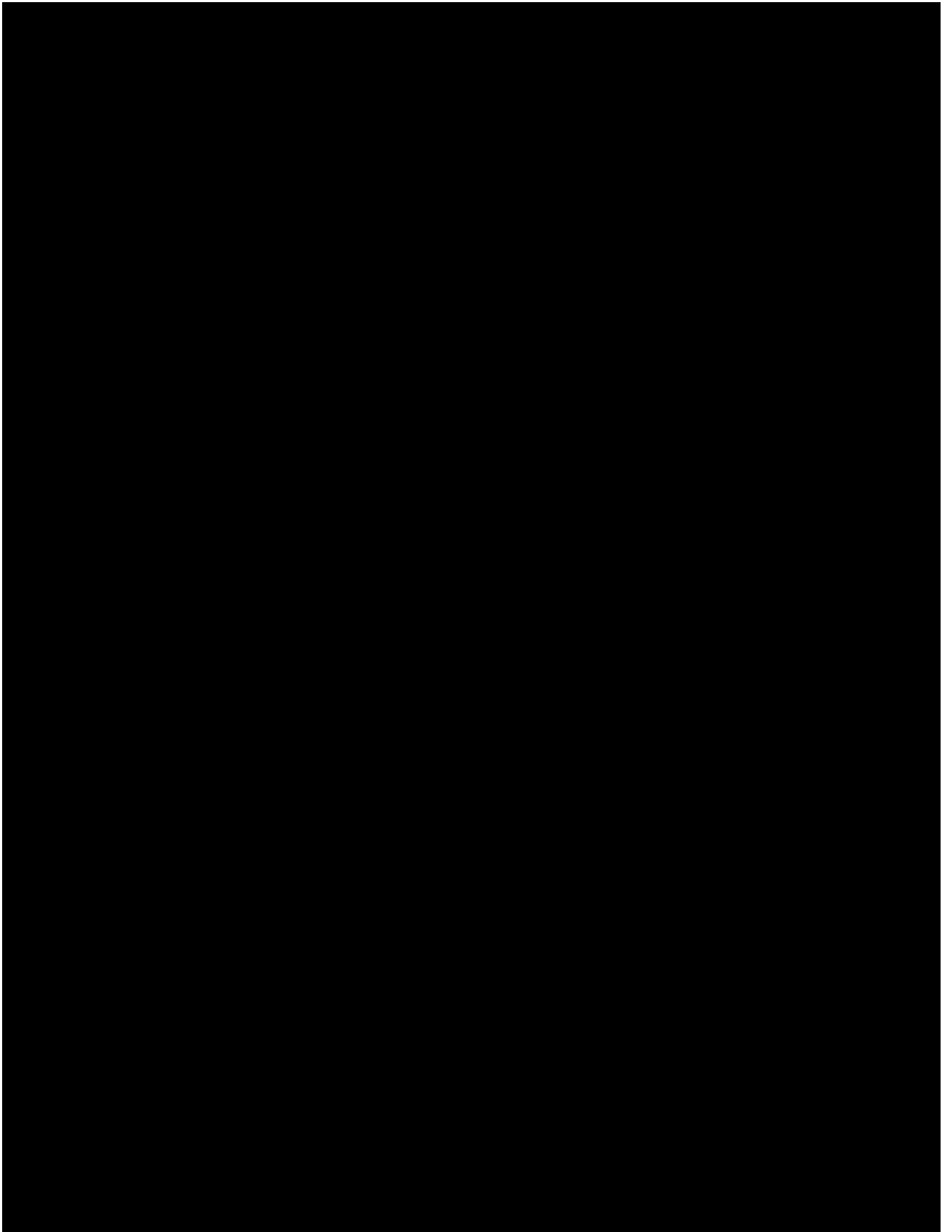


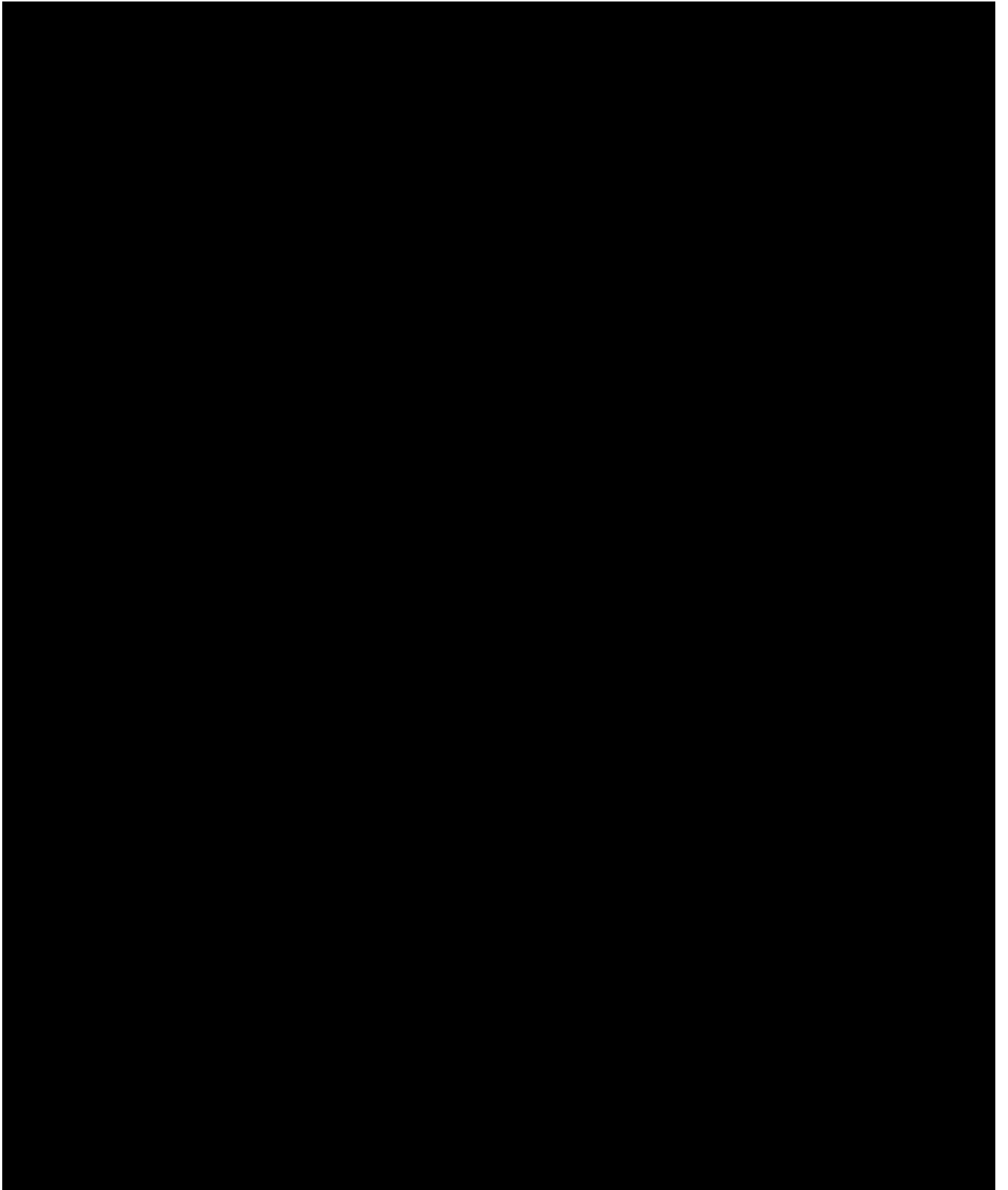


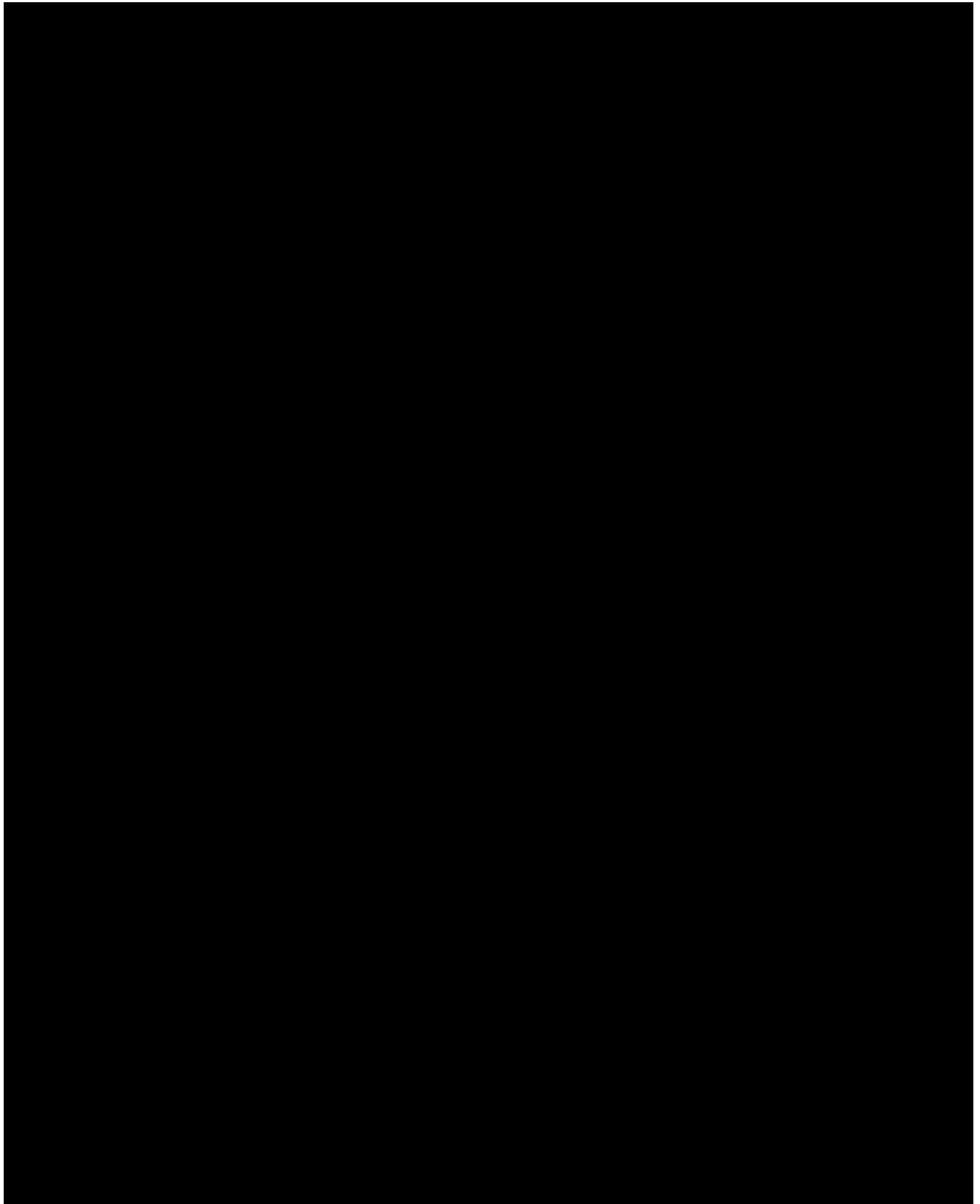


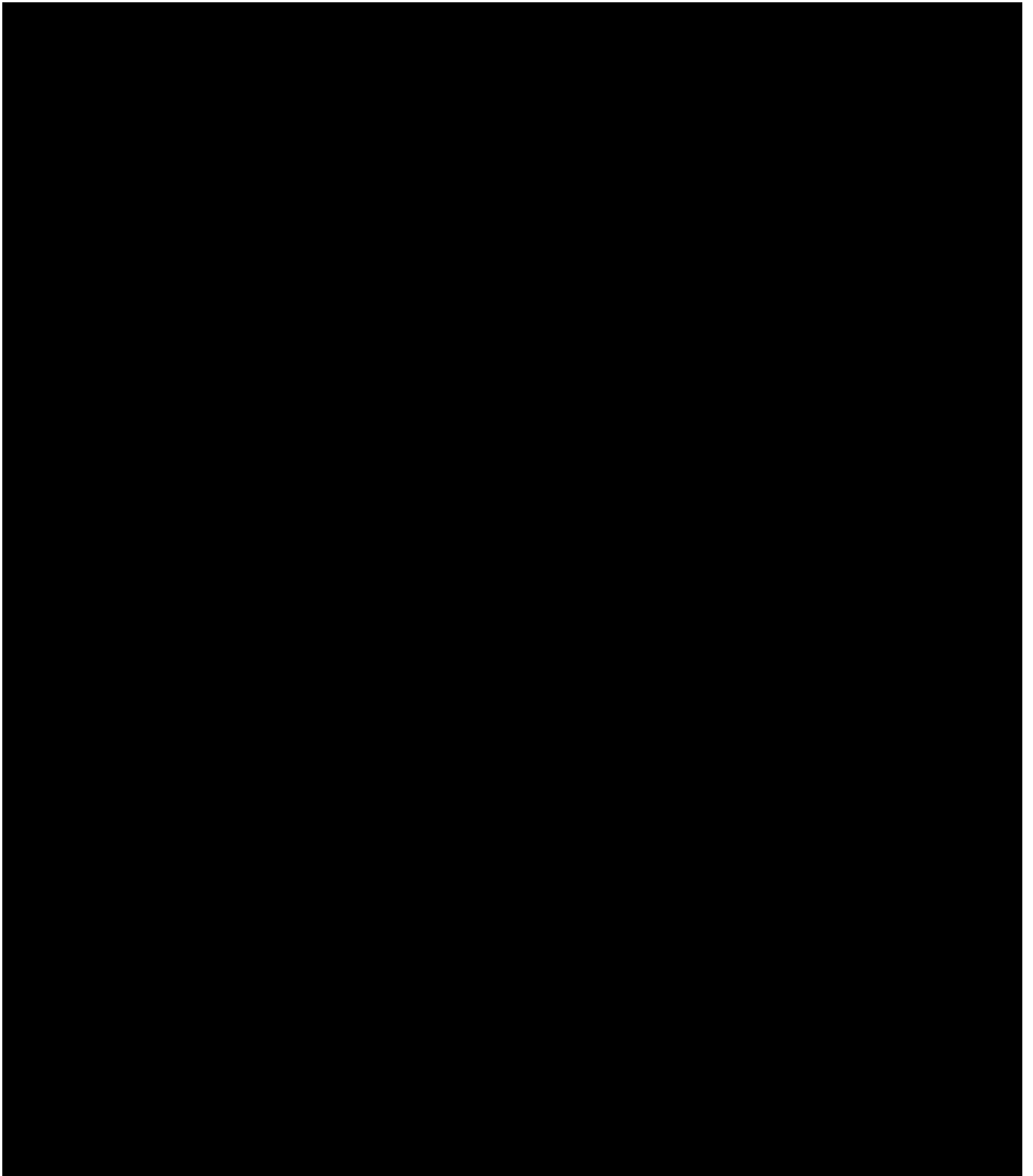


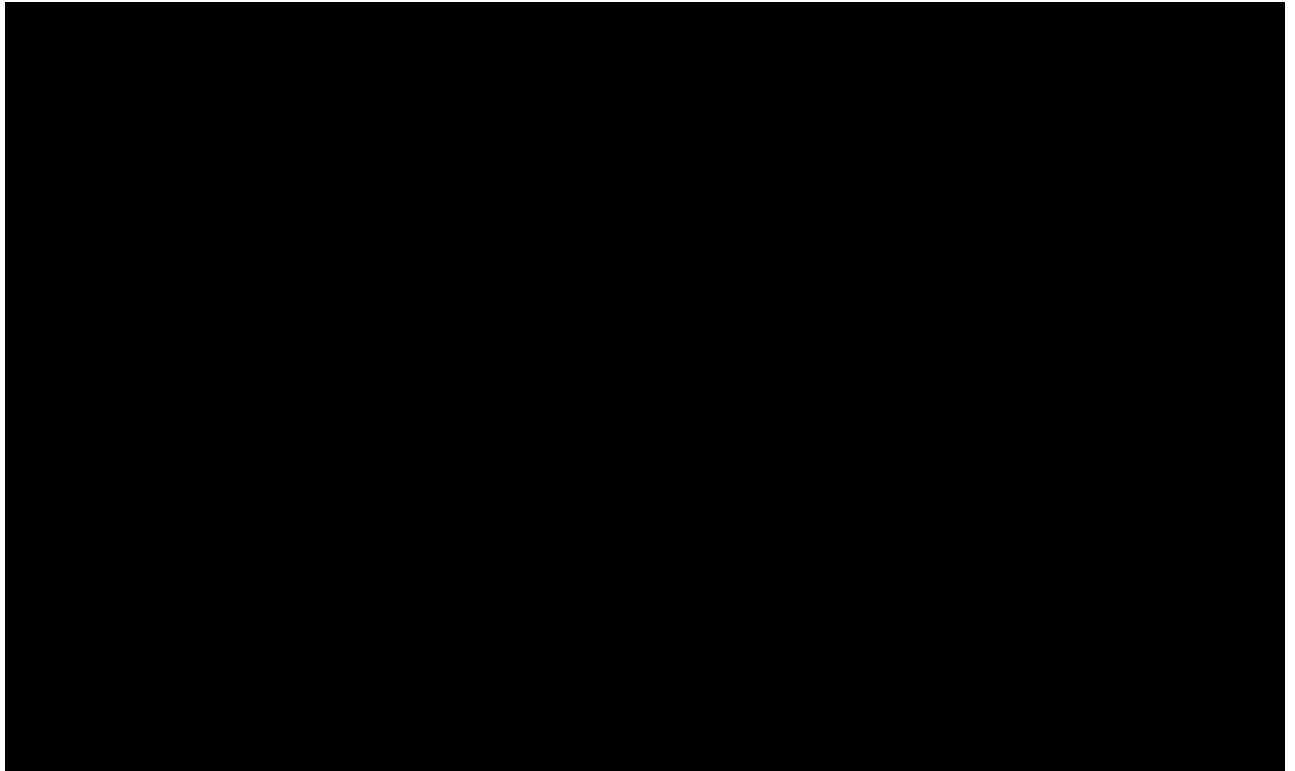


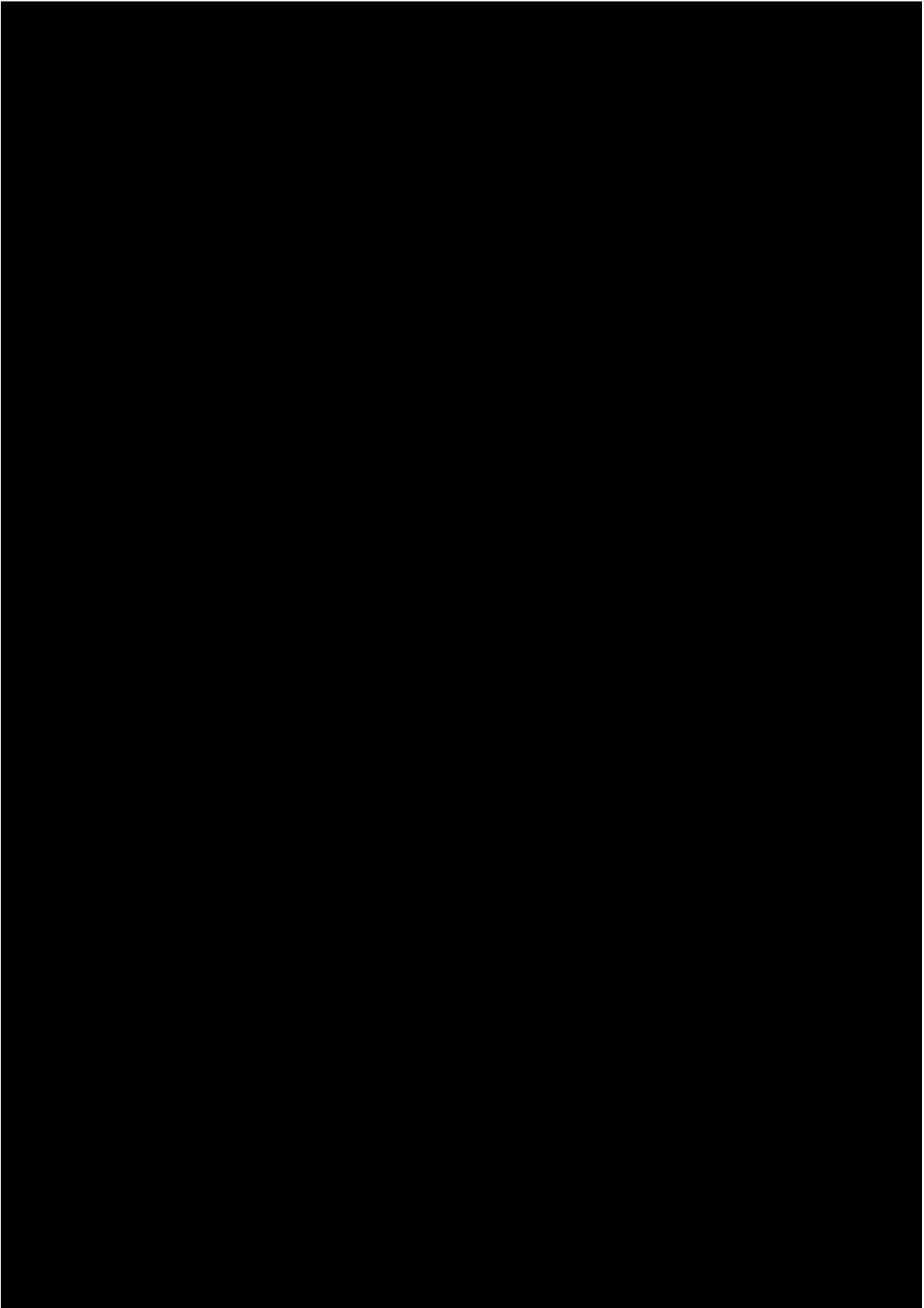


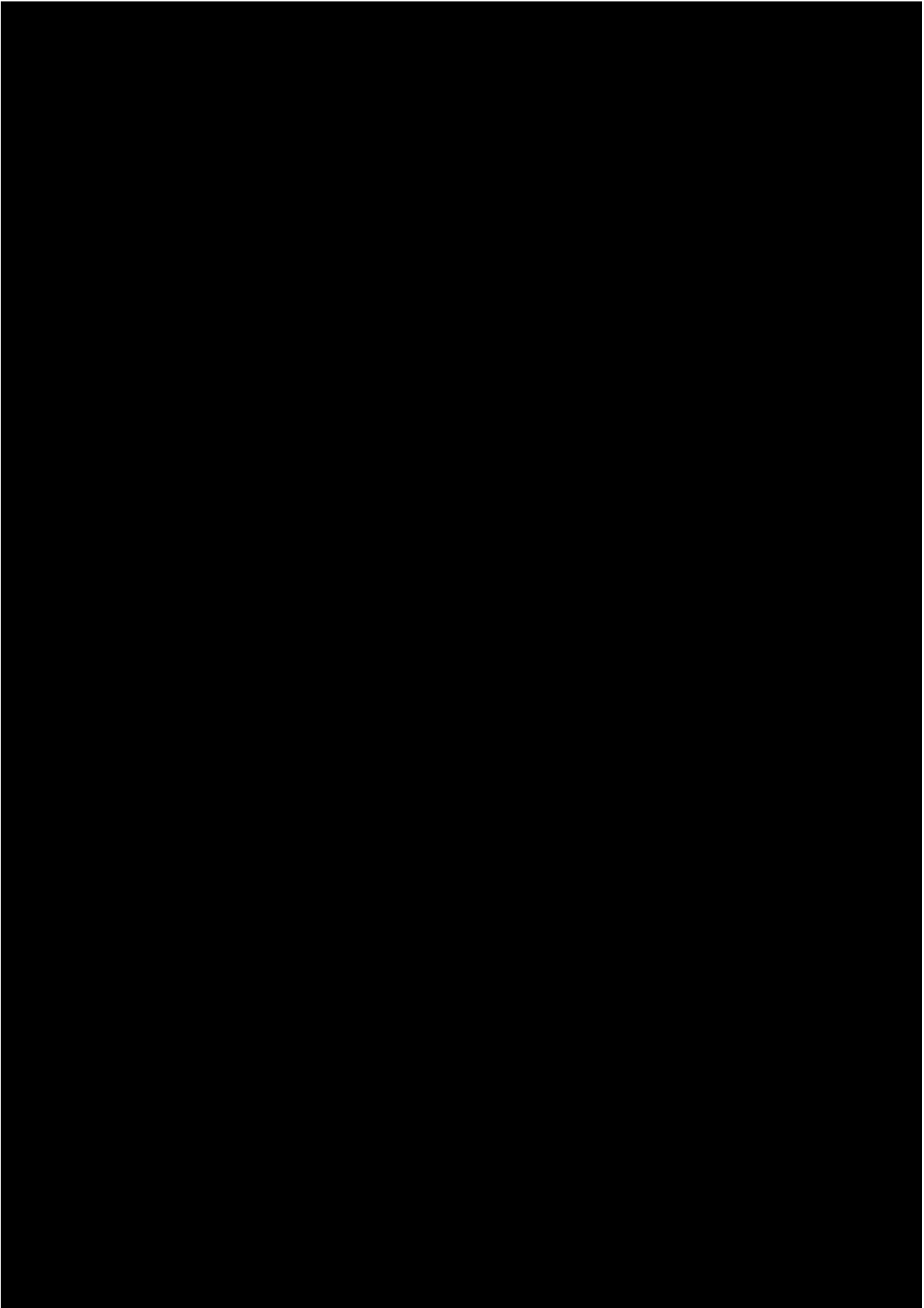


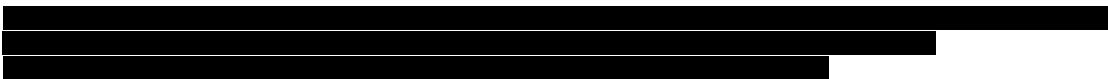
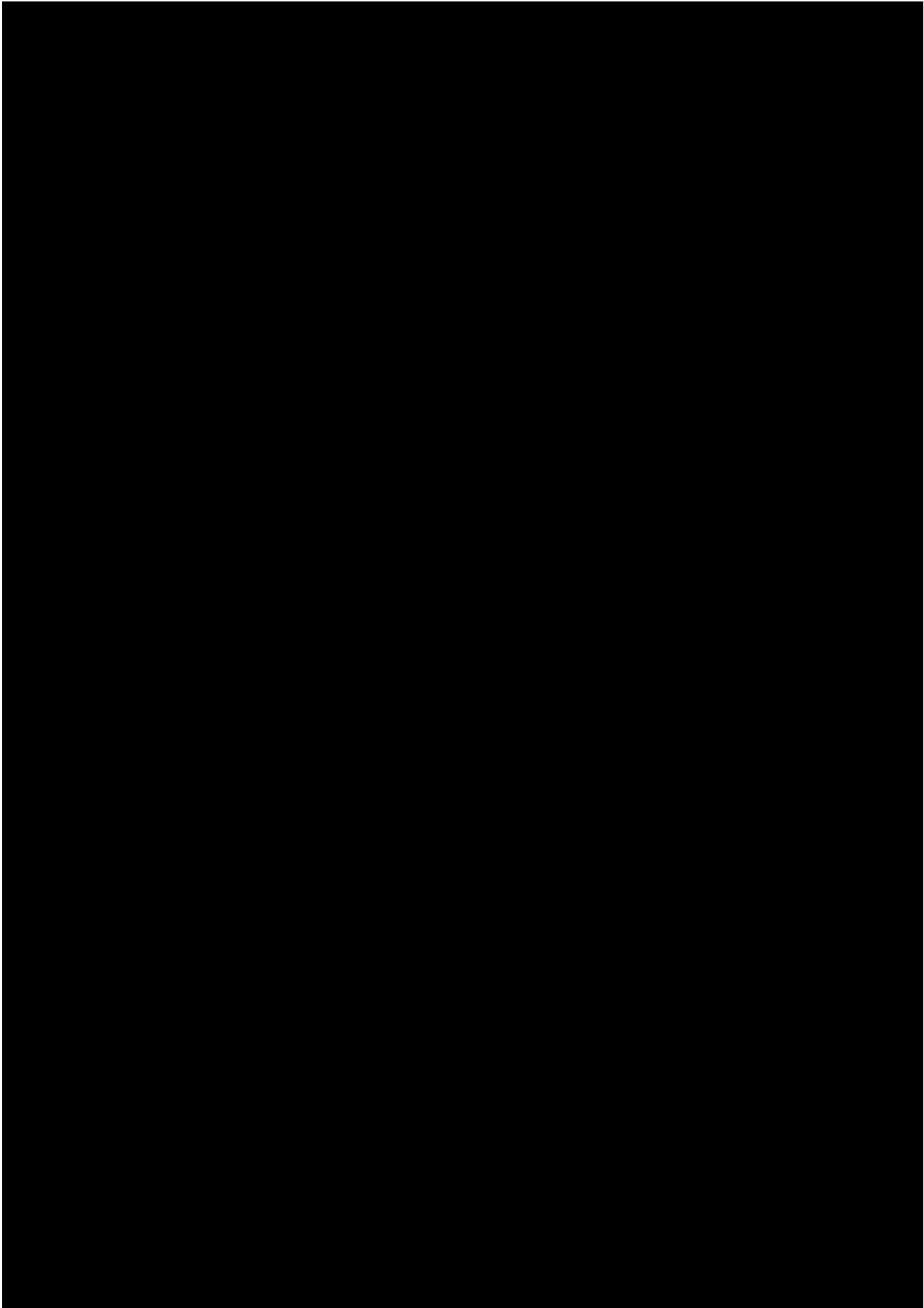


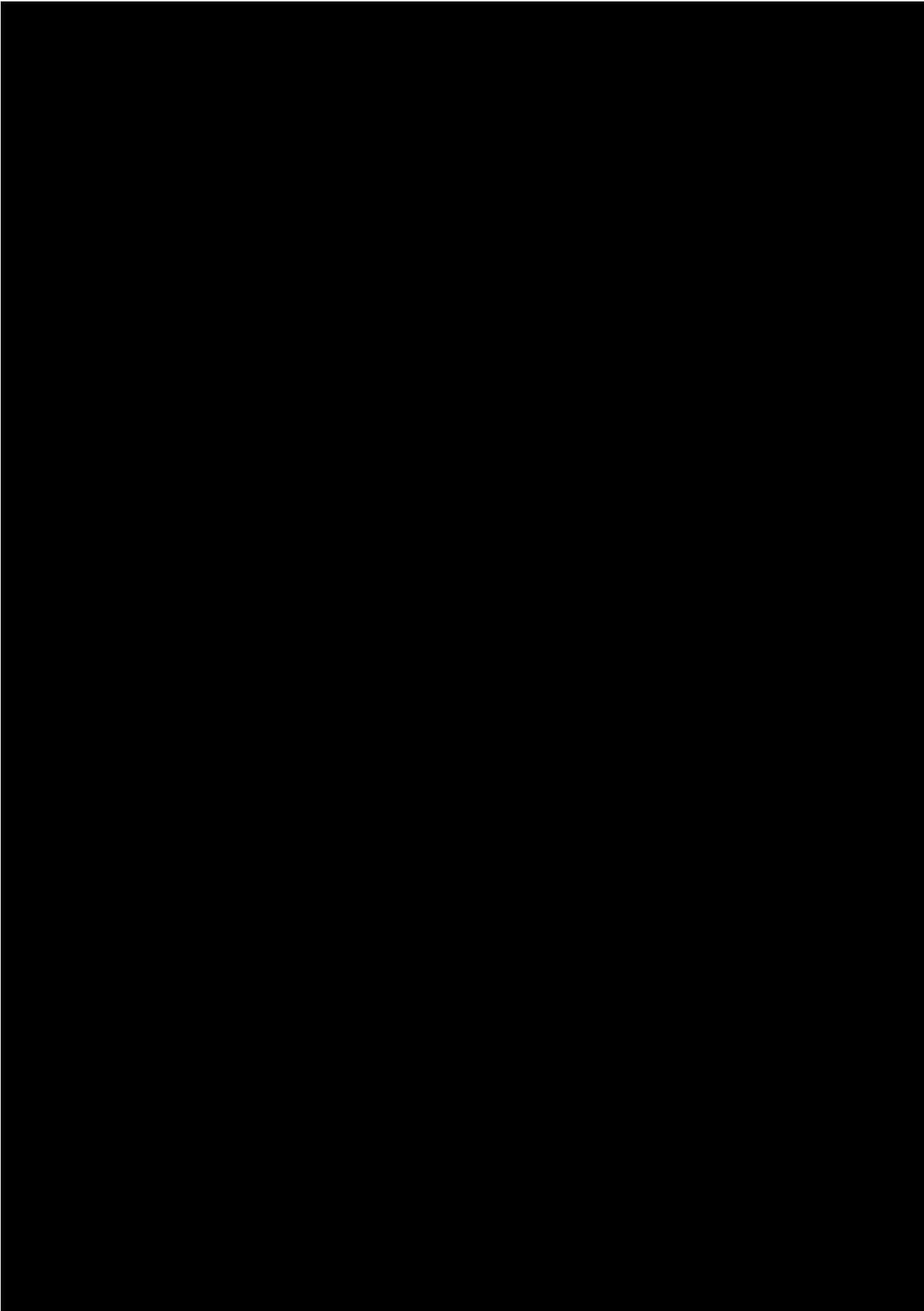


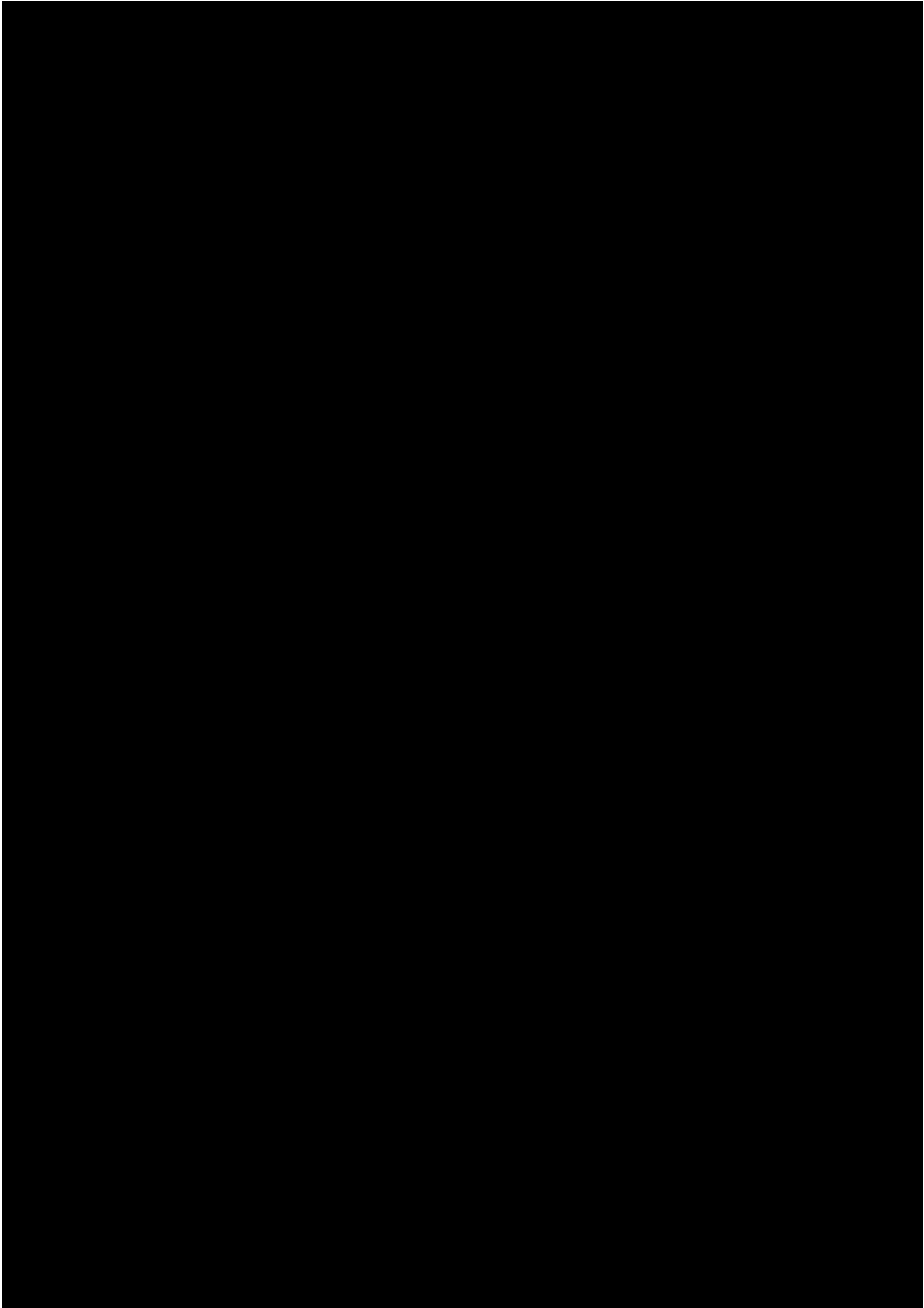


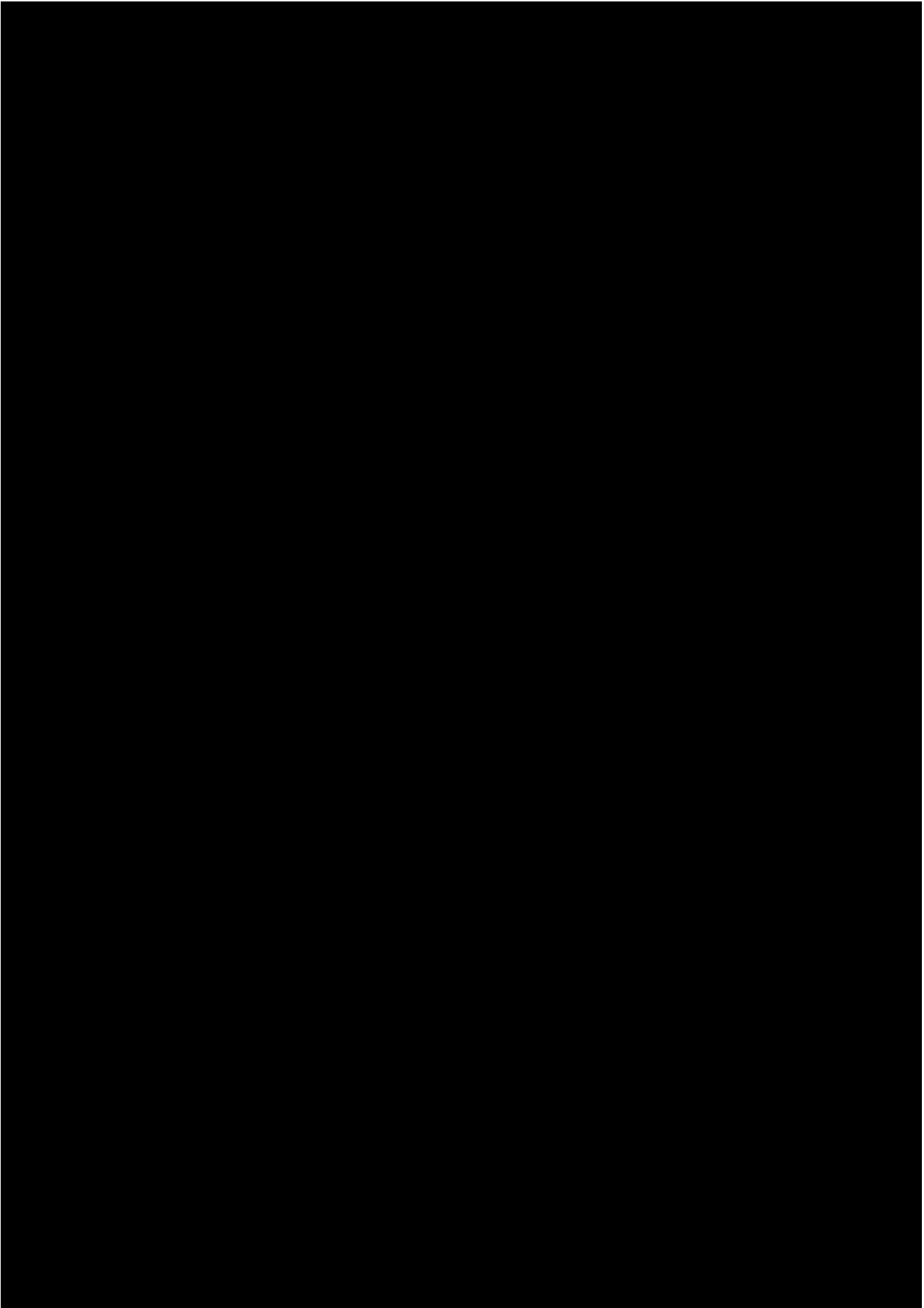


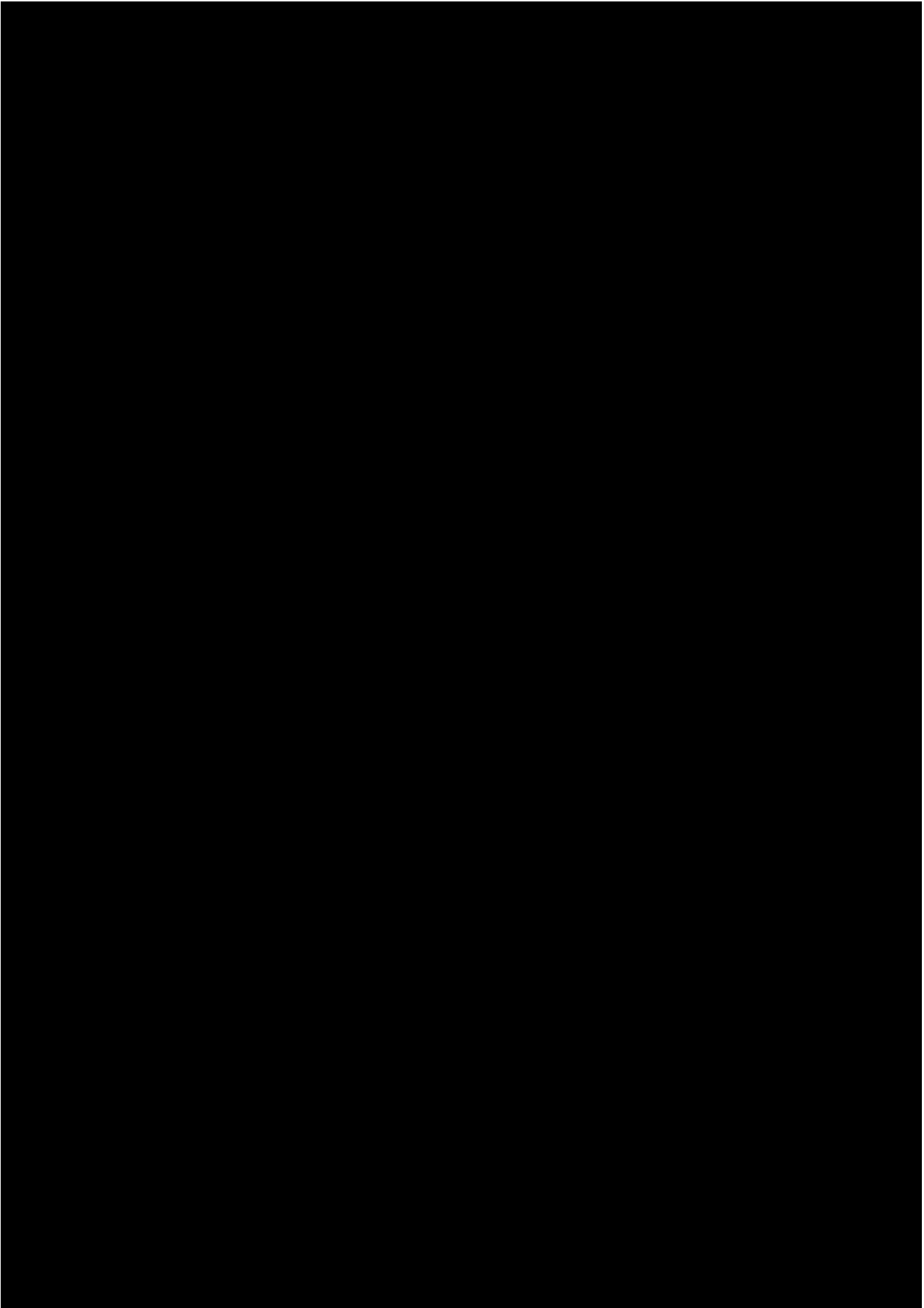


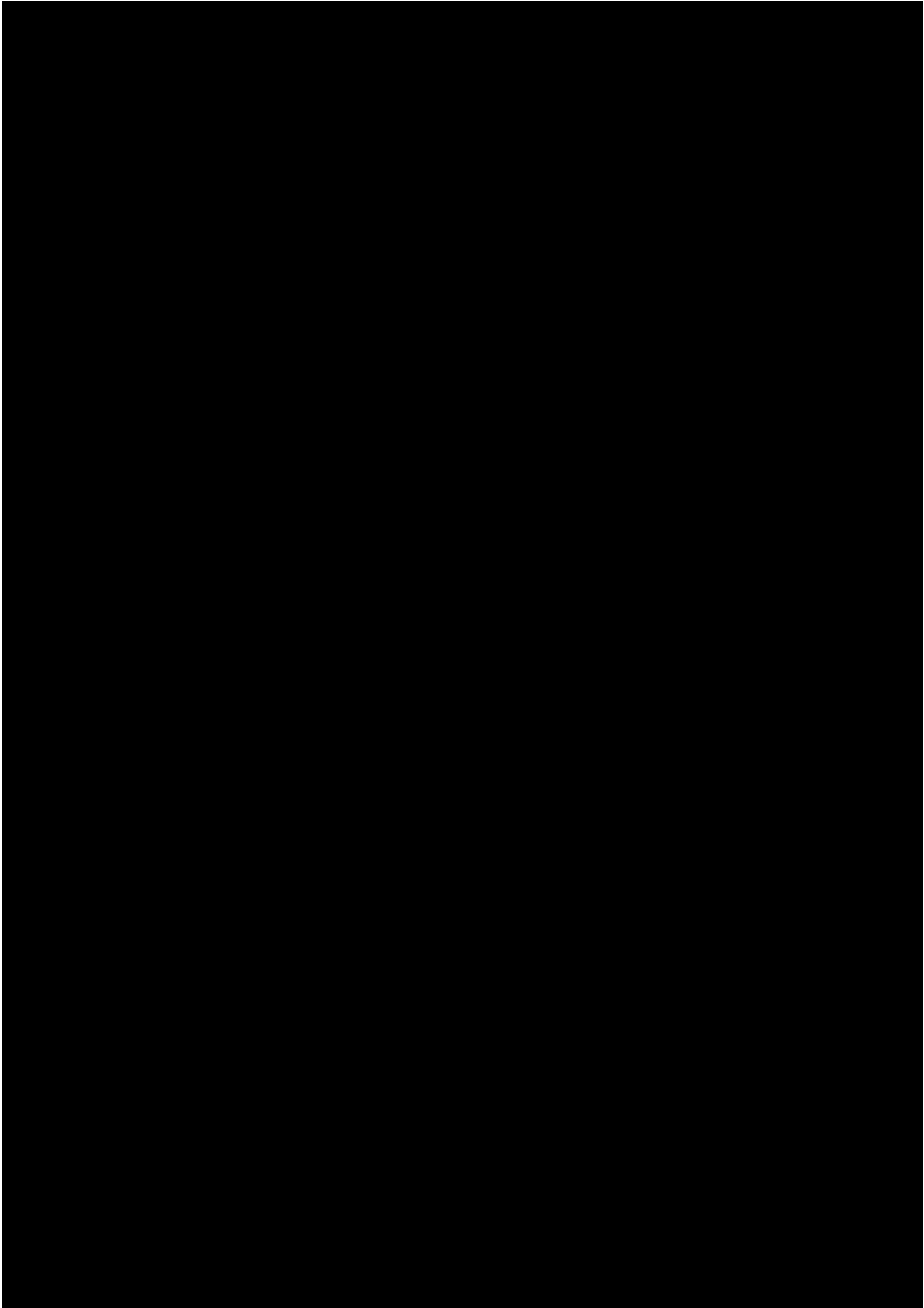


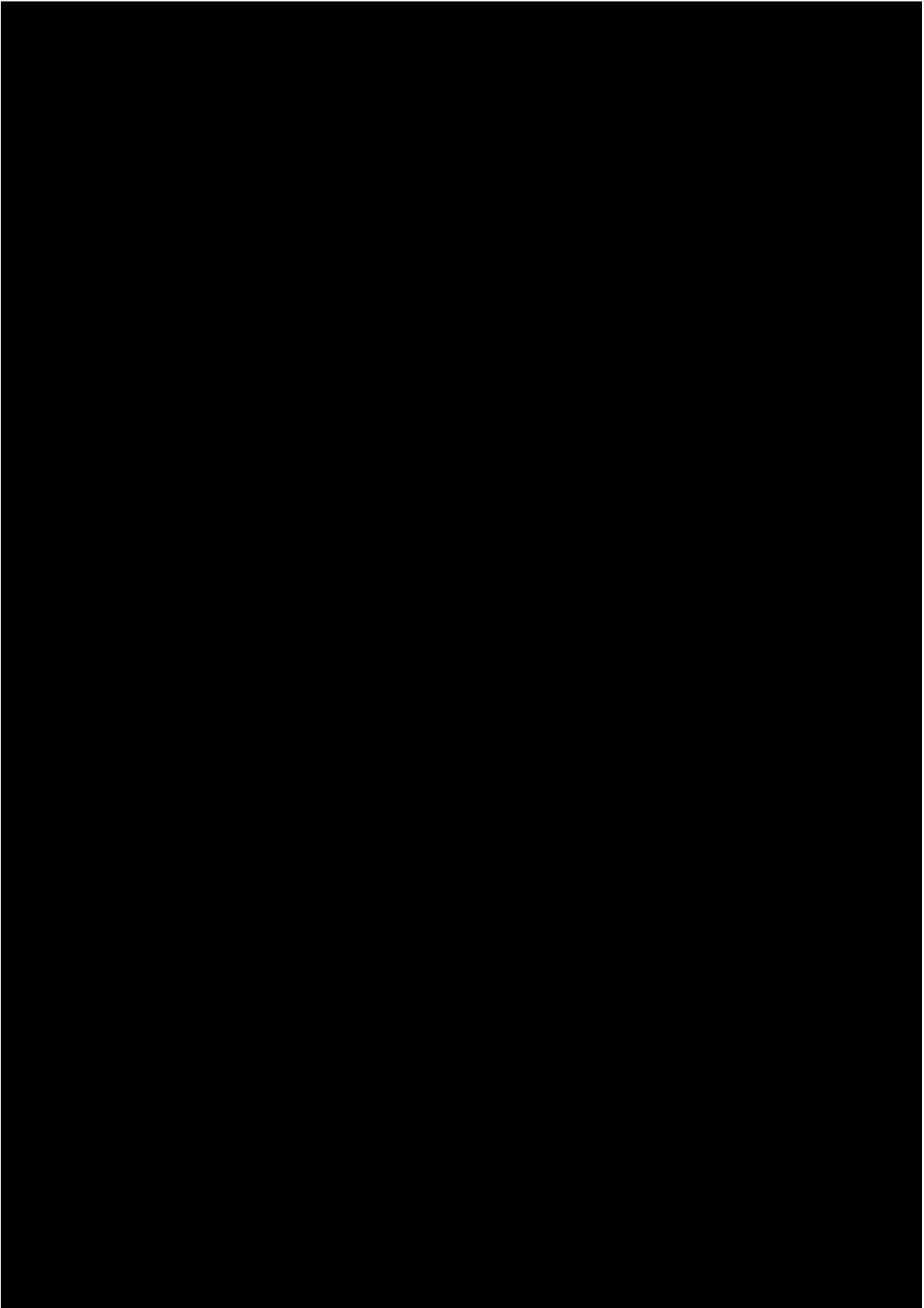


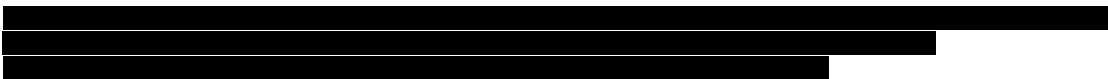
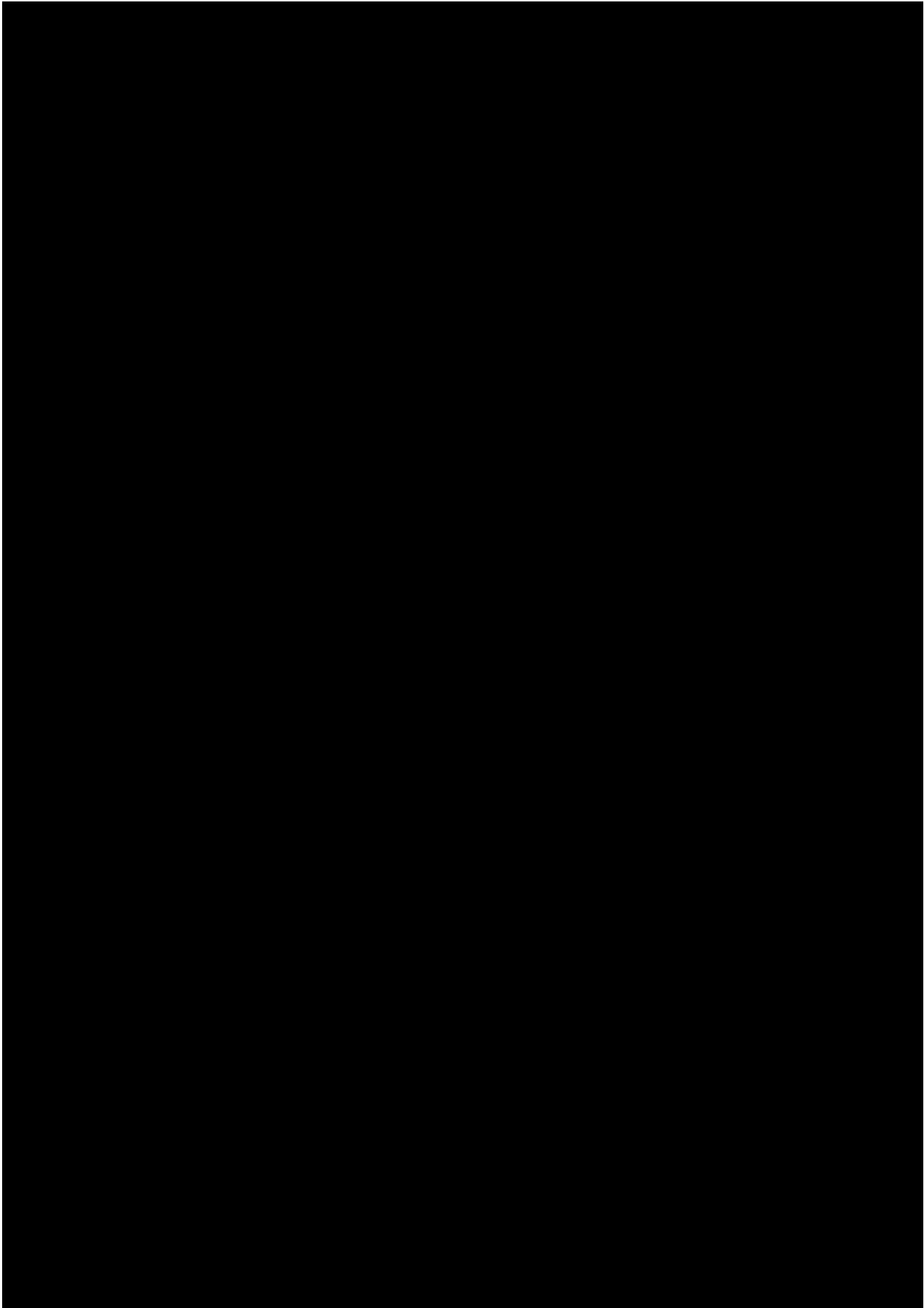


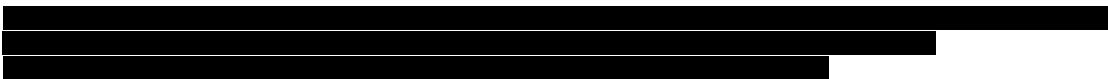
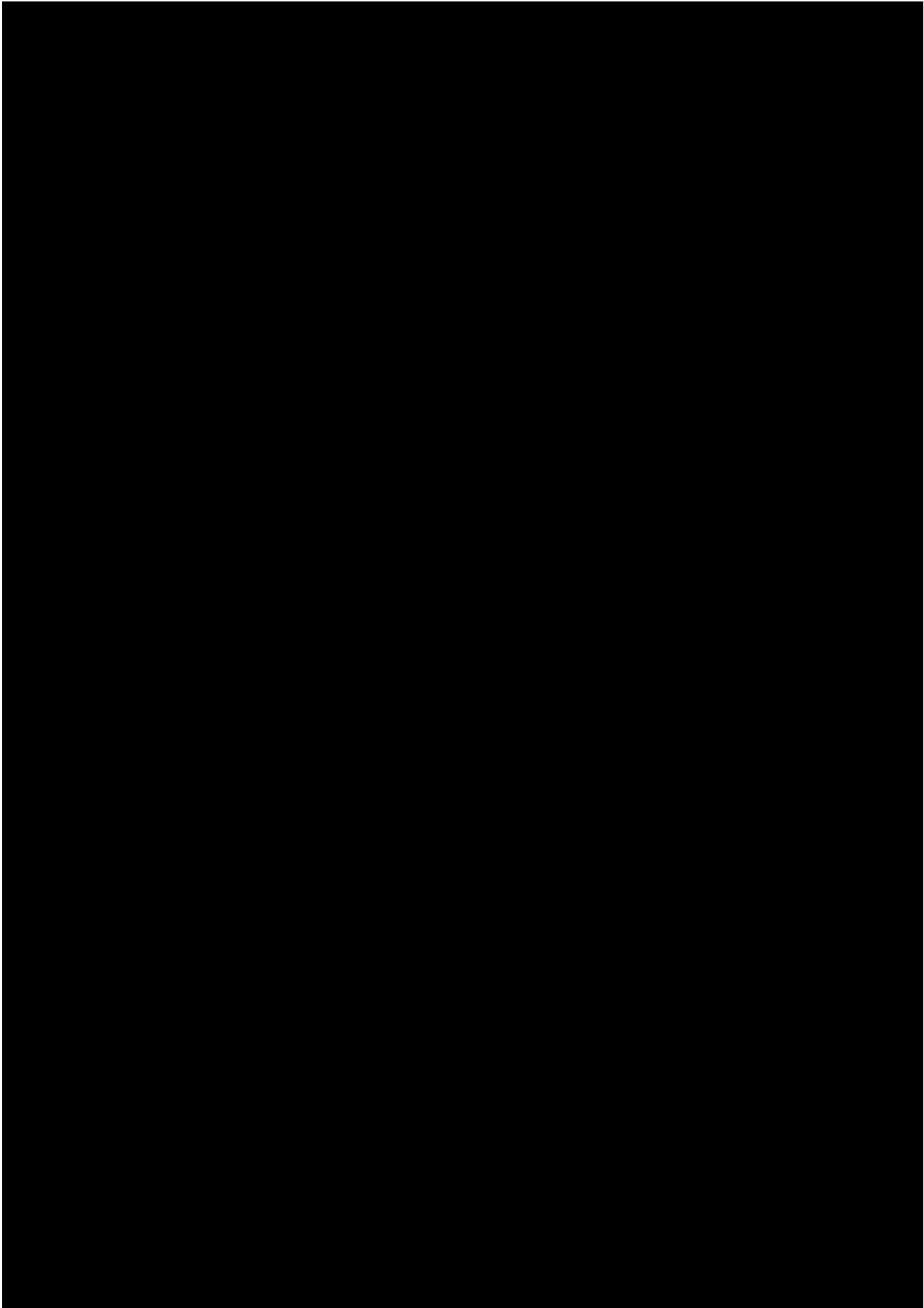


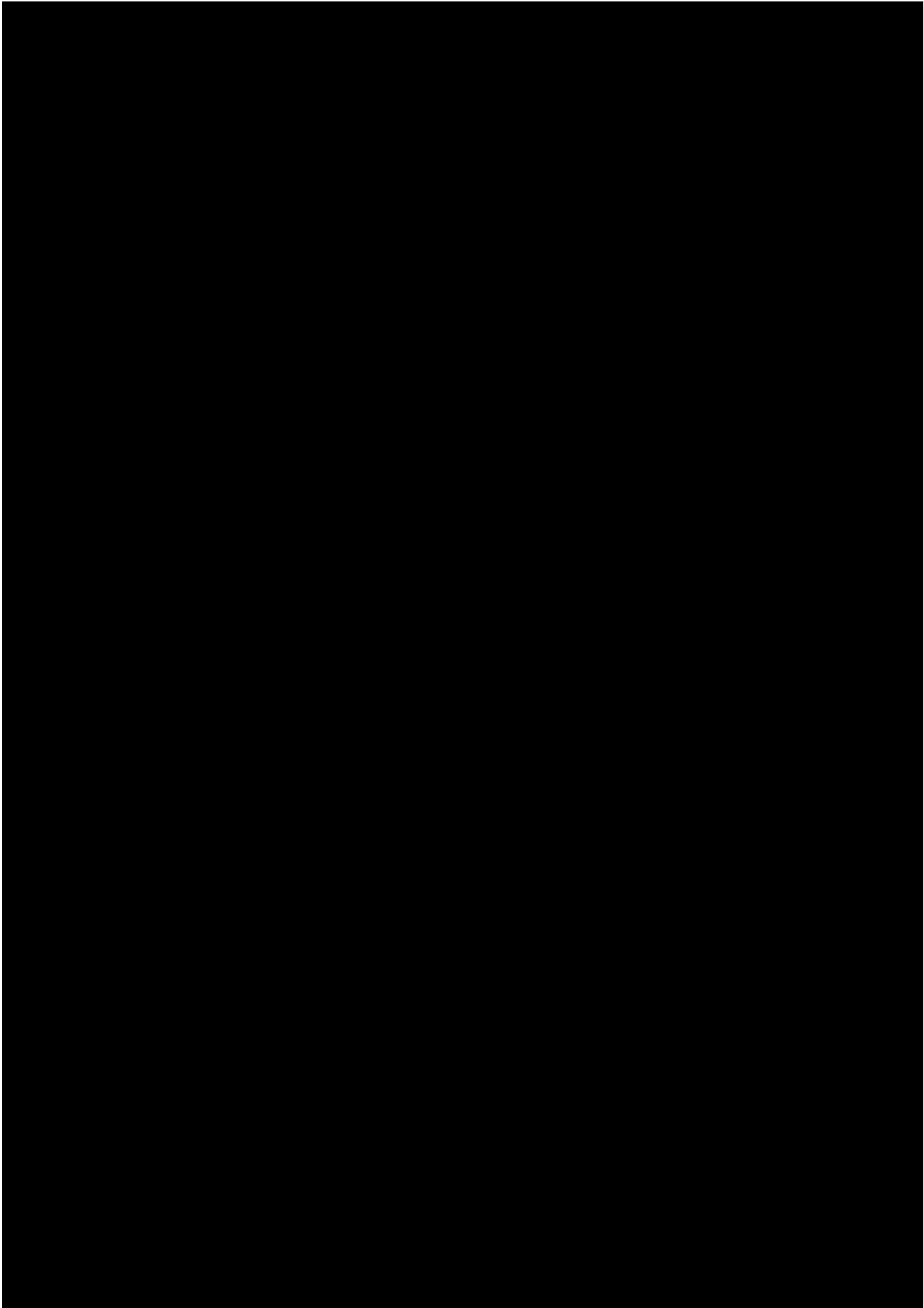


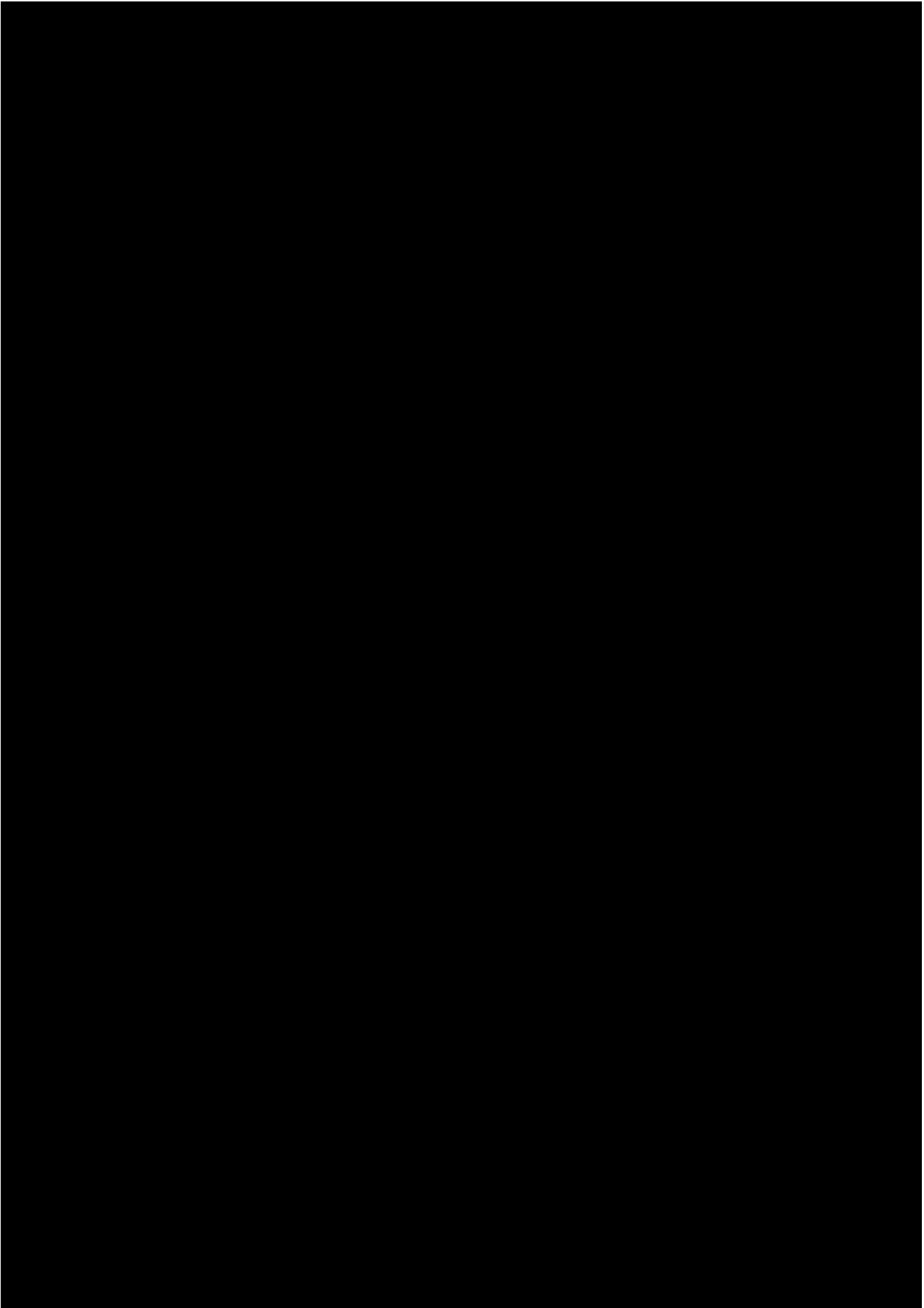


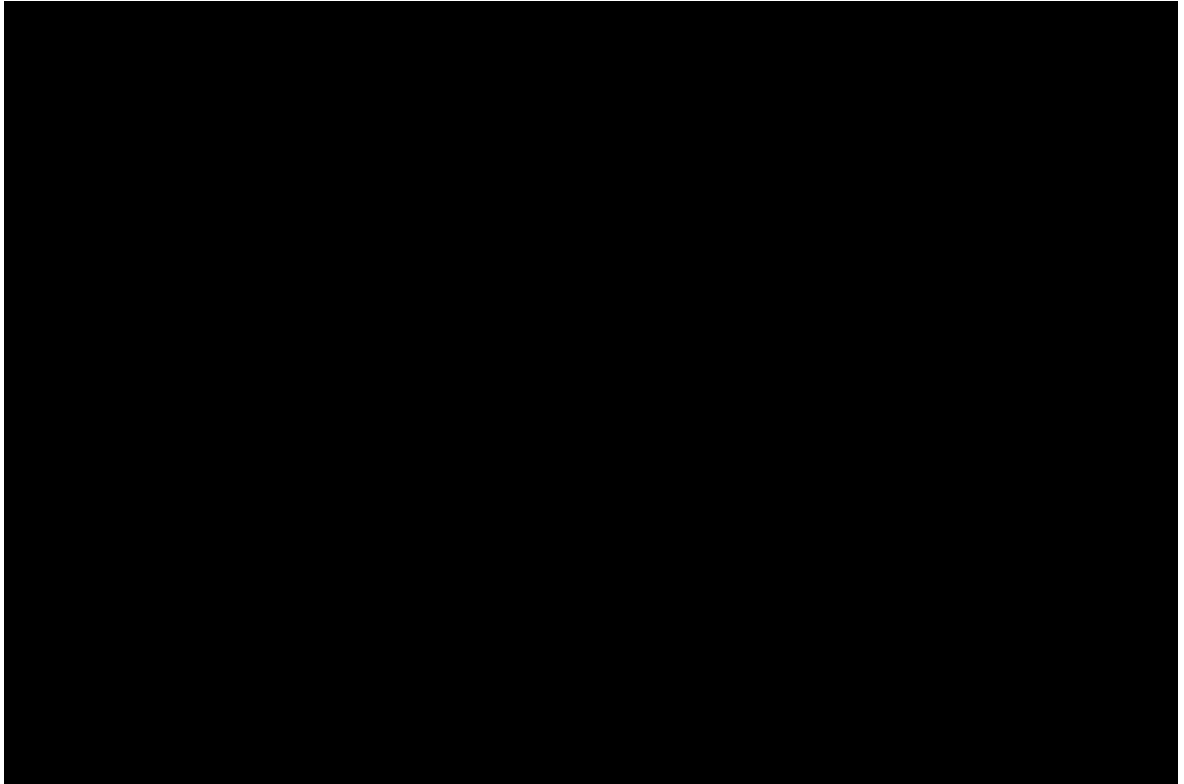


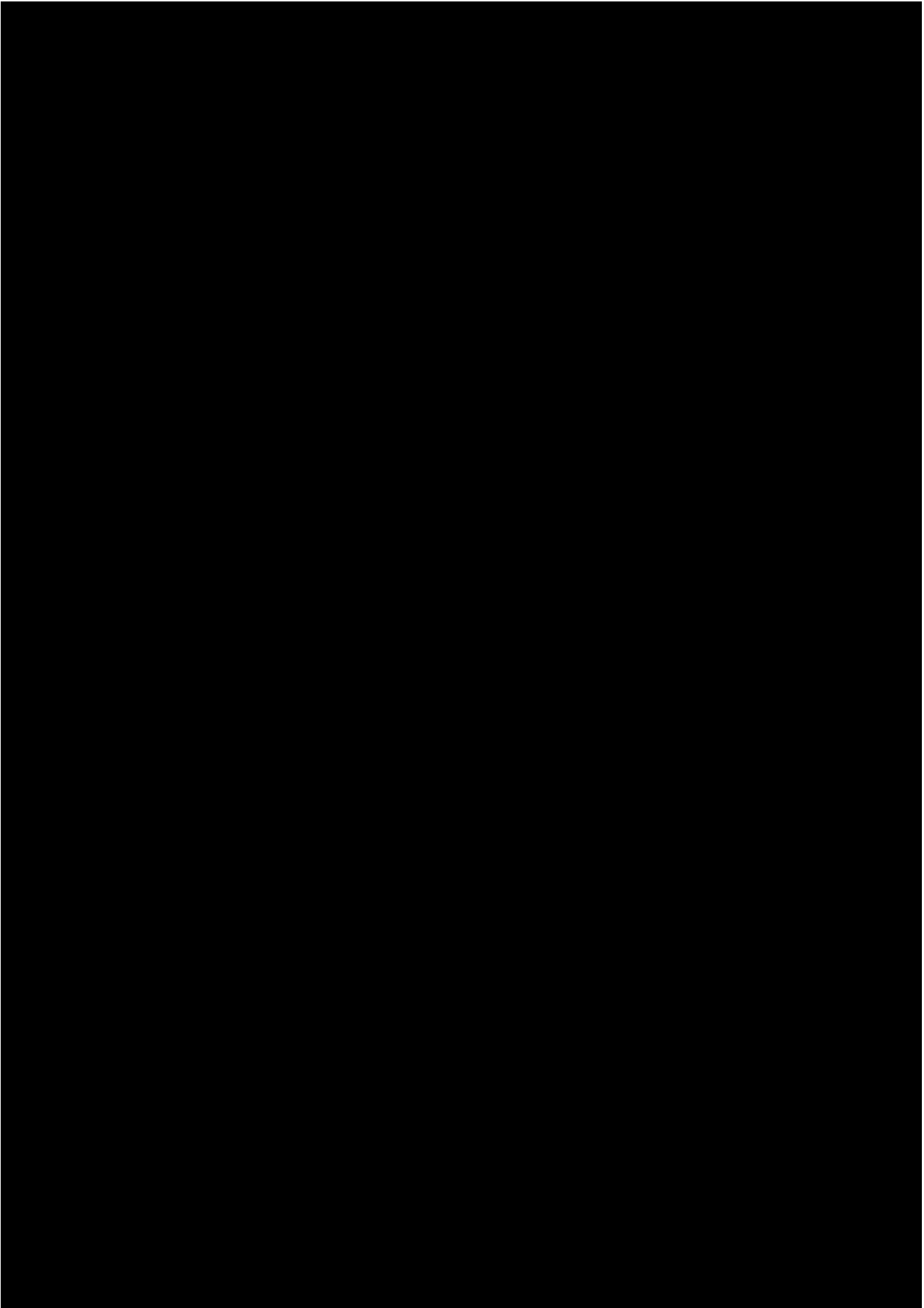












19 Appendix 4: Quality of life Questionnaire EuroQol EQ-5D-5L (EQ-5D-5L)

Samples of questionnaires provided here are for illustrative purposes only

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

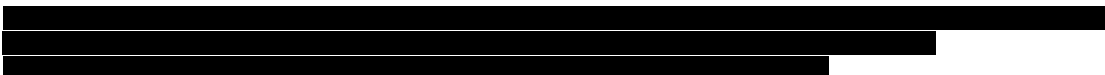
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

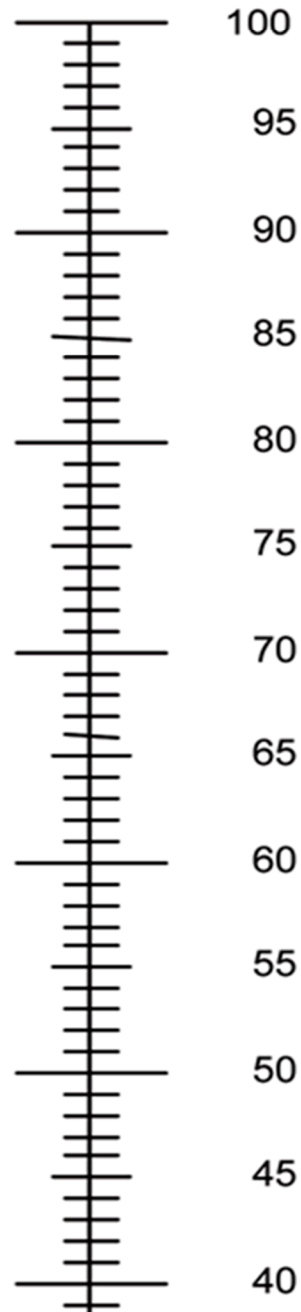
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



20 Appendix 5: St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)

(A) Guidelines for Administering the SGRQ-C Questionnaire:

Before the Trial Begins

Study coordinators should familiarize themselves with the questionnaires and training materials in the trial, and identify any items where a patient's response might highlight issues of potential concern.

Before Completion

Explain to the patient why they are completing the questionnaires, and how important it is for us to understand how they feel about their illness and the effect it has on their daily life. Ask the patient to complete the questionnaires as honestly as possible and stress that there are no right or wrong answers, simply the answer that the patient feels applies to them. Explain that they should answer every question and that someone will be close at hand to answer any queries.

Patients should be provided with the correct questionnaires at the appropriate visits, and in the appropriate language (The same language should be used by the patient for all visits).

Patients should have adequate space and time to complete the forms.

Patients should be provided with a firm writing surface (such as a table or a clip board) and a pencil.

Questionnaires should be completed before the clinical assessments.

During Completion

The administrator may clarify the questions but may not influence the response. The questionnaires are designed to elicit the patient's opinion of his/her health, not someone else's opinion of it. If the spouse or partner has accompanied the patient they should be asked to wait in a separate area. Do not allow patients to take the questionnaires home to be completed.

Ensure there is only one response for each question

Also see 'Addressing Problems and Concerns' on the next page.

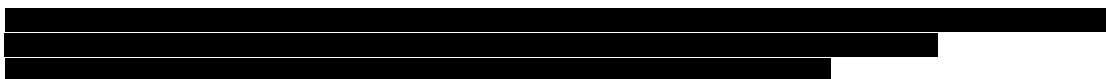
After Completion

Check for completeness but not for content

Check for multiple responses that were made in error

File completed questionnaires in the patient study file notebooks provided for the study

Any response which may directly impact on or reflect the patient's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator.



Addressing Problems and Concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

(1) The patient does not want to complete the questionnaire(s):

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental, and social health problems of patients. Emphasize that this information is as important as any of the other medical information, and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline, and thank the patient.

(2) The patient is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and it has to be read verbatim.

(3) The patient wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the patient provide responses to the questions.

(4) The patient does not want to finish completing the questionnaire(s)

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim*, but do not rephrase the question. Guidance notes on queries of understanding for specific questions from the SGRQ-C User Manual are provided below. If the respondent is still unable to complete the questionnaire, accept it as incomplete.

(5) The patient is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed forms are not routinely shared with treating staff, and that their responses will only be seen by you (to check for completeness), and possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

(6) The patient asks the meaning of a question / item

While completing a questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim*. If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what they think the questions mean. However there are some guidance notes in the SGRQ-C User Manual regarding queries relating to specific questions that may be of use. They are provided below.



Responding to a patient's queries regarding completion of the questionnaire

If a patient asks for help with a question, do not provide an answer for them. The questionnaire is designed to get an understanding of how the patient views his or her illness. It is appropriate to clarify a question but not to provide an answer. Questions may be read aloud if patients have difficulty with reading, but the responses must be theirs alone. If a patient gives an answer you disagree with it is not appropriate to challenge their response or to query it. It is their view of their condition we are interested in – no matter how strange the response!

The following are notes that may help you explain to patients what is required

1. In Part 1 of the questionnaire, emphasize to patients that you are interested in how much chest trouble they have recently. The exact period is not important. We are looking for an impression or perception of health.
2. An attack of chest trouble (Part 1, Question 5) is any episode of worse symptoms that constitutes an attack in the patient's own judgment. Not just severe attacks as judged by medical staff.
3. COPD can vary day-to-day. Part 2 is concerned with the patient's current state (i.e. on average over 'these days'), not necessarily just today.
4. For Part 1 Question 6, emphasize that you are interested in the number of good days that they have had.
5. In Part 2, Questions 8 and 14 require a single response, but Questions 9 to 13 require a response to every question. It may be worth emphasizing this to the patient.
6. Many patients do not engage in physical activity. It is important to determine whether this is because they do not wish to (in which case the answer would be 'False') or cannot engage in these activities because of their chest trouble (in which case the answer would be 'True').
7. Responses to Questions 12 and 13 concern limitations due to breathing difficulties and not any other problems. If the patient does not engage in an activity for another reason, they should tick 'False'.



(B) Sample of the questionnaire (the samples provided here are for illustrative purposes only):

**ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
for COPD patients (SGRQ-C)**

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

ID : _____

Date : ____ / ____ / ____ (dd/mm/yy)

<i>Before completing the rest of the questionnaire:</i>				
<i>Please tick in one box to show how you describe your current health:</i>				
Very good	Good	Fair	Poor	Very poor
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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PART 1

Questions about how much chest trouble you have.

Please tick (✓) **ONE** box for each question:

Question 1. I cough:

- most days a week a
- several days a week..... b
- only with chest infections..... c
- not at all..... d

Question 2. I bring up phlegm (sputum):

- most days a week a
- several days a week..... b
- only with chest infections ... c
- not at all..... d

Question 3. I have shortness of breath:

- most days a week a
- several days a week..... b
- not at all..... c

Question 4. I have attacks of wheezing:

- most days a week a
- several days a week..... b
- a few days a month..... c
- only with chest infections..... d
- not at all..... e

Question 5. How many attacks of chest trouble did you have during the last year?

- 3 or more attacks..... a
- 1 or 2 attacks..... b
- none..... c



Question 6. How often do you have good days (with little chest trouble) ?

No good days..... a

a few good days..... b

most days are good..... c

every day is good..... d

Question 7. If you have a wheeze, is it worse in the morning?

No.....

Yes.....



PART 2

8. How would you describe your chest condition?

Please tick (✓) **ONE**:

Causes me a lot of problems or is the most important problem I have..... a

Causes me a few problems..... b

Causes no problem..... c

9. Questions about what activities usually make you feel breathless

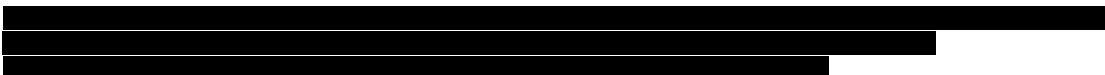
For each statement please tick (✓) in the box that applies to you these days:

	True	False
Getting washed or dressed.....	<input type="checkbox"/>	<input type="checkbox"/> a
Walking around the home.....	<input type="checkbox"/>	<input type="checkbox"/> b
Walking outside on the level.....	<input type="checkbox"/>	<input type="checkbox"/> c
Walking up a flight of stairs.....	<input type="checkbox"/>	<input type="checkbox"/> d
Walking up hills.....	<input type="checkbox"/>	<input type="checkbox"/> e

10. Some more questions about your cough and breathlessness

For each statement please tick (✓) in the box that applies to you these days:

	True	False
My cough hurts.....	<input type="checkbox"/>	<input type="checkbox"/> a
My cough makes me tired.....	<input type="checkbox"/>	<input type="checkbox"/> b
I am breathless when I talk.....	<input type="checkbox"/>	<input type="checkbox"/> c
I am breathless when I bend over.....	<input type="checkbox"/>	<input type="checkbox"/> d
My cough or breathing disturbs my sleep.....	<input type="checkbox"/>	<input type="checkbox"/> e
I get exhausted easily.....	<input type="checkbox"/>	<input type="checkbox"/> f



11. Questions about other effects that your chest trouble may have on you

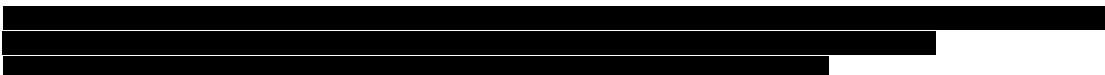
For each statement please tick (✓) in the box that applies to you these days:

	True	False
My cough or breathing is embarrassing in public	<input type="checkbox"/>	<input type="checkbox"/> a
My chest trouble is a nuisance to my family, friends or neighbours....	<input type="checkbox"/>	<input type="checkbox"/> b
I get afraid or panic when I cannot get my breath.....	<input type="checkbox"/>	<input type="checkbox"/> c
I feel that I am not in control of my chest problem.....	<input type="checkbox"/>	<input type="checkbox"/> d
I have become frail or an invalid because of my chest.....	<input type="checkbox"/>	<input type="checkbox"/> e
Exercise is not safe for me.....	<input type="checkbox"/>	<input type="checkbox"/> f
Everything seems too much of an effort.....	<input type="checkbox"/>	<input type="checkbox"/> g

12. These are questions about how your activities might be affected by your breathing.

For each statement please tick (✓) in the box that applies to you because of your breathing:

	True	False
I take a long time to get washed or dressed.....	<input type="checkbox"/>	<input type="checkbox"/> a
I cannot take a bath or shower, or I take a long time.....	<input type="checkbox"/>	<input type="checkbox"/> b
I walk slower than other people, or I stop for rests.....	<input type="checkbox"/>	<input type="checkbox"/> c
Jobs such as housework take a long time, or I have to stop for rests....	<input type="checkbox"/>	<input type="checkbox"/> d
If I walk up one flight of stairs, I have to go slowly or stop.....	<input type="checkbox"/>	<input type="checkbox"/> e
If I hurry or walk fast, I have to stop or slow down.....	<input type="checkbox"/>	<input type="checkbox"/> f
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	<input type="checkbox"/>	<input type="checkbox"/> g
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim.....	<input type="checkbox"/>	<input type="checkbox"/> h



PART 2

13 . We would like to know how your chest trouble usually affects your daily life.

For each statement please tick (✓) in *the* box that applies to you *because of your breathing*:

	True	False
I cannot play sports or games.....	<input type="checkbox"/>	<input type="checkbox"/> a
I cannot go out for entertainment or recreation.....	<input type="checkbox"/>	<input type="checkbox"/> b
I cannot go out of the house to do the shopping.....	<input type="checkbox"/>	<input type="checkbox"/> c
I cannot do housework.....	<input type="checkbox"/>	<input type="checkbox"/> d
I cannot move far from my bed or chair.....	<input type="checkbox"/>	<input type="checkbox"/> e

14. How does your chest trouble affect you?

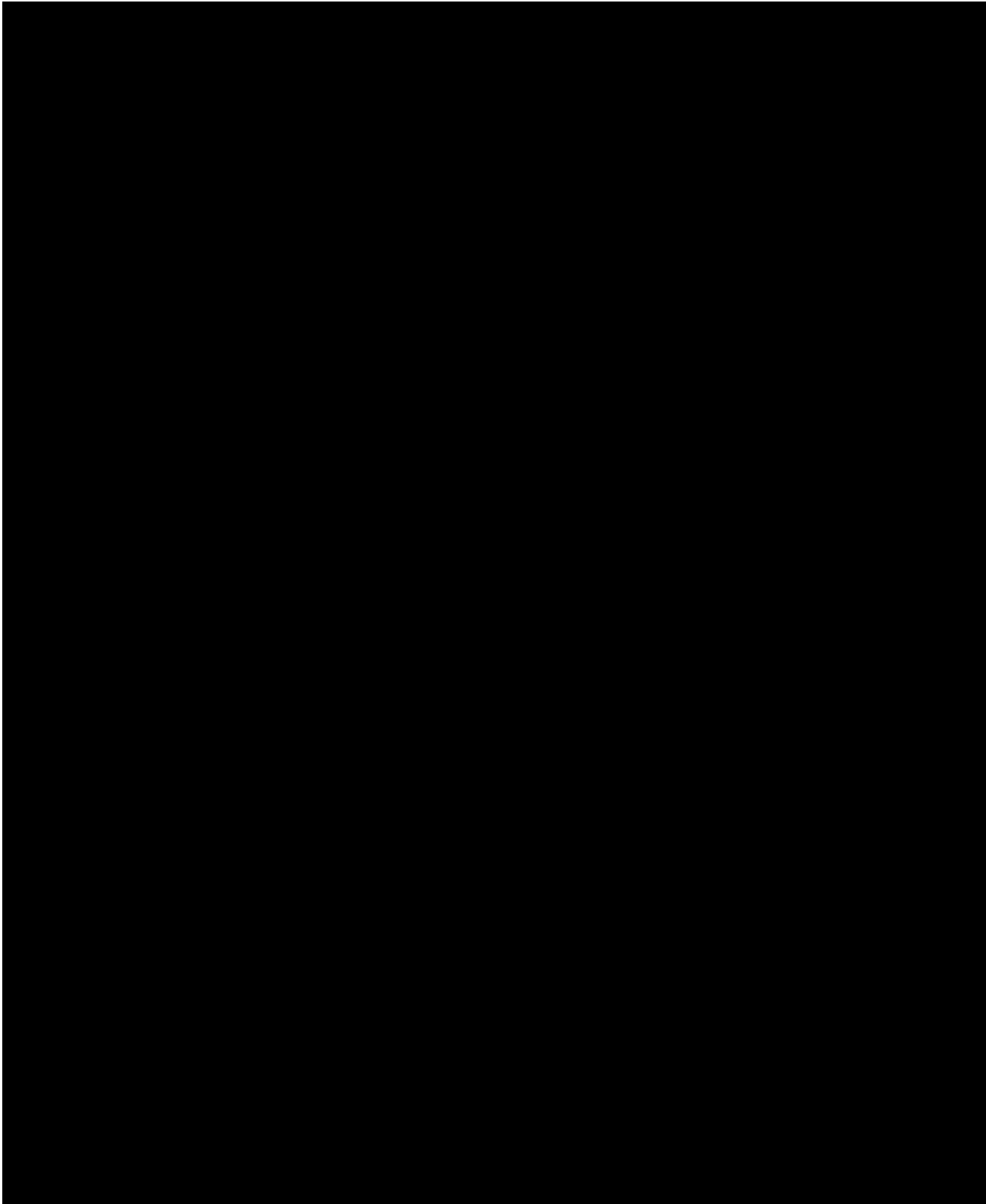
Please tick (✓) *ONE*:

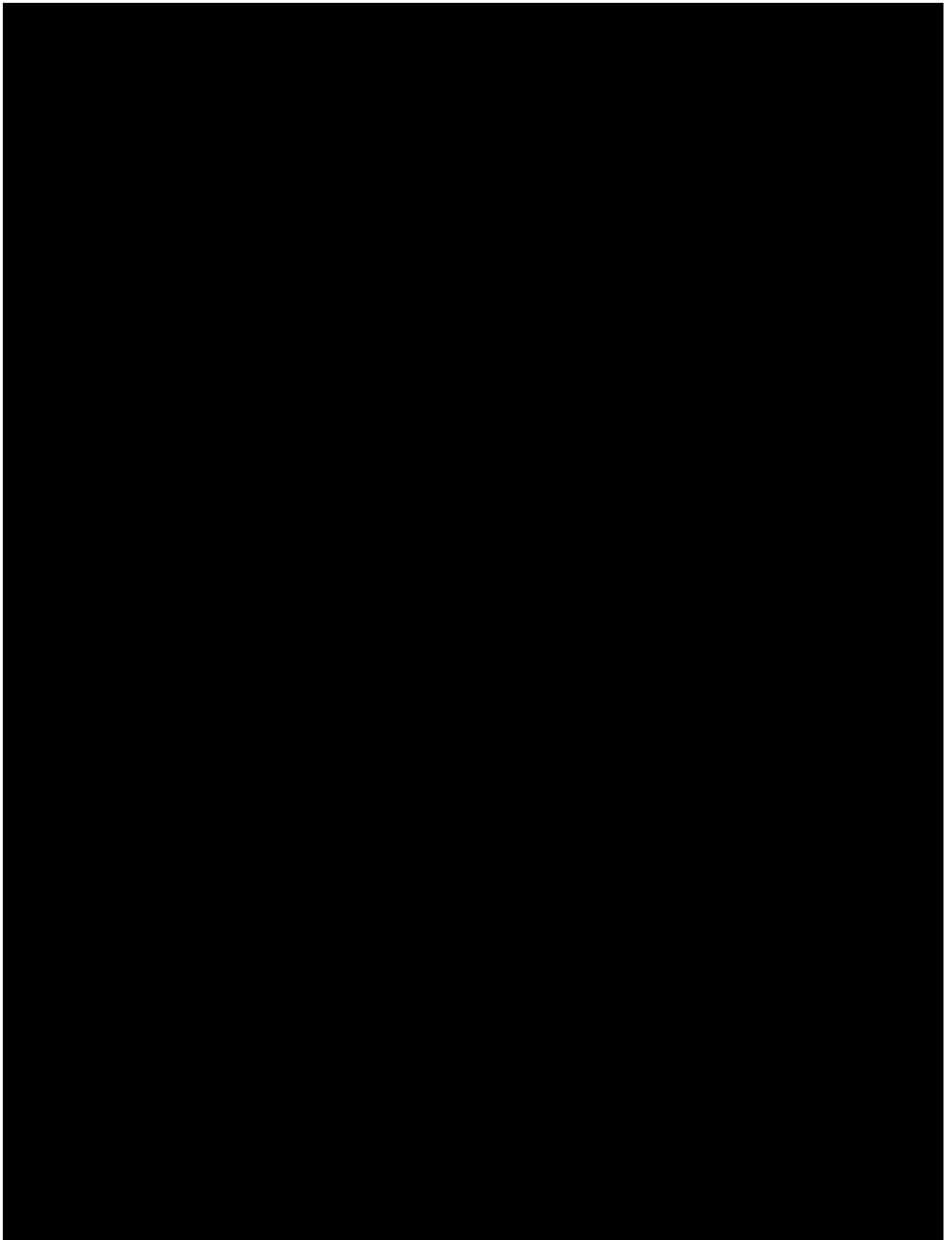
- It does not stop me doing anything I would like to do..... a
- It stops me doing one or two things I would like to do..... b
- It stops me doing most of the things I would like to do..... c
- It stops me doing everything I would like to do..... d

Thank you for filling in this questionnaire.

Before you finish, would you please check to see that you have answered all the questions.







23 Appendix 8: Exacerbations

COPD exacerbation is defined as:

A worsening of the following two or more major symptoms for at least 2 consecutive days:

- dyspnea
- sputum volume
- sputum purulence

OR

A worsening of any 1 major symptom together with an increase in any one of the following minor symptoms for at least 2 consecutive days:

- sore throat
- colds (nasal discharge and/or nasal congestion)
- fever without other cause
- cough
- wheeze

A COPD exacerbation is considered of moderate severity if treatment with systemic corticosteroids or antibiotics or both was required and severe, if hospitalization was required. An emergency room (ER) visit of longer than 24 hours will be considered a hospitalization.

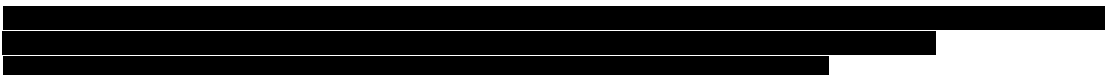
A COPD exacerbation is considered of mild severity if there is a worsening of symptoms that either do not meet the above symptom definition but is treated by the investigator with systemic corticosteroids or antibiotics, or that meets the symptom definition but is not treated with antibiotics and/or systemic corticosteroids.

The above criteria for a COPD exacerbation are based on a worsening of symptoms occurring after randomization as compared to the baseline threshold established during the run-in period. The baseline threshold is determined by subject recording of daily symptoms using an electronic diary device supplied at the start of the study.

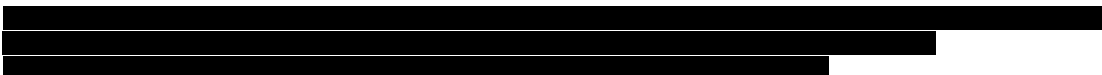
An increase in ICS dose will not be counted as an exacerbation. In the event of a COPD exacerbation matching the above definition occurring at any time after signing of informed consent, subjects should be treated for the exacerbation as deemed necessary by the investigator.

Pneumonia will be defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum and fever, i.e. body temperature greater than 38 °C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator. Radiographic imaging, preferably a chest x-ray, will be required to facilitate the diagnosis. The diagnosis of COPD exacerbation will not preclude a diagnosis of pneumonia. The investigator will use clinical judgment to determine if the events are occurring simultaneously.

Subjects who develop a COPD exacerbation during screening will be screen failed but will be permitted to be re-screened after a minimum of 6 weeks and after the resolution of the COPD exacerbation.



Following treatment for the exacerbation, the subject will be expected to continue in the study provided the investigator considers that the subject can safely return to his/her pre- exacerbation medications.



24 Appendix 9: Concept2 Inhaler Unique Device Identification

The label adhered to the Concept2 inhaler base includes the unique 16 characters long unique identification of the device (MAC Address) as described hereafter. The characters are alphanumeric.



25 Appendix 10: GOLD 2017 guidelines

Spirometry is required to make the diagnosis of COPD; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation.

Classification of severity of airflow obstruction according to GOLD 2017 guidelines are shown in Table 25-1. Spirometry should be performed after the administration of an adequate dose of at least one short-acting inhaled bronchodilator in order to minimize variability.

Table 25-1 Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1)

Spirometric grade		In patients with $FEV_1/FVC < 0.70$:
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

In the refined assessment scheme of the GOLD 2017 guidelines (Figure 25-1), patients however should undergo, in addition to spirometry to determine the severity of airflow limitation (i.e., spirometric grade), also assessment of either dyspnea using mMRC or symptoms using CATTM. Finally, their history of exacerbations (including prior hospitalizations) should be recorded.

Figure 25-1 The refined ABCD assessment tool GOLD Strategy 2017

