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Seebri Breezhaler (glycopyrronium bromide, NVA237) Ultibro Breezhaler (indacaterol maleate/glycopyrronium bromide, QVA149)

CNVA237ADE01 Non-Interventional Study Final Report
(Recruitment Phases 1 and 2)

Die ambulante Versorgung mit langwirksamen Bronchodilatatoren: COPD-Register in Deutschland (English translation: Outpatient care with long-acting bronchodilators: COPD register in Germany)

REDACTED STUDY REPORT

Author	[redacted], Novartis Pharma GmbH, Germany

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Research question and objectives

The main aim of DACCORD was to generate data on the course of COPD under typical treatment conditions in Germany.

Objectives included:

1. To measure patient-reported outcomes (PROs) in terms of COPD Assessment Test (CAT), modified Medical Research Council dyspnea scale (mMRC), and symptoms (using a questionnaire).
2. To document exacerbations retrospectively (six months preceding inclusion) and prospectively (including number, severity) after inclusion.
3. To evaluate comorbidities (number, type, impact).
4. To analyze longitudinal changes in lung function including forced expiratory volume in 1 second (FEV_1) decline.
5. To establish safety and tolerability, in terms of adverse events and serious adverse events.
6. To assess the implementation of pharmacological treatment recommendations in German COPD guidelines at the participating centers.
7. To evaluate potential differences in the treatment of COPD between primary and secondary care
8. To assess patient adherence to pharmacological COPD treatments.
9. To evaluate the dropout rate.

Country(-ies) of study

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1 Abstract

Title

Die ambulante Versorgung mit langwirksamen Bronchodilatatoren: COPD-Register in Deutschland (English translation: Outpatient care with long-acting bronchodilators: COPD register in Germany)

Version and date

1.0, 25-January-2019

Name and affiliation of main author

[redacted], Novartis Pharma GmbH, Germany

Keywords

Chronic obstructive pulmonary disease; exacerbations; symptoms

Rationale and background

Randomized controlled trials (RCTs) generally recruit highly selected populations, often excluding patients with significant or unstable comorbidities. Although data from RCTs can be helpful in informing treatment decisions, data that are more representative of 'real-life' populations are important. The main aim of Study CNVA237ADE01 is to generate data on the course of chronic obstructive pulmonary disease (COPD) under real-life treatment conditions in Germany.

Study CNVA237ADE01 is a longitudinal, prospective non-interventional study. One of the key inclusion criteria was that patients were to have initiated or changed COPD maintenance medication; given the non-interventional nature of the study, the decision to initiate or change medication was to have been taken prior to entry to the study. Furthermore, to ensure that conditions within the trial are as close as possible to real-life, there were no limitations within the trial as to concomitant COPD maintenance treatment, and no limitations on changing, adding, or discontinuing treatment. All treatments were open-label.

Research question and objectives

The main aim of DACCORD was to generate data on the course of COPD under typical treatment conditions in Germany.

Objectives included:

1. To measure patient-reported outcomes (PROs) in terms of COPD Assessment Test (CAT), modified Medical Research Council dyspnea scale (mMRC), and symptoms (using a questionnaire).
2. To document exacerbations retrospectively (six months preceding inclusion) and prospectively (including number and severity) after inclusion.
3. To evaluate comorbidities (number, type, impact).
4. To analyze longitudinal changes in lung function including forced expiratory volume in 1 second (FEV_1) decline.
5. To establish safety and tolerability, in terms of adverse events and serious adverse events.
6. To assess the implementation of pharmacological treatment recommendations in German COPD guidelines at the participating centers.
7. To evaluate potential differences in the treatment of COPD between primary and secondary care
8. To assess patient adherence to pharmacological COPD treatments.
9. To evaluate the dropout rate.

Study design

This was a longitudinal, prospective non-interventional study, which sought to generate data on the course of COPD under real-life treatment conditions. The decision to treat patients was taken prior to inclusion in the study, and there were no limitations on concomitant treatment, or on changing, adding, or discontinuing treatment.

Recruitment into the study is in three phases, as illustrated in Figure 9-1. The first recruitment phase was of patients receiving either a regimen that included glycopyrronium bromide or a regimen of other anti-obstructive therapy (i.e., maintenance COPD therapy excluding glycopyrronium bromide), the aim being to recruit patients in an approximate 2 to 1 ratio. Recruitment Phase 2 was of patients receiving either a regimen that included a fixed-dose combination (FDC) of a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), or a regimen of other anti-obstructive therapy, again with the aim of an approximate 2 to 1 ratio. Recruitment Phase 3 is ongoing (and is not included in the current report). It should be noted that there was no randomization of patients, and so there was no balancing of baseline characteristics, as would typically be the case in a randomized clinical trial.

Given the non-interventional nature of the study, the only data collected were from assessments that would typically be conducted as part of the care of patients with COPD. Visits were suggested at a three-monthly interval (in accordance with typical COPD management), with patients in each recruitment phase followed for two years.

Data were reported by investigators via electronic case report forms (eCRFs) that were completed at study visits; since the schedule was only suggested and not mandated (given this is a non-interventional study), many of these visits could be further than three months apart. The relationship of an adverse event to the study was the decision of the reporting investigator.

Setting

Primary and secondary care throughout Germany.

Subjects and study size, including dropouts

The main inclusion criteria were: a diagnosis of COPD fulfilling the German COPD Disease Management Program (DMP) criteria (one of which is that COPD is confirmed by spirometry testing); age ≥40 years; and initiating or changing COPD maintenance medication. Given the non-interventional nature of the study, the decision to initiate or change medication was to have been made prior to inclusion in DACCORD. Current, ex- and never-smokers were eligible, and all patients were to provide written informed consent prior to inclusion.

In order to recruit as broad a population as possible, patients were excluded only if they were in the Asthma DMP, or if they were participating in a randomized clinical trial.

There was no specific sample size calculation. The overall size of the study was determined by a need to collect data that are representative of COPD management throughout Germany. Phase 1 aimed to recruit approximately 6000 patients, with Phase 2 recruiting a further 6000 patients.

Variables and data sources

All data were recorded by the investigating physician following standard clinical assessments. Given the observational nature of the study, there were no standardized procedures or centralized assessments, and the only training provided was on the study protocol and how to complete the CRFs.

At the baseline visit, data collected were: demographic and disease characteristics (including comorbidities and smoking status); prescribed COPD and non-COPD medication; non-drug COPD therapy; CAT; exacerbations in the six months prior to entry (defined based on prescription of oral steroids and/or antibiotics or hospitalization); and FEV_1. Data on exacerbations and prescribed COPD medication were then collected every three months, with CAT, FEV_1, comorbidities, COPD symptoms, smoking status, prescribed COPD and non-COPD medication recorded at annual visits, and CAT also recorded at the first three-month visit for Recruitment Phase 2. A study-specific PRO questionnaire was completed at baseline, three months and annually.

Statistical methods

The majority of data are presented descriptively only, as the number and percentage of patients. Exacerbation rates, CAT and pulmonary function (FEV_1) are presented as mean and standard deviation.

Results

Of 12,390 patients recruited into the study, 11,441 had valid baseline data and post-baseline data from at least one visit and so are included in the safety set, the population used for all safety analyses. The efficacy data were analyzed in the 'per protocol V8 set', which comprised 6611 patients with valid baseline data, who completed visits at the end of 1 and 2 years and at least two of the three intermediate quarterly visits each year, and who had no major protocol deviations.

The majority of the baseline demographics were similar across groups, although a slightly higher percentage of patients in the 'other anti-obstructive therapy' group had been diagnosed more than one year previously. Disease characteristics were also similar across groups, although patients in the LABA/LAMA fixed combination group had slightly worse lung function than the other groups, whereas those in the glycopyrronium bromide group were more likely to have at least one COPD symptom. In terms of comorbid conditions at baseline, patients in the glycopyrronium bromide group were less likely to have cardiovascular disease and type 2 diabetes, and were slightly more likely to have a psychiatric disorder, but differences between groups were small. On entry to the study (i.e., at the baseline visit), 46.2% of patients in the glycopyrronium bromide group were receiving LAMA monotherapy (i.e., glycopyrronium bromide); however, more than half of patients were receiving glycopyrronium bromide in combination with other therapies, most commonly as an inhaled triple therapy regimen (LABA plus LAMA plus inhaled corticosteroid [ICS]). In contrast, 85.8% of patients in the LABA/LAMA fixed combination group were receiving only LABA plus LAMA. The most frequent therapies in the 'other' group were LAMA monotherapy and inhaled triple therapy. COPD maintenance therapy on entry to the study was also analysed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grouping, based on history of exacerbations in the six months prior to entry (where one exacerbation was considered high risk) and CAT total score at the baseline visit (with a score ≥10 considered 'more symptoms'). Whereas the overall analysis was conducted in the safety set, the GOLD grouping analyses were conducted in the smaller per protocol V8 set. Approximately 20% of patients in GOLD Group A (low risk, less symptoms) were receiving an inhaled corticosteroid (ICS)-containing regimen on entry to DACCORD (Table 10-5), compared with approximately 25% in GOLD Group B (low risk, more symptoms) (Table 10-6), 22% in GOLD Group C (high risk, less symptoms) (Table 10-7) and over 30% in GOLD Group D (high risk, more symptoms) (Table 10-8).

Prior to study entry, the majority of patients in all groups and managed both in primary and secondary care were receiving some form of maintenance COPD therapy, ranging from 72.1% of the patients in the 'other' group managed in primary care to 83.7% of those in the glycopyrronium bromide group managed in secondary care (Table 10-10). There was no consistent pattern to therapy groups, and no consistency between primary and secondary care.

A similar proportion of patients in all three groups had experienced exacerbations in the six months prior to entry (Table 10-12). Over the following two years, the highest proportion of patients experiencing exacerbations was in the 'other' group, with the lowest propotion being in the LABA/LAMA fixed combination group.

At baseline, the mean CAT total score was highest (i.e., worst) in patients in the glycopyrronium bromide group, with the value similar in the other two groups (Table 10-15). There was a clinically meaningful improvement from baseline in mean score at Year 1 and Year 2 in both the glycopyrronium bromide and LABA/LAMA fixed combination groups, although not in the 'other' group. More than 50% of patients in the glycopyrronium bromide and LABA/LAMA fixed combination groups had a clinically relevant improvement in CAT total score (i.e., decrease ≥2 unit) at each of the visits.

Pulmonary function (in terms of mean FEV_1) was similar at baseline across the three groups, with no change across the course of the study (Table 10-16). Note, however, that given this was a non-interventional study these pulmonary function assessments were performed without requiring washout (or standardization of time post-dose) of maintenance medication, and were not post-salbutamol.

At baseline, the majority of patients had at least one COPD symptom – most commonly exertional dyspnea (Table 10-17). The proportion of patients reporting no symptoms improved from baseline at Year 1 and Year 2 in all three groups, with the most marked improvement observed in the glycopyrronium bromide group.

Persistence was high in all three groups, with nearly three-quarters of patients in the glycopyrronium bromide and 'other' groups considered persistent at Year 2 (Table 10-18). The highest persistence was observed in the LABA/LAMA fixed combination group, with 82.0% of patients persistent at Year 2 and a further 7.9% having added another therapeutic class to their LABA/LAMA fixed combination.

A similar proportion of patients reported at least one non-serious adverse event in the three groups, both overall and for the majority of MedDRA system organ classes, with the most commonly reported system organ class in all three groups being respiratory, thoracic and mediastinal, followed by 'General disorders and administration site conditions' (Table 10-19). A lower proportion of patients in the LABA/LAMA fixed combination group reported events in the 'General disorders and administration site conditions' MedDRA class than in the other two groups, accounting for much of the difference between groups. The event rate per 100 patient-years was higher in the glycopyrronium bromide group than the 'other' or LABA/LAMA fixed combination groups.

As with the overall experience of non-serious AEs, slightly more patients in the glycopyrronium bromide group than in the other groups had non-serious AEs that were either considered related to the study or had the causal relationship not assigned – with much of the difference due to decreased exercise tolerance (Table 10-21).

The overall incidence of serious adverse events was similar in the three groups, although the event rate was highest in the glycopyrronium group (Table 10-24). The most commonly-reported MedDRA system organ class in all three groups was respiratory, thoracic and mediastinal.

A slightly higher proportion of serious adverse events were considered related to the study in the LABA/LAMA fixed combination group than in either of the other two groups, with the differences predominantly due to a higher incidence of the events COPD, cough and dyspnea (Table 10-26).

Discussion

Overall, DACCORD evaluated the impact and progression of COPD in a population newly initiating or switching COPD maintenance therapy in Germany. This population had a high symptom load, with a subset of patients also having an exacerbation history. A substantial proportion of patients also had comordidities (more than half having cardiovascular disease).

There were few differences between the three treatment groups in terms of disease progression or symptoms – and the substantial use of concomitant COPD maintenance medication complicates the interpretation of the data. However, the study overall shows the efficacy benefits possible through switching medication (in particular with the use of a LABA/LAMA fixed combination).

Although there were some imbalances in the adverse event profiles between the groups, the open-label study design may have influenced the results.

Conclusion

Given this study recruited a broad, geographically diverse population from primary and secondary care, the results can be generalized to patients with COPD across Germany who newly initiate COPD maintenance therapy, or who need a change in their maintenance therapy.

Overall, this study provides useful data on the course of COPD in Germany. The safety data do not change the overall benefit-risk profile of glycopyrronium or the glycopyrronium/indacaterol fixed-dose combination.

Marketing Authorization Holder(s)

Novartis Pharma GmbH

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted], Germany

2 List of abbreviations

ADR	adverse drug reaction
AE	adverse event
CAT	COPD Assessment Test
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
DMP	Disease Management Program
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
FDC	fixed-dose combination
FEV_1	forced expiratory volume in 1 second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GVP	Good Pharmacovigilance Practice
ICS	inhaled corticosteroid
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	modified Medical Research Council dyspnea scale
NOS	not otherwise specified
PAS	post-authorization study
PASS	post-authorization safety study
PDE4	phosphodiesterase-4
PMS	post marketing surveillance
PRO	patient-reported outcome
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
SmPC	summary of product characteristics
WHO	World Health Organisation

3 Investigators

Principal investigator: [redacted], Germany.

All other investigators are listed in Annex 1.

4 Other responsible parties

Not applicable.

5 Milestones

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	5 November 2012	5 November 2012	
End of data collection (Last date of data collection)	1 July 2020		This is the end of data collection for the ongoing Recruitment Phase 3
Registration in the EU PAS register	7 April 2014	7 April 2014	
Interim safety report 1	Not applicable	18 June 2015	
Interim safety report 2	Not applicable	30 August 2016	
Study progress report (current report)	Not applicable	25 January 2019	Contains data from Recruitment Phases 1 and 2
Final report of study results	1 July 2021		On completion of Recruitment Phase 3

6 Rationale and background

Randomized controlled trials (RCTs) generally recruit highly selected populations, often excluding patients with significant or unstable comorbidities. Although data from RCTs can be helpful in informing treatment decisions, data that are more representative of 'real-life' populations are important. The main aim of Study CNVA237ADE01 was to generate data on the course of chronic obstructive pulmonary disease (COPD) under real-life treatment conditions in the community.

Study CNVA237ADE01 is a longitudinal, prospective non-interventional study. One of the key inclusion criteria for the study was that patients were to have initiated or changed COPD maintenance medication; given the non-interventional nature of the study, the decision to initiate or change medication was to have been taken prior to entry to the study. Furthermore, to ensure that conditions within the trial were as close as possible to real-life, there were no limitations within the trial as to concomitant COPD maintenance treatment, and no limitations on changing, adding, or discontinuing treatment. All treatments were open-label.

7 Research question and objectives

The main aim of DACCORD was to generate data on the course of COPD under typical treatment conditions in Germany.

Objectives included:

1. To measure patient-reported outcomes (PROs) in terms of COPD Assessment Test (CAT), modified Medical Research Council dyspnea scale (mMRC), and symptoms (using a questionnaire).
2. To document exacerbations retrospectively (six months preceding inclusion) and prospectively (including number and severity) after inclusion.
3. To evaluate comorbidities (number, type, impact).
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5. To establish safety and tolerability, in terms of adverse events and serious adverse events.
6. To assess the implementation of pharmacological treatment recommendations in German COPD guidelines at the participating centers.
7. To evaluate potential differences in the treatment of COPD between primary and secondary care
8. To assess patient adherence to pharmacological COPD treatments.
9. To evaluate the dropout rate.

8 Amendments and updates to the protocol

Number	Date	Section of study protocol	Amendment or update	Reason
1	17 June 2013	Safety	This amendment added adaptions to safety processes.	To reflect the latest wording for adverse event capture in post-marketing surveillance (PMS) studies according to the Good Pharmacovigilance Practice (GVP) guidelines from the European Medicines Agency (EMA).

Number	Date	Section of study protocol	Amendment or update	Reason
2	23 October 2013	Study design Efficacy evaluations Inclusion criteria	This amendment added Recruitment Period 2, the additional evaluation of CAT questionnaire at Visit 1 and the inclusion criterion 'Use of drug therapy in accordance with the label (Summary of Product Characteristics (SmPC)) … '.	To add Recruitment Period 2, reflecting the approval of long-acting β_2-agonist/long-acting muscarinic antagonist (LABA/LAMA) combination inhalers, to collect on-treatment data from the validated CAT questionnaire, and to emphasize that all therapies were to be used in accordance with the approved SmPCs.
3	8 November 2013	Study design	This non-substantial amendment was implemented to remove inconsistencies from the observational plan.	To correct inconsistencies.

9 Research methods

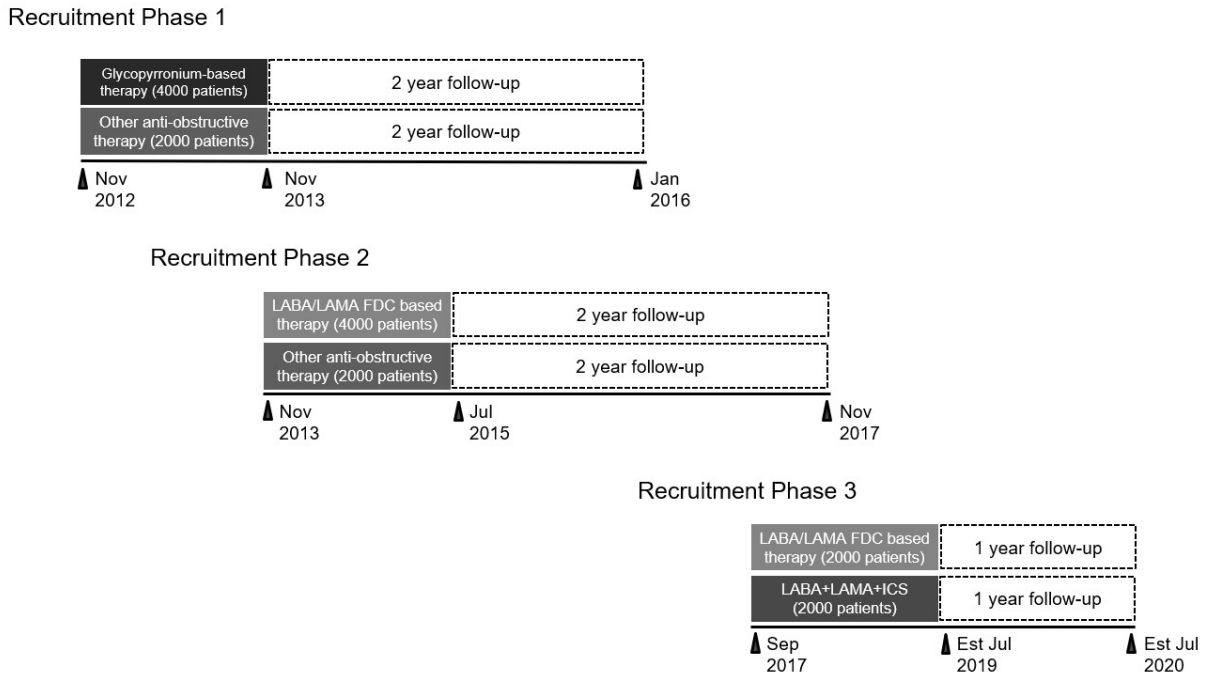
9.1 Study design

This is a longitudinal, prospective non-interventional study, which seeks to generate data on the course of COPD under real-life treatment conditions. The decision to treat patients was taken prior to inclusion in the study, and there were no limitations on concomitant treatment, or on changing, adding, or discontinuing treatment.

Recruitment into the study is in three phases, as illustrated in Figure 9-1. The first recruitment phase was of patients receiving either a regimen that included glycopyrronium bromide or a regimen of other anti-obstructive therapy (i.e., maintenance COPD therapy excluding glycopyrronium bromide), the aim being to recruit patients in an approximate 2 to 1 ratio. Recruitment Phase 2 was of patients receiving either a regimen that included a fixed-dose combination (FDC) of a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), or a regimen of other anti-obstructive therapy, again with the aim of an approximate 2 to 1 ratio. Recruitment Phase 3 is ongoing (and is not included in the current report). It should be noted that there was no randomization of patients, and so there was no

balancing of baseline characteristics, as would typically be the case in a randomized clinical trial.

Figure 9-1 Recruitment phases of CNVA237ADE01



LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

Given the non-interventional nature of the study, the only data collected were from assessments that would typically be conducted as part of the standard care of patients with COPD. Visits were suggested at a three-monthly interval (in accordance with typical COPD management), and patients in each recruitment phase were followed for two years (one year for Recruitment Phase 3).

Data were reported by investigators via electronic case report forms (eCRFs) that were completed at study visits; since the schedule was only suggested and not mandated, many of these visits could be further than three months apart. The relationship of an adverse event to the study was the decision of the reporting investigator.

9.2 Setting

Primary and secondary care throughout Germany.

9.3 Subjects

The inclusion criteria were:

- Written consent of the patients to participation in the study.
- Age: ≥ 40 years.
- Diagnosis of COPD confirmed by the physician.

- Initiation or modification of pharmacological COPD treatment at the start of the study (Visit 0).
- Recruitment to the COPD DMP or fulfilment of the DMP inclusion criteria.
- Use of drug therapy in accordance with the label (Summary of Product Characteristics (SmPC)).

Given the non-interventional nature of the study, the decision to initiate or change medication was to have been made prior to inclusion in DACCORD. Current, ex- and never-smokers were eligible, and all patients were to provide written informed consent prior to inclusion.

In order to recruit as broad a population as possible, patients were excluded only if they were in the Asthma DMP, or if they were participating in a RCT.

9.4 Variables

9.4.1 Visit schedule

Since this was a non-interventional study, visit schedules could not be mandated in the protocol. It was anticipated that most patients would visit their physician once every three months (prescription of medication is usually quarterly); the COPD DMP mandates a minimum of one visit per year.

9.4.2 Efficacy assessments

9.4.2.1 Assessment of efficacy

At the baseline visit, data collected in eCRFs were: demographic and disease characteristics (including comorbidities and smoking status); prescribed COPD and non-COPD medication; non-drug COPD therapy; CAT; exacerbations in the six months prior to entry (defined based on prescription of oral steroids and/or antibiotics or hospitalization); and FEV_1. Data on exacerbations and prescribed COPD medication were then collected every three months, with CAT, FEV_1, comorbidities, COPD symptoms, smoking status, prescribed COPD and non-COPD medication recorded at annual visits, and CAT also recorded at the first three-month visit for Recruitment Phase 2. A study-specific PRO questionnaire was completed at baseline, three months and annually.

9.4.3 Safety assessments

9.4.3.1 Assessment of safety

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.

9.4.3.1.1 Adverse events

AEs were defined as any untoward medical occurrence (unfavorable and unintended sign or symptom, complication, significant change of laboratory parameters or electrocardiogram [ECG] etc.) in a patient after the administration of the medication irrespective of the relation to the therapy or intended use. Non-serious exacerbations in which the physician did not suspect

a causal link with glycopyrronium bromide or indacaterol/glycopyrronium were not to be reported as AEs. This is because an exacerbation is often accompanied by progression of COPD, and a significant reduction in the exacerbation risk was demonstrated for this substance in Phase III studies. Note that all serious exacerbations, regardless of causality, were included in the analyses.

Each AE has to be documented in the eCRF independent of its causal relationship to the study. The physician has to report start and duration of the event and to assess the intensity and the causal relationship as well as to document the outcome and potential counteractive measures. Note that since patients could be receiving multiple COPD maintenance therapies, the assessment of causality is whether the event was related to the study, rather than related to study drug.

Additional AE data were extracted from the Argus database. This contained data only for patients receiving the sponsor's products, with causality based only on the final sponsor's assessment, with percentages calculated using the number of patients with at least one event as the denominator.

In general, SAEs and non-serious AEs are differentiated. Both of these terms are used to describe AEs regardless of their relationship to study. For the purpose of the statistical analysis, events are further distinguished according to their relationship to study.

SAEs are all events that:

- are fatal
- are life-threatening
- require inpatient hospitalization or result in prolongation of existing hospitalization
- result in persistent or significant disability/incapacity
- result in a congenital anomaly/birth defect
- are medically important events, i.e. require medical or surgical intervention to prevent one of the other outcomes listed in the definition above.

Inpatient hospitalization was not to be considered an SAE, if any of the following was the case:

- Hospitalizations that had already been planned before inclusion into the study.
- Elective hospitalizations for treatment of preexisting conditions, which had no relationship to the study indication or to the study medication.
- Outpatient hospital treatments, which did not lead to hospitalization (in this context it had to be checked whether one of the other criteria was present, e.g. life-threatening event)
- Hospitalizations that were part of the normal treatment or control of the study indication and that were not caused by a progression of the disease.

The assessment of seriousness was only dependent on the presence of any of the above mentioned formal criteria and was independent of the question whether a causal relationship between the intake of the medication and the occurrence of the SAE was assumed.

All SAEs that occurred after baseline examination and up to 30 days after discontinuation of the study participation were to be documented in the eCRF. All SAEs that occurred after the 30 days deadline only had to be reported if causality was suspected.

Reoccurring events, complications or worsening of documented SAE were documented as follow-up reports.

9.4.3.1.2 Pregnancies

To ensure patient safety, each pregnancy in a patient administered any Novartis preparation was to be reported to Novartis.

9.5 Data sources and measurement

All data were recorded by the investigating physician following standard clinical assessments. Given the observational nature of the study, there were no standardized procedures or centralized assessments, and the only training provided was on the study protocol and how to complete the eCRFs.

9.6 Bias

To minimize selection bias, investigators were asked to recruit consecutive eligible patients. Observer bias was minimized by recording data following standard clinical assessments, and by including comparator groups in each recruitment phase.

9.7 Study size

There was no specific sample size calculation. The overall size of the study was determined by a need to collect data that are representative of COPD management throughout Germany. Phase 1 aimed to recruit approximately 6000 patients, with Phase 2 recruiting a further 6000 patients.

9.8 Data transformation

Data are presented for two main populations:

- The ‘safety set’, which comprises all patients with valid baseline data and post-baseline data from at least one visit. This population was used for all safety and baseline analyses.
- The ‘per protocol V8 set’, which comprises all patients with valid baseline data, who completed visits at the end of 1 and 2 years and at least two of the three intermediate quarterly visits each year, and who had no major protocol deviations. This population was used for all efficacy analyses.

The data are based on a pooled analysis of Recruitment Phases 1 and 2. Importantly, to keep assignments to different arms consistent, patients enrolled into the “other anti-obstructive therapy” treatment arm in Recruitment Phase 2 who were taking glycopyrronium bromide were included in the glycopyrronium bromide group for all analyses.

9.9 Statistical methods

9.9.1 Main summary measures

The majority of data are presented descriptively only, as the number and percentage of patients. Exacerbation rates, CAT and pulmonary function (FEV_1) are presented as mean and standard deviation.

9.9.2 Main statistical methods

Exacerbation rates were estimated using a negative binomial regression model with annualized numbers of exacerbation as dependent variable and no independent variable. For CAT total score, absolute changes from baseline are presented, together with the number and percentage of patients with a clinically relevant improvement (i.e., a decrease in total score ≥2 unit).

9.9.3 Missing values

Not applicable.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

All data management processes are based on the respective valid standard operating procedure (SOP) for non-regulatory studies of the contracted contract research organization (CRO).

Programmed routines checked the information during data entry for plausibility and completeness and automatically generated respective queries to the study center personnel. The treating physician had to confirm that the data were correct and complete.

Data entry was checked daily by the CRO. Free text fields of newly entered or updated data via eCRF were checked for possible hidden AEs by the data management team. Open queries were tracked and communicated to the practices/centers. The processing of queries by the practices/centers were sent via post or fax; then the respective query form had to be filled and signed by the physician and sent back to the contracted CRO for data entry. A signed copy had to be filed by the physician.

Obvious incorrect data could be corrected and documented by the data management team in a final validation.

The reported concomitant medication was coded according to the anatomical therapeutic chemical classification system of the World Health Organization (WHO) drug dictionary. Coding of medical history and current concomitant diseases as well as AEs is performed according to Medical Dictionary for Regulatory Activities (MedDRA) system.

All procedures and guidelines for SAE reporting and cumulative AE reporting were according to SOPs of Novartis Pharma GmbH.

Paper CRFs (for this study only applicable for the patient survey PRO and in exceptional cases AE/SAE-Forms) that arrived at the CRO were registered in the study database and checked for (S)AE or hidden (S)AE. After data entry predefined basic data were checked according to a query logic. Queries were generated and sent to the investigator for resolution and completion. In case of failure of response a reminder was sent. The processing of incomplete or missing

documentation of (hidden) AEs was performed according to Novartis SOPs (Amendment of observational plan No.1; addition of paper CRF processing).

Regulations for data protection of the personal patient data were followed.

10 Results

10.1 Participants

Of the 12,390 patients recruited into the study, 12,320 had valid baseline data, 11,441 of whom had post-baseline data from at least one visit (Table 10-1). A total of 7533 patients completed the visit at the end of two years, 6611 of whom had also completed the Year 1 visit and at least two of the three quarterly visits each year with no major protocol deviations.

Table 10-1 Disposition of patients

	Glycopyrronium bromide (N=4612)	LABA/LAMA fixed combination (N=4483)	Other anti-obstructive therapy (N=3295)	Total (N=12,390)
All patients recruited into the study	4612	4483	3295	12,390
Patients with no valid baseline data	17	20	33	70
Patients with valid baseline data	4595	4463	3262	12,320
Patients with no post-baseline data	340	278	261	879
Patients with post-baseline data (safety set)	4255	4185	3001	11,441
Patients with 2-year visit not completed	1574	1355	979	3908
- because lost to follow-up	793	788	576	2157
- because withdrawn from study	781	567	403	1751
Patients who completed the 2-year visit	2681	2830	2022	7533
Patients excluded from per-protocol population completed 2 years	363	304	255	922
- because of major protocol deviation(s)	195	182	129	506

	Glycopyrronium bromide (N=4612)	LABA/LAMA fixed combination (N=4483)	Other anti-obstructive therapy (N=3295)	Total (N=12,390)
- because missing more than 1 quarterly visit per year	168	122	126	416
Patients included in per-protocol population completed 2 years (per protocol V8 set)	2318	2526	1767	6611

Source: Table 1.1-1

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.2 Descriptive data

The majority of the baseline demographics were similar across groups, although a slightly higher percentage of patients in the 'other' group had been diagnosed more than one year previously (Table 10-2). Disease characteristics were also similar across groups. Patients in the LABA/LAMA fixed combination group had slightly worse lung function than the other groups, whereas those in the glycopyrronium bromide group were more likely to have at least one COPD symptom.

Table 10-2 Baseline demographics, disease characteristics and symptoms (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Sex				
Male	2545 (59.8%)	2486 (59.4%)	1734 (57.8%)	6765 (59.1%)
Female	1710 (40.2%)	1699 (40.6%)	1267 (42.2%)	4676 (40.9%)
Age (years), mean (SD)	65.5 (10.3)	66.5 (10.2)	66.5 (10.4)	66.1 (10.3)
Age groups				
< 65 years	1975 (46.4%)	1806 (43.2%)	1290 (43.0%)	5071 (44.3%)
65 - 75 years	1535 (36.1%)	1485 (35.5%)	1075 (35.8%)	4095 (35.8%)
> 75 years	745 (17.5%)	894 (21.4%)	636 (21.2%)	2275 (19.9%)
Height (cm), mean (SD)	170.3 (9.0)	170.4 (8.8)	169.9 (8.6)	170.2 (8.8)
Weight (kg), mean (SD)	79.6 (18.5)	80.2 (18.5)	79.7 (17.9)	79.9 (18.3)
BMI (kg/m²), mean (SD)	27.4 (5.6)	27.6 (5.8)	27.6 (5.6)	27.5 (5.7)
Duration since primary diagnosis				
≤ 1 year	1169 (27.5%)	1142 (27.3%)	771 (25.7%)	3082 (26.9%)
> 1 year	3086 (72.5%)	3043 (72.7%)	2230 (74.3%)	8359 (73.1%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Symptoms of COPD†				
None	113 (2.7%)	142 (3.4%)	131 (4.4%)	386 (3.4%)
Exertional dyspnea	3673 (86.3%)	3625 (86.6%)	2605 (86.8%)	9903 (86.6%)
Dyspnea at rest	822 (19.3%)	607 (14.5%)	424 (14.1%)	1853 (16.2%)
Chest tightness / chest pain	1102 (25.9%)	1106 (26.4%)	683 (22.8%)	2891 (25.3%)
Cough	2909 (68.4%)	2767 (66.1%)	1914 (63.8%)	7590 (66.3%)
Wheezing or grunting	1091 (25.6%)	1148 (27.4%)	716 (23.9%)	2955 (25.8%)
Prolonged expiration	863 (20.3%)	917 (21.9%)	583 (19.4%)	2363 (20.7%)
Restricted exercise tolerance	2603 (61.2%)	2612 (62.4%)	1694 (56.4%)	6909 (60.4%)
Missing	10	16	12	38
Type of cough				
No cough	1346 (31.6%)	1418 (34.0%)	1087 (36.3%)	3851 (33.7%)
Productive	1767 (41.5%)	1632 (39.1%)	1080 (36.0%)	4479 (39.2%)
Dry	1141 (26.8%)	1125 (26.9%)	829 (27.7%)	3095 (27.1%)
Missing	1	10	5	16
Number of symptoms				
1	510 (12.3%)	574 (14.3%)	476 (16.7%)	1560 (14.2%)
2	1153 (27.9%)	980 (24.3%)	723 (25.3%)	2856 (25.9%)
3	949 (23.0%)	948 (23.5%)	697 (24.4%)	2594 (23.5%)
>3	1520 (36.8%)	1525 (37.9%)	962 (33.7%)	4007 (36.4%)
FEV_1 (liters), mean (SD)	1.9 (6.8)	1.7 (1.1)	1.9 (7.5)	1.8 (5.7)
FEV_1 predicted, mean (SD)	68.3 (221.8)	61.8 (38.3)	69.4 (264.9)	66.2 (192.7)
Smoking status				
Ex-smoker	1683 (40.2%)	1680 (40.2%)	1200 (40.4%)	4563 (40.3%)
Smoker	1664 (39.8%)	1636 (39.1%)	1135 (38.2%)	4435 (39.1%)
Non-smoker	837 (20.0%)	863 (20.7%)	636 (21.4%)	2336 (20.6%)
Missing	71	6	30	107
Years smoking*, mean (SD)	34.3 (11.4)	34.1 (11.9)	33.9 (11.9)	34.1 (11.7)
Pack-years*, mean (SD)	39.1 (28.2)	36.1 (28.1)	37.5 (28.3)	37.6 (28.2)

Sources 1.2, 1.3-1, 1.3-4 and 1.3-5

†More than one symptom possible per patient; *only current smokers and ex-smokers. BMI = body mass index; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

In terms of comorbid conditions at baseline, patients in the glycopyrronium bromide group were less likely to report cardiovascular disease and type 2 diabetes, and were slightly more likely to have a psychiatric disorder, but differences between groups were small (Table 10-3).

Table 10-3 Comorbid conditions at baseline (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Alpha-1 antitrypsin deficiency	10 (0.2%)	5 (0.1%)	4 (0.1%)	19 (0.2%)
Bronchial carcinoma	65 (1.5%)	80 (1.9%)	48 (1.6%)	193 (1.7%)
Bronchiectasis NOS	53 (1.2%)	58 (1.4%)	46 (1.5%)	157 (1.4%)
Cardiovascular disease	2194 (51.6%)	2365 (56.5%)	1611 (53.7%)	6170 (53.9%)
Diabetes mellitus type 2	618 (14.5%)	784 (18.7%)	526 (17.5%)	1928 (16.9%)
Osteoporosis	268 (6.3%)	256 (6.1%)	194 (6.5%)	718 (6.3%)
Psychiatric disorders	507 (11.9%)	412 (9.8%)	280 (9.3%)	1199 (10.5%)
Sleep apnea	367 (8.6%)	372 (8.9%)	237 (7.9%)	976 (8.5%)

Source: Table 1.3-6

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; NOS = not otherwise specified.

On entry to the study (i.e., at the baseline visit), 46.2% of patients in the glycopyrronium bromide group were receiving LAMA monotherapy (i.e., glycopyrronium bromide alone); however, more than half of patients were receiving glycopyrronium bromide in combination with other therapies, most commonly as an inhaled triple therapy regimen (LABA plus LAMA plus ICS) (Table 10-4). In contrast, 85.8% of patients in the LABA/LAMA fixed combination group were receiving only LABA plus LAMA. The most frequent therapies in the 'other' group were LAMA monotherapy and inhaled triple therapy.

Table 10-4 COPD maintenance treatment on study entry (safety set)

Therapy group	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
LABA monotherapy	1 (0.0%)	2 (0.0%)	273 (9.1%)	276 (2.4%)
LAMA monotherapy	1965 (46.2%)	10 (0.2%)	730 (24.3%)	2705 (23.6%)
ICS monotherapy	1 (0.0%)	0	35 (1.2%)	36 (0.3%)
LABA plus LAMA	661 (15.5%)	3590 (85.8%)	439 (14.6%)	4690 (41.0%)
LABA plus ICS	5 (0.1%)	12 (0.3%)	427 (14.2%)	444 (3.9%)
LAMA plus ICS	67 (1.6%)	1 (0.0%)	28 (0.9%)	96 (0.8%)
LABA plus LAMA plus ICS	1235 (29.0%)	393 (9.4%)	699 (23.3%)	2327 (20.3%)
Regimen containing PDE-4 inhibitor or theophylline	288 (6.8%)	165 (3.9%)	224 (7.5%)	677 (5.9%)
Missing values	32 (0.8%)	12 (0.3%)	146 (4.9%)	190 (1.7%)

Source: Table 1.4-2.3.2

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE4 = phosphodiesterase-4.

COPD maintenance therapy on entry to the study was also analysed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) grouping, based on history of

exacerbations in the six months prior to entry (where one exacerbation was considered high risk) and CAT total score at the baseline visit (with a score ≥10 considered 'more symptoms'). Whereas the overall analysis was conducted in the safety set, the GOLD grouping analyses were conducted in the smaller per protocol V8 set. Approximately 20% of patients in GOLD Group A (low risk, less symptoms) were receiving an inhaled corticosteroid (ICS)-containing regimen on entry to DACCORD (Table 10-5), compared with approximately 25% in GOLD Group B (low risk, more symptoms) (Table 10-6), 22% in GOLD Group C (high risk, less symptoms) (Table 10-7) and over 30% in GOLD Group D (high risk, more symptoms) (Table 10-8).

Table 10-5 COPD maintenance treatment on study entry: GOLD Group A (per protocol V8 set)

Therapy group	Glycopyrronium bromide (N=166)	LABA/LAMA fixed combination (N=284)	Other anti-obstructive therapy (N=194)	Total (N=644)
LABA/LAMA	23 (13.9%)	257 (90.5%)	37 (19.1%)	317 (49.2%)
LAMA	91 (54.8%)	2 (0.7%)	58 (29.9%)	151 (23.4%)
LABA/LAMA/ICS	47 (28.3%)	20 (7.0%)	23 (11.9%)	90 (14.0%)
LABA/ICS	0	0	37 (19.1%)	37 (5.7%)
LABA	0	0	26 (13.4%)	26 (4.0%)
Theophylline or PDE-4 inhibitor containing treatment	3 (1.8%)	5 (1.8%)	6 (3.1%)	14 (2.2%)
LAMA/ICS	2 (1.2%)	0	1 (0.5%)	3 (0.5%)

Source: Table 1.4-2.3.1.3a

GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE4 = phosphodiesterase-4.

Table 10-6 COPD maintenance treatment on study entry: GOLD Group B (per protocol V8 set)

Therapy group	Glycopyrronium bromide (N=1551)	LABA/LAMA fixed combination (N=1613)	Other anti-obstructive therapy (N=1150)	Total (N=4314)
LABA/LAMA	269 (17.3%)	1377 (85.4%)	197 (17.1%)	1843 (42.7%)
LAMA	676 (43.6%)	3 (0.2%)	276 (24.0%)	955 (22.1%)
LABA/LAMA/ICS	471 (30.4%)	158 (9.8%)	285 (24.8%)	914 (21.2%)
Theophylline or PDE-4 inhibitor containing treatment	105 (6.8%)	63 (3.9%)	90 (7.8%)	258 (6.0%)
LABA/ICS	0	8 (0.5%)	150 (13.0%)	158 (3.7%)
LABA	0	1 (<0.1%)	92 (8.0%)	93 (2.2%)
LAMA/ICS	27 (1.7%)	0	8 (0.7%)	35 (0.8%)
ICS	0	0	13 (1.1%)	13 (0.3%)

Source: Table 1.4-2.3.1.3a

GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE4 = phosphodiesterase-4.

Table 10-7 COPD maintenance treatment on study entry: GOLD Group C (per protocol V8 set)

Therapy group	Glycopyrronium bromide (N=29)	LABA/LAMA fixed combination (N=39)	Other anti-obstructive therapy (N=23)	Total (N=91)
LABA/LAMA	5 (17.2%)	37 (94.9%)	0	42 (46.2%)
LAMA	11 (37.9%)	0	7 (30.4%)	18 (19.8%)
LABA/LAMA/ICS	10 (34.5%)	2 (5.1%)	4 (17.4%)	16 (17.6%)
Theophylline or PDE-4 inhibitor containing treatment	3 (10.3%)	0	3 (13.0%)	6 (6.6%)
LABA	0	0	4 (17.4%)	4 (4.4%)
LABA/ICS	0	0	3 (13.0%)	3 (3.3%)
ICS	0	0	1 (4.3%)	1 (1.1%)

Source: Table 1.4-2.3.1.3a

GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE4 = phosphodiesterase-4.

Table 10-8 COPD maintenance treatment on study entry: GOLD Group D (per protocol V8 set)

Therapy group	Glycopyrronium bromide (N=572)	LABA/LAMA fixed combination (N=590)	Other anti-obstructive therapy (N=400)	Total (N=1562)
LABA/LAMA	76 (13.3%)	495 (83.9%)	29 (7.3%)	600 (38.4%)
LABA/LAMA/ICS	194 (33.9%)	65 (11.0%)	147 (36.8%)	406 (26.0%)
LAMA	229 (40.0%)	1 (0.2%)	76 (19.0%)	306 (19.6%)
Theophylline or PDE-4 inhibitor containing treatment	59 (10.3%)	29 (4.9%)	38 (9.5%)	126 (8.1%)
LABA/ICS	0	0	57 (14.3%)	57 (3.6%)
LABA	0	0	28 (7.0%)	28 (1.8%)
LAMA/ICS	14 (2.4%)	0	7 (1.8%)	21 (1.3%)
ICS	0	0	8 (2.0%)	8 (0.5%)

Source: Table 1.4-2.3.1.3a

GOLD = Global Initiative for Chronic Obstructive Lung Disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE4 = phosphodiesterase-4.

10.3 Outcome data

The safety set comprised 11,441 patients, with the per protocol V8 set (used for the efficacy analyses) comprising 6611 patients (Table 10-9).

Table 10-9 Analysis populations

	Glycopyrronium bromide	LABA/LAMA fixed combination	Other anti-obstructive therapy	Total
Safety set	4225	4185	3001	11,441
Per protocol V8 set	2318	2526	1767	6611

Source: Table 1.1-3

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.4 Main results

10.4.1 COPD maintenance treatment by type of physician

Prior to study entry, the majority of patients in all groups managed either in primary or secondary care were receiving some form of maintenance COPD therapy, ranging from 72.1% of the patients in the 'other' group managed in primary care to 83.7% in the glycopyrronium bromide group managed in secondary care (Table 10-10). There was no consistent pattern to therapy groups, and no consistency between primary and secondary care.

On entry to the study (i.e., at baseline), with the exception of LABA/LAMA in the LABA/LAMA fixed combination group (prescribed to 87.4% of patients managed in primary care and 83.7% of patients in secondary care), there was little consistency between primary and secondary care therapy choices (Table 10-11). Secondary care physicians were more likely to prescribe inhaled triple therapy and regimens containing theophylline or a PDE4-inhibitor, whereas primary care physicians were more likely to prescribe LAMA monotherapy.

Table 10-10 COPD maintenance treatment prior to study entry by type of physician (per protocol V8 set)

	Glycopyrronium bromide		LABA/LAMA fixed combination		Other anti-obstructive therapy	
	Primary care (N=940)	Secondary care (N=1378)	Primary care (N=1409)	Secondary care (N=1117)	Primary care (N=837)	Secondary care (N=936)
Number (%) of patients with therapy group(s)	689 (73.3%)	1154 (83.7%)	1150 (81.6%)	906 (81.1%)	599 (72.1%)	727 (77.7%)
LABA/ICS	217 (23.1%)	330 (23.9%)	342 (24.3%)	139 (12.4%)	231 (27.8%)	200 (21.4%)
LAMA	129 (13.7%)	102 (7.4%)	305 (21.6%)	168 (15.0%)	119 (14.3%)	77 (8.2%)
LABA/LAMA/ICS	120 (12.8%)	224 (16.3%)	161 (11.4%)	194 (17.4%)	60 (7.2%)	128 (13.7%)
LABA	97 (10.3%)	176 (12.8%)	140 (9.9%)	77 (6.9%)	93 (11.2%)	112 (12.0%)
LABA/LAMA	40 (4.3%)	117 (8.5%)	116 (8.2%)	239 (21.4%)	30 (3.6%)	86 (9.2%)

	Glycopyrronium bromide		LABA/LAMA fixed combination		Other anti-obstructive therapy	
	Primary care (N=940)	**Secondary care (N=1378)**	**Primary care (N=1409)**	**Secondary care (N=1117)**	**Primary care (N=837)**	**Secondary care (N=936)**
Theophylline or PDE-4 inhibitor containing treatment	60 (6.4%)	159 (11.5%)	54 (3.8%)	52 (4.7%)	40 (4.8%)	100 (10.7%)
ICS	20 (2.1%)	34 (2.5%)	20 (1.4%)	26 (2.3%)	24 (2.9%)	16 (1.7%)
LAMA/ICS	6 (0.6%)	12 (0.9%)	12 (0.9%)	11 (1.0%)	2 (0.2%)	8 (0.9%)

Source: Table 1.4-1.3.1.4

LABA = long-acting β_2-agonist; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase-4.

Table 10-11 COPD maintenance treatment on study entry by type of physician (per protocol V8 set)

	Glycopyrronium bromide		LABA/LAMA fixed combination		Other anti-obstructive therapy	
	Primary care (N=940)	**Secondary care (N=1378)**	**Primary care (N=1409)**	**Secondary care (N=1117)**	**Primary care (N=837)**	**Secondary care (N=936)**
Number (%) of patients with therapy group(s)	938 (99.8%)	1377 (>99.9%)	1406 (99.8%)	1117 (100.0%)	787 (94.7%)	924 (98.7%)
LABA/LAMA	81 (8.6%)	292 (21.2%)	1231 (87.4%)	935 (83.7%)	67 (8.1%)	196 (20.9%)
LAMA	587 (62.4%)	420 (30.5%)	4 (0.3%)	2 (0.2%)	213 (25.6%)	204 (21.8%)
LABA/LAMA/ICS	215 (22.9%)	507 (36.8%)	117 (8.3%)	128 (11.5%)	192 (23.1%)	267 (28.5%)
Theophylline or PDE-4 inhibitor containing treatment	45 (4.8%)	125 (9.1%)	45 (3.2%)	52 (4.7%)	40 (4.8%)	97 (10.4%)
LABA/ICS	0	0	8 (0.6%)	0	178 (21.4%)	69 (7.4%)
LABA	0	0	1 (<0.1%)	0	73 (8.8%)	77 (8.2%)
LAMA/ICS	10 (1.1%)	33 (2.4%)	0	0	9 (1.1%)	7 (0.7%)
ICS	0	0	0	0	15 (1.8%)	7 (0.7%)

Source: Table 1.4-2.3.1.4a

LABA = long-acting β_2-agonist; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase-4.

10.4.2 Exacerbations

A similar proportion of patients in all three groups had experienced exacerbations in the six months prior to entry (Table 10-12). Over the following two years, the highest proportion of patients experiencing exacerbations was in the 'other' group, with the lowest proportion in the LABA/LAMA fixed combination group.

Table 10-12 Percentage of patients with exacerbations (per protocol V8 set)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Baseline visit (previous 6 months)				
Percent base	2308	2518	1760	6586
Yes	601 (26.0%)	629 (25.0%)	423 (24.0%)	1653 (25.1%)
No	1707 (74.0%)	1889 (75.0%)	1337 (76.0%)	4933 (74.9%)
missing values	10	8	7	25
Year 1				
Percent base	2075	2413	1642	6130
Yes	555 (26.7%)	485 (20.1%)	488 (29.7%)	1528 (24.9%)
No	1520 (73.3%)	1928 (79.9%)	1154 (70.3%)	4602 (75.1%)
missing values	243	113	125	481
Year 2				
Percent base	2147	2404	1646	6197
Yes	484 (22.5%)	460 (19.1%)	439 (26.7%)	1383 (22.3%)
No	1663 (77.5%)	1944 (80.9%)	1207 (73.3%)	4814 (77.7%)
missing values	171	122	121	414

Source: Table 2.1.1

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

Consistent with this, the lowest annualized exacerbation rates in both Year 1 and Year 2 were in the LABA/LAMA fixed combination group, either when patients with missing data were excluded from the analyses or when the missing data for these patients was set to zero (i.e., assuming that missing data meant that the patient had not exacerbated) (Table 10-13). The highest exacerbation rates were in the 'other' group; the non-overlapping confidence intervals suggest that the differences between the LABA/LAMA fixed combination and 'other' groups would be statistically significant.

When the data were analyzed according to exacerbations during the six months prior to entry, the rates in all three groups were highest in patients who had exacerbated prior to entry (especially those with ≥2 exacerbations during the six-month period), with the rates similar in Year 1 and Year 2 (Table 10-13).

Table 10-13 Annualized exacerbation rates (per protocol V8 set)

		Glycopyrronium bromide (N=2318)		LABA/LAMA fixed combination (N=2526)		Other anti-obstructive therapy (N=1767)		Total (N=6611)	
		n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)
All patients									
Year 1	missings excluded	1974	0.355 (0.322, 0.392)	2371	0.279 (0.253, 0.309)	1587	0.406 (0.368, 0.448)	5932	0.338 (0.319, 0.358)
	missings=0	2273	0.344 (0.312, 0.378)	2511	0.276 (0.250, 0.304)	1741	0.392 (0.356, 0.431)	6525	0.330 (0.312, 0.349)
Year 2	missings excluded	2091	0.307 (0.277, 0.341)	2387	0.257 (0.233, 0.284)	1600	0.364 (0.328, 0.404)	6078	0.303 (0.285, 0.321)
	missings=0	2293	0.297 (0.269, 0.328)	2525	0.254 (0.230, 0.280)	1751	0.365 (0.330, 0.404)	6569	0.298 (0.282, 0.316)
Years 1+2	missings excluded	1804	0.316 (0.288, 0.347)	2261	0.265 (0.243, 0.289)	1451	0.384 (0.351, 0.420)	5516	0.313 (0.297, 0.330)
	missings=0	2249	0.310 (0.285, 0.337)	2511	0.263 (0.242, 0.285)	1725	0.374 (0.344, 0.407)	6485	0.309 (0.294, 0.324)
Patients without exacerbations within 6 months prior to baseline									
Year 1	missings excluded	1462	0.235 (0.207, 0.267)	1770	0.185 (0.162, 0.212)	1197	0.264 (0.233, 0.299)	4429	0.223 (0.207, 0.240)
	missings=0	1684	0.225 (0.199, 0.253)	1883	0.182 (0.160, 0.208)	1322	0.258 (0.228, 0.291)	4889	0.217 (0.202, 0.233)

		Glycopyrronium bromide (N=2318)		LABA/LAMA fixed combination (N=2526)		Other anti-obstructive therapy (N=1767)		Total (N=6611)	
		n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)
Year 2	missings excluded	1542	0.218 (0.189, 0.252)	1770	0.182 (0.160, 0.207)	1206	0.254 (0.221, 0.292)	4518	0.214 (0.197, 0.231)
	missings=0	1696	0.213 (0.185, 0.244)	1888	0.182 (0.160, 0.207)	1327	0.251 (0.219, 0.287)	4911	0.211 (0.196, 0.228)
Years 1+2	missings excluded	1340	0.217 (0.194, 0.244)	1675	0.181 (0.162, 0.203)	1091	0.264 (0.235, 0.295)*	4106	0.215 (0.201, 0.229)*
	missings=0	1674	0.214 (0.193, 0.237)*	1883	0.182 (0.164, 0.202)	1312	0.251 (0.226, 0.279)*	4869	0.212 (0.199, 0.225)
Patients with exacerbations within 6 months prior to baseline									
Year 1	missings excluded	506	0.703 (0.610, 0.811)	594	0.555 (0.482, 0.640)	385	0.850 (0.741, 0.975)	1485	0.682 (0.628, 0.740)
	missings=0	580	0.691 (0.602, 0.795)	620	0.555 (0.484, 0.637)	412	0.824 (0.720, 0.944)	1612	0.673 (0.621, 0.729)
Year 2	missings excluded	541	0.556 (0.480, 0.643)	610	0.475 (0.408, 0.552)	387	0.708 (0.612, 0.819)	1538	0.562 (0.516, 0.612)
	missings=0	587	0.536 (0.465, 0.618)	629	0.468 (0.403, 0.543)	417	0.730 (0.633, 0.843)	1633	0.559 (0.514, 0.608)
Years 1+2	missings excluded	459	0.603 (0.526, 0.692)	579	0.504 (0.444, 0.572)	355	0.758 (0.668, 0.861)	1393	0.602 (0.558, 0.649)
	missings=0	566	0.591 (0.522, 0.670)	620	0.508 (0.451, 0.573)	406	0.773 (0.685, 0.872)	1592	0.605 (0.564, 0.650)

		Glycopyrronium bromide (N=2318)		LABA/LAMA fixed combination (N=2526)		Other anti-obstructive therapy (N=1767)		Total (N=6611)	
		n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)	n	Annualized exacerbation rate (95% confidence limit)
Patients with ≥2 exacerbations within 6 months prior to baseline									
Year 1	missings excluded	135	1.144 (0.925, 1.414)	177	0.889 (0.718, 1.101)	101	1.207 (0.949, 1.534)	413	1.050 (0.924, 1.194)
	missings=0	157	1.133 (0.914, 1.404)	181	0.891 (0.723, 1.099)	108	1.174 (0.927, 1.487)	446	1.045 (0.920, 1.187)
Year 2	missings excluded	146	0.790 (0.635, 0.983)	180	0.595 (0.449, 0.788)	105	0.843 (0.638, 1.113)	431	0.722 (0.621, 0.838)
	missings=0	160	0.784 (0.638, 0.964)	183	0.591 (0.447, 0.781)	112	0.872 (0.671, 1.131)	455	0.728 (0.631, 0.840)
Years 1+2	missings excluded	116	0.969 (0.790, 1.187)	175	0.729 (0.590, 0.900)	96	0.956 (0.745, 1.225)	387	0.857 (0.754, 0.974)
	missings=0	150	0.916 (0.757, 1.108)	181	0.733 (0.598, 0.898)	108	1.009 (0.807, 1.262)	439	0.863 (0.766, 0.972)

Source: Table 2.1.3.2

Exacerbation rate was estimated as overall using a negative binomial regression model with annualized numbers of exacerbation as dependent variable and no independent variable. Estimates are only presented if N>1, if at least one patient had exacerbations in the respective year(s) and if model assumptions are valid.*The validity of the model fit is questionable. LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

Patients in the LABA/LAMA fixed combination group were least likely to have been hospitalized due to an exacerbation in the six months prior to entry (10.6%) (Table 10-14). However, during the two-year follow-up, a similar proportion of patients were hospitalized in each group.

Table 10-14 Percentage of patients with hospital stay due to exacerbations (per protocol V8 set)

	Glycopyrronium bromide	LABA/LAMA fixed combination	Other anti-obstructive therapy	Total
Baseline visit (previous 6 months)				
Percent base	591	624	416	1631
Yes	87 (14.7%)	66 (10.6%)	73 (17.5%)	226 (13.9%)
No	498 (84.3%)	555 (88.9%)	340 (81.7%)	1393 (85.4%)
Unknown	6 (1.0%)	3 (0.5%)	3 (0.7%)	12 (0.7%)
missing values	10	5	7	22
Year 1				
Percent base	555	485	488	1528
Yes	75 (13.5%)	64 (13.2%)	55 (11.3%)	194 (12.7%)
No/unknown/missing	480 (86.5%)	421 (86.8%)	433 (88.7%)	1334 (87.3%)
Year 2				
Percent base	484	460	439	1383
Yes	71 (14.7%)	65 (14.1%)	54 (12.3%)	190 (13.7%)
No/unknown/missing	413 (85.3%)	395 (85.9%)	385 (87.7%)	1193 (86.3%)

Source: Table 2.1.4

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

For these data, percentages are calculated based on 'percent base' (i.e., those patients with exacerbations in the given timeframe).

10.4.3 COPD Assessment Test

At baseline, the mean CAT total score was highest (i.e., worst) in patients in the glycopyrronium bromide group, with the value similar in the other two groups (Table 10-15). There was a clinically meaningful improvement from baseline in mean score (i.e., ≥2 unit decrease) at Year 1 and Year 2 in both the glycopyrronium bromide and LABA/LAMA fixed combination groups, although not in the 'other' group. More than 50% of patients in the glycopyrronium bromide and LABA/LAMA fixed combination groups had a clinically relevant improvement in CAT total score (i.e., decrease ≥2 unit) at each of the visits.

Table 10-15 Course of COPD Assessment Test score (per protocol V8 set)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Baseline visit				
Total score, mean (SD)	20.4 (7.6)	18.7 (7.8)	18.9 (7.6)	19.4 (7.7)
Year 1				
Change from baseline in total score, mean (SD)	–2.0 (5.7)	–2.5 (5.8)	–1.5 (5.4)	–2.1 (5.7)
Patients with a clinically relevant improvement from baseline, n (%)	1211 (52.2%)	1509 (59.7%)	851 (48.2%)	3571 (54.0%)
Year 2				
Change from baseline in total score, mean (SD)	–2.7 (6.5)	–3.0 (6.7)	–1.5 (6.2)	–2.5 (6.5)
Patients with a clinically relevant improvement from baseline, n (%)	1336 (57.6%)	1550 (61.4%)	876 (49.6%)	3762 (56.9%)

Source: Table 2.3

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; SD = standard deviation.

10.4.4 Pulmonary function

Pulmonary function (in terms of mean FEV_1) was similar at baseline across the three groups, with no change across the course of the study (Table 10-16). Note, however, that given this was a non-interventional study these pulmonary function assessments were performed without requiring washout (or standardization of time post-dose) of maintenance medication, and were not post-salbutamol.

Table 10-16 Course of pulmonary function (per protocol V8 set)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Baseline visit				
FEV_1 (L), mean (SD)	1.6 (0.7)	1.7 (0.6)	1.7 (0.6)	1.7 (0.6)
Year 1				
FEV_1 (L), mean (SD)	1.7 (0.7)	1.7 (0.6)	1.7 (0.7)	1.7 (0.7)
Year 2				
FEV_1 (L), mean (SD)	1.7 (0.7)	1.7 (0.6)	1.6 (0.6)	1.7 (0.7)

Source: Table 2.6.1

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 sec; SD = standard deviation.

10.4.5 COPD symptoms

At baseline, the majority of patients had at least one COPD symptom – most commonly exertional dyspnea, with the proportion of patients with no symptoms lowest in the glycopyrronium group (2.2%) (Table 10-17). The proportion of patients reporting no symptoms improved from baseline at Year 1 and Year 2 in all three groups, with the most marked improvement observed in the glycopyrronium bromide group.

Table 10-17 Course of COPD symptoms (per protocol V8 set)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Baseline visit				
None	52 (2.2%)	99 (3.9%)	84 (4.8%)	235 (3.6%)
Exertional dyspnea	2071 (89.3%)	2190 (86.7%)	1549 (87.7%)	5810 (87.9%)
Dyspnea at rest	447 (19.3%)	334 (13.2%)	240 (13.6%)	1021 (15.4%)
Chest tightness / chest pain	629 (27.1%)	697 (27.6%)	413 (23.4%)	1739 (26.3%)
Cough	1616 (69.7%)	1684 (66.7%)	1149 (65.0%)	4449 (67.3%)
Wheezing or grunting	573 (24.7%)	700 (27.7%)	409 (23.1%)	1682 (25.4%)
Prolonged expiration	497 (21.4%)	546 (21.6%)	350 (19.8%)	1393 (21.1%)
Restricted exercise tolerance	1492 (64.4%)	1600 (63.3%)	1016 (57.5%)	4108 (62.1%)
Year 1				
None	644 (27.8%)	208 (8.2%)	373 (21.1%)	1225 (18.5%)
Exertional dyspnea	1514 (65.3%)	1991 (78.8%)	1242 (70.3%)	4747 (71.8%)
Dyspnea at rest	254 (11.0%)	186 (7.4%)	175 (9.9%)	615 (9.3%)
Chest tightness / chest pain	326 (14.1%)	442 (17.5%)	273 (15.4%)	1041 (15.7%)
Cough	1022 (44.1%)	1462 (57.9%)	855 (48.4%)	3339 (50.5%)
Wheezing or grunting	286 (12.3%)	420 (16.6%)	242 (13.7%)	948 (14.3%)
Prolonged expiration	313 (13.5%)	396 (15.7%)	256 (14.5%)	965 (14.6%)
Restricted exercise tolerance	1096 (47.3%)	1427 (56.5%)	840 (47.5%)	3363 (50.9%)
Year 2				
None	724 (31.2%)	265 (10.5%)	387 (21.9%)	1376 (20.8%)
Exertional dyspnea	1417 (61.1%)	1891 (74.9%)	1210 (68.5%)	4518 (68.3%)
Dyspnea at rest	247 (10.7%)	172 (6.8%)	155 (8.8%)	574 (8.7%)
Chest tightness / chest pain	241 (10.4%)	368 (14.6%)	233 (13.2%)	842 (12.7%)
Cough	889 (38.4%)	1326 (52.5%)	787 (44.5%)	3002 (45.4%)
Wheezing or grunting	242 (10.4%)	338 (13.4%)	201 (11.4%)	781 (11.8%)
Prolonged expiration	269 (11.6%)	347 (13.7%)	223 (12.6%)	839 (12.7%)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Restricted exercise tolerance	990 (42.7%)	1288 (51.0%)	805 (45.6%)	3083 (46.6%)

Source: Table 2.8.1

More than one symptom possible per patient. LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

10.4.6 Treatment persistence

Persistence was high in all three groups, with more than three-quarters of patients overall considered persistent at Year 2 (Table 10-18). The highest persistence was observed in the LABA/LAMA fixed combination group, with 82.0% of patients persistent at Year 2 and a further 7.9% having added another therapeutic class to their LABA/LAMA fixed combination.

Table 10-18 Course of treatment persistence (per protocol V8 set)

	Glycopyrronium bromide (N=2318)	LABA/LAMA fixed combination (N=2526)	Other anti-obstructive therapy (N=1767)	Total (N=6611)
Baseline visit	2315 (100.0%)	2523 (100.0%)	1689 (100.0%)	6527 (100.0%)
Year 1				
Persistent	1837 (79.4%)	2202 (87.3%)	1376 (81.5%)	5415 (83.0%)
Switched	242 (10.5%)	190 (7.5%)	150 (8.9%)	582 (8.9%)
Add-on	236 (10.2%)	131 (5.2%)	163 (9.7%)	530 (8.1%)
Year 2				
Persistent	1697 (73.3%)	2070 (82.0%)	1255 (74.3%)	5022 (76.9%)
Switched	288 (12.4%)	253 (10.0%)	219 (13.0%)	760 (11.6%)
Add-on	330 (14.3%)	200 (7.9%)	215 (12.7%)	745 (11.4%)

Source: Table 2.9

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

10.5 Other analyses

Not applicable

10.6 Adverse events/adverse reactions

10.6.1 Adverse events

10.6.1.1 Display of adverse events

A similar proportion of patients reported at least one non-serious adverse event in the three groups, both overall and for the majority of MedDRA system organ classes, with the most

commonly reported system organ class in all three groups being respiratory, thoracic and mediastinal, followed by 'General disorders and administration site conditions' (Table 10-19). A lower proportion of patients in the LABA/LAMA fixed combination group reported events in the 'General disorders and administration site conditions' MedDRA class than in the other two groups, accounting for much of the difference between groups. The event rate per 100 patient-years was higher in the glycopyrronium bromide group than the 'other' or LABA/LAMA fixed combination groups.

Table 10-19 Non-serious adverse events (by patients and overall event rates) - overall and by MedDRA system organ class (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	931 (21.9%)	774 (18.5%)	578 (19.3%)	2283 (20.0%)
Event rates per 100 patient-years	34.954	22.734	27.852	
Blood and lymphatic system disorders	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)
Cardiac disorders	30 (0.7%)	29 (0.7%)	21 (0.7%)	80 (0.7%)
Congenital, familial and genetic disorders	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	4 (<0.1%)
Ear and labyrinth disorders	5 (0.1%)	2 (<0.1%)	0	7 (<0.1%)
Endocrine disorders	5 (0.1%)	2 (<0.1%)	2 (<0.1%)	9 (<0.1%)
Eye disorders	19 (0.4%)	12 (0.3%)	4 (0.1%)	35 (0.3%)
Gastrointestinal disorders	84 (2.0%)	42 (1.0%)	20 (0.7%)	146 (1.3%)
General disorders and administration site conditions	359 (8.4%)	249 (5.9%)	243 (8.1%)	851 (7.4%)
Hepatobiliary disorders	0	0	1 (<0.1%)	1 (<0.1%)
Immune system disorders	2 (<0.1%)	3 (<0.1%)	1 (<0.1%)	6 (<0.1%)
Infections and infestations	100 (2.4%)	78 (1.9%)	54 (1.8%)	232 (2.0%)
Injury, poisoning and procedural complications	17 (0.4%)	13 (0.3%)	7 (0.2%)	37 (0.3%)
Investigations	94 (2.2%)	101 (2.4%)	65 (2.2%)	260 (2.3%)
Metabolism and nutrition disorders	13 (0.3%)	7 (0.2%)	4 (0.1%)	24 (0.2%)
Musculoskeletal and connective tissue disorders	44 (1.0%)	42 (1.0%)	25 (0.8%)	111 (1.0%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	5 (0.1%)	3 (<0.1%)	2 (<0.1%)	10 (<0.1%)
Nervous system disorders	46 (1.1%)	40 (1.0%)	13 (0.4%)	99 (0.9%)
Product issues	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Psychiatric disorders	25 (0.6%)	32 (0.8%)	15 (0.5%)	72 (0.6%)
Renal and urinary disorders	17 (0.4%)	5 (0.1%)	2 (<0.1%)	24 (0.2%)
Reproductive system and breast disorders	2 (<0.1%)	1 (<0.1%)	2 (<0.1%)	5 (<0.1%)
Respiratory, thoracic and mediastinal disorders	575 (13.5%)	469 (11.2%)	363 (12.1%)	1407 (12.3%)
Skin and subcutaneous tissue disorders	15 (0.4%)	15 (0.4%)	17 (0.6%)	47 (0.4%)
Social circumstances	0	2 (<0.1%)	1 (<0.1%)	3 (<0.1%)
Surgical and medical procedures	3 (<0.1%)	3 (<0.1%)	1 (<0.1%)	7 (<0.1%)
Vascular disorders	3 (<0.1%)	7 (0.2%)	5 (0.2%)	15 (0.1%)

Source: Tables 3.1-2.1.3 and 3.1-2.10 (event rates)
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.1.2 Analysis of adverse events

The most frequent non-serious adverse events by preferred term in all three groups were related to COPD – most commonly decreased exercise tolerance, exertional dyspnea and cough (Table 10-20).

Table 10-20 Non-serious adverse events (by patients and event rates) - overall and most common preferred term (>/=0.5% in any treatment group) (safety set)

	Glycopyrronium bromide (N=4255)		LABA/LAMA fixed combination (N=4185)		Other anti-obstructive therapy (N=3001)		Total (N=11,441)
	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)
Patients with at least one event	931 (21.9%)	34.954	774 (18.5%)	22.734	578 (19.3%)	27.852	2283 (20.0%)
Exercise tolerance decreased	237 (5.6%)	4.185	120 (2.9%)	1.883	167 (5.6%)	3.945	524 (4.6%)

	Glycopyrronium bromide (N=4255)		LABA/LAMA fixed combination (N=4185)		Other anti-obstructive therapy (N=3001)		Total (N=11,441)
	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)
Dyspnea exertional	182 (4.3%)	2.764	79 (1.9%)	1.286	110 (3.7%)	2.238	371 (3.2%)
Cough	151 (3.5%)	2.356	177 (4.2%)	2.514	104 (3.5%)	2.220	432 (3.8%)
Wheezing	124 (2.9%)	2.119	64 (1.5%)	0.982	57 (1.9%)	1.321	245 (2.1%)
Grunting	123 (2.9%)	2.053	63 (1.5%)	0.971	57 (1.9%)	1.321	243 (2.1%)
Chest pain	119 (2.8%)	2.053	97 (2.3%)	1.614	87 (2.9%)	2.165	303 (2.6%)
Prolonged expiration	119 (2.8%)	2.027	53 (1.3%)	0.842	76 (2.5%)	1.982	248 (2.2%)
Chest discomfort	113 (2.7%)	2.014	99 (2.4%)	1.602	91 (3.0%)	2.257	303 (2.6%)
Productive cough	94 (2.2%)	1.342	86 (2.1%)	1.076	84 (2.8%)	1.541	264 (2.3%)
Dyspnea at rest	88 (2.1%)	1.513	38 (0.9%)	0.561	49 (1.6%)	1.138	175 (1.5%)
Forced expiratory volume decreased	63 (1.5%)	0.895	81 (1.9%)	1.006	53 (1.8%)	1.064	197 (1.7%)
Chronic obstructive pulmonary disease	61 (1.4%)	1.040	80 (1.9%)	1.158	43 (1.4%)	0.881	184 (1.6%)
Dyspnea	29 (0.7%)	0.447	47 (1.1%)	0.667	8 (0.3%)	0.183	84 (0.7%)
Dry mouth	24 (0.6%)	0.355	5 (0.1%)	0.058	2 (<0.1%)	0.055	31 (0.3%)
Headache	20 (0.5%)	0.276	13 (0.3%)	0.175	2 (<0.1%)	0.037	35 (0.3%)
Cardiovascular disorder	19 (0.4%)	0.263	19 (0.5%)	0.222	16 (0.5%)	0.294	54 (0.5%)
Nasopharyngitis	16 (0.4%)	0.250	19 (0.5%)	0.234	8 (0.3%)	0.183	43 (0.4%)
Dizziness	13 (0.3%)	0.171	19 (0.5%)	0.257	5 (0.2%)	0.092	37 (0.3%)

Sources: Tables 3.1-2.1.3 (numbers and percentages) and 3.1-2.11 (event rates)
Data are sorted by percentage in the glycopyrronium bromide group
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.1.3 Suspected relationship of non-serious adverse events to the study

The decision on whether an AE was related to the study was taken by the investigator (note that the majority of patients were receiving multiple COPD maintenance therapies, and so even when adverse events were considered related by the investigators causality cannot be assigned to a specific treatment). To take a conservative approach, if the investigator did not complete a causality assessment events are considered suspected related.

As with the overall experience of non-serious AEs, slightly more patients in the glycopyrronium bromide group than in the other groups had non-serious AEs that were either considered related to the study or had the causal relationship not assigned – with much of the difference due to decreased exercise tolerance (Table 10-21).

Table 10-21 Non-serious adverse events suspected study-related or relationship not assigned - overall and most common preferred term (>/=0.5% in any treatment group) (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	612 (14.4%)	533 (12.7%)	354 (11.8%)	1499 (13.1%)
Exercise tolerance decreased	170 (4.0%)	82 (2.0%)	115 (3.8%)	367 (3.2%)
Dyspnea exertional	123 (2.9%)	55 (1.3%)	66 (2.2%)	244 (2.1%)
Cough	112 (2.6%)	139 (3.3%)	75 (2.5%)	326 (2.8%)
Grunting	90 (2.1%)	48 (1.1%)	45 (1.5%)	183 (1.6%)
Wheezing	90 (2.1%)	49 (1.2%)	45 (1.5%)	184 (1.6%)
Prolonged expiration	89 (2.1%)	45 (1.1%)	64 (2.1%)	198 (1.7%)
Chest discomfort	83 (2.0%)	70 (1.7%)	65 (2.2%)	218 (1.9%)
Chest pain	83 (2.0%)	69 (1.6%)	65 (2.2%)	217 (1.9%)
Dyspnea at rest	63 (1.5%)	29 (0.7%)	35 (1.2%)	127 (1.1%)
Productive cough	52 (1.2%)	39 (0.9%)	51 (1.7%)	142 (1.2%)
Forced expiratory volume decreased	41 (1.0%)	55 (1.3%)	33 (1.1%)	129 (1.1%)
Dry mouth	23 (0.5%)	5 (0.1%)	1 (<0.1%)	29 (0.3%)
Dyspnea	14 (0.3%)	27 (0.6%)	2 (<0.1%)	43 (0.4%)
Chronic obstructive pulmonary disease	13 (0.3%)	32 (0.8%)	11 (0.4%)	56 (0.5%)

Source 3.1-2.1.2

Data are sorted by percentage in the glycopyrronium bromide group

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.1.4 Outcome of non-serious adverse events

Given the non-interventional nature of the study, data on the outcome of the non-serious adverse events is missing from many cases. Where data are available, the majority of patients in all three groups recovered (Table 10-22).

Table 10-22 Outcome of non-serious adverse events (by patients) (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Number (%) of patients with at least one event	931 (21.9%)	774 (18.5%)	578 (19.3%)
Condition improved	123 (2.9%)	115 (2.7%)	91 (3.0%)
Condition worsened	15 (0.4%)	18 (0.4%)	8 (0.3%)
Not recovered	200 (4.7%)	225 (5.4%)	142 (4.7%)
Recovered	438 (10.3%)	297 (7.1%)	220 (7.3%)
Recovered with sequelae	0	1 (0.0%)	0
Unknown	119 (2.8%)	90 (2.2%)	56 (1.9%)
Missing values	333 (7.8%)	265 (6.3%)	233 (7.8%)
Not reported	6 (0.1%)	34 (0.8%)	13 (0.4%)

Source: Table 3.1-2.2.4

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.1.5 Non-serious adverse events of special interest

Non-serious adverse events of special interest (as specified for Ultibro® Breezhaler®) are listed in Table 10-23. The incidence of these events was similar in the glycopyrronium bromide and 'other' groups, and was lowest in the LABA/LAMA fixed combination group. There were no non-serious adverse events of special interest for glycopyrronium bromide.

Table 10-23 Non-serious adverse events of special interest (for Ultibro Breezhaler) (by patients) - overall, and by MedDRA system organ class and preferred term (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	15 (0.4%)	5 (0.1%)	8 (0.3%)	28 (0.2%)
Asthma/bronchospasm	0	1 (<0.1%)	2 (<0.1%)	3 (<0.1%)
Asthma	0	1 (<0.1%)	2 (<0.1%)	3 (<0.1%)
Cardiac arrhythmia	3 (<0.1%)	1 (<0.1%)	2 (<0.1%)	6 (<0.1%)
Arrhythmia	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Extrasystoles	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Heart rate irregular	0	0	1 (<0.1%)	1 (<0.1%)
Sinus tachycardia	1 (<0.1%)	0	0	1 (<0.1%)
Diabetes mellitus/ hyperglycemia	3 (<0.1%)	1 (<0.1%)	3 (<0.1%)	7 (<0.1%)
Blood glucose increased	3 (<0.1%)	1 (<0.1%)	0	4 (<0.1%)
Glucose tolerance impaired	0	0	1 (<0.1%)	1 (<0.1%)
Glycosylated hemoglobin increased	0	0	1 (<0.1%)	1 (<0.1%)
Type 2 diabetes mellitus	0	0	2 (<0.1%)	2 (<0.1%)
Ischemic heart disease	2 (<0.1%)	0	0	2 (<0.1%)
Angina pectoris	2 (<0.1%)	0	0	2 (<0.1%)
Narrow angle glaucoma	7 (0.2%)	2 (<0.1%)	1 (<0.1%)	10 (<0.1%)
Eye pain	2 (<0.1%)	0	0	2 (<0.1%)
Glaucoma	1 (<0.1%)	0	0	1 (<0.1%)
Intraocular pressure increased	2 (<0.1%)	1 (<0.1%)	0	3 (<0.1%)
Vision blurred	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)	4 (<0.1%)

Source 3.1-2.4.3.2
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.2 Serious adverse events

10.6.2.1 Display of serious adverse events

The overall incidence of serious adverse events was similar in the three groups, although the event rate was highest in the glycopyrronium group (Table 10-24). The most commonly-reported MedDRA system organ class in all three groups was respiratory, thoracic and mediastinal.

Table 10-24 Serious adverse events (by patients and overall event rates) - overall and by MedDRA system organ class (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	579 (13.6%)	557 (13.3%)	364 (12.1%)	1500 (13.1%)
Event rates per 100 patient-years	28.163	21.436	19.522	

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Blood and lymphatic system disorders	5 (0.1%)	6 (0.1%)	8 (0.3%)	19 (0.2%)
Cardiac disorders	107 (2.5%)	71 (1.7%)	76 (2.5%)	254 (2.2%)
Congenital, familial and genetic disorders	3 (<0.1%)	1 (<0.1%)	1 (<0.1%)	5 (<0.1%)
Ear and labyrinth disorders	1 (<0.1%)	0	2 (<0.1%)	3 (<0.1%)
Endocrine disorders	3 (<0.1%)	2 (<0.1%)	0	5 (<0.1%)
Eye disorders	7 (0.2%)	8 (0.2%)	4 (0.1%)	19 (0.2%)
Gastrointestinal disorders	46 (1.1%)	30 (0.7%)	18 (0.6%)	94 (0.8%)
General disorders and administration site conditions	112 (2.6%)	125 (3.0%)	76 (2.5%)	313 (2.7%)
Hepatobiliary disorders	9 (0.2%)	4 (<0.1%)	2 (<0.1%)	15 (0.1%)
Immune system disorders	0	4 (<0.1%)	2 (<0.1%)	6 (<0.1%)
Infections and infestations	131 (3.1%)	111 (2.7%)	56 (1.9%)	298 (2.6%)
Injury, poisoning and procedural complications	36 (0.8%)	21 (0.5%)	21 (0.7%)	78 (0.7%)
Investigations	72 (1.7%)	74 (1.8%)	40 (1.3%)	186 (1.6%)
Metabolism and nutrition disorders	31 (0.7%)	29 (0.7%)	11 (0.4%)	71 (0.6%)
Musculoskeletal and connective tissue disorders	31 (0.7%)	26 (0.6%)	12 (0.4%)	69 (0.6%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	72 (1.7%)	66 (1.6%)	40 (1.3%)	178 (1.6%)
Nervous system disorders	56 (1.3%)	36 (0.9%)	26 (0.9%)	118 (1.0%)
Product issues	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)
Psychiatric disorders	16 (0.4%)	13 (0.3%)	14 (0.5%)	43 (0.4%)
Renal and urinary disorders	19 (0.4%)	25 (0.6%)	10 (0.3%)	54 (0.5%)
Reproductive system and breast disorders	4 (<0.1%)	4 (<0.1%)	4 (0.1%)	12 (0.1%)
Respiratory, thoracic and mediastinal disorders	316 (7.4%)	324 (7.7%)	201 (6.7%)	841 (7.4%)
Skin and subcutaneous tissue disorders	5 (0.1%)	13 (0.3%)	5 (0.2%)	23 (0.2%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Surgical and medical procedures	6 (0.1%)	16 (0.4%)	8 (0.3%)	30 (0.3%)
Vascular disorders	38 (0.9%)	46 (1.1%)	21 (0.7%)	105 (0.9%)

Sources: Tables 3.1-3.1.3 (numbers and percentages) and 3.1-3.9 (event rate)
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.2.2 Analysis of serious adverse events

As with the non-serious adverse events, the most frequently reported serious adverse events by preferred term were those related to the underlying condition – with the most common being COPD (Table 10-25).

Table 10-25 Serious adverse events (by patients and event rates) - overall and most common preferred term (>/=0.3% in any treatment group) (safety set)

	Glycopyrronium bromide (N=4255)		LABA/LAMA fixed combination (N=4185)		Other anti-obstructive therapy (N=3001)		Total (N=11,441)
	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)
Patients with at least one event	579 (13.6%)	28.163	557 (13.3%)	21.436	364 (12.1%)	19.522	1500 (13.1%)
Chronic obstructive pulmonary disease	228 (5.4%)	4.777	233 (5.6%)	3.789	154 (5.1%)	3.871	615 (5.4%)
Infective exacerbation of chronic obstructive airways disease	48 (1.1%)	0.711	29 (0.7%)	0.363	16 (0.5%)	0.385	93 (0.8%)
Pneumonia	46 (1.1%)	0.763	31 (0.7%)	0.444	23 (0.8%)	0.514	100 (0.9%)
Exercise tolerance decreased	40 (0.9%)	0.658	24 (0.6%)	0.363	22 (0.7%)	0.514	86 (0.8%)
Dyspnea at rest	37 (0.9%)	0.619	43 (1.0%)	0.620	21 (0.7%)	0.477	101 (0.9%)
Dyspnea exertional	34 (0.8%)	0.592	25 (0.6%)	0.374	11 (0.4%)	0.202	70 (0.6%)
Cardiac failure	33 (0.8%)	0.592	11 (0.3%)	0.222	22 (0.7%)	0.422	66 (0.6%)
Forced expiratory volume decreased	31 (0.7%)	0.526	41 (1.0%)	0.561	22 (0.7%)	0.440	94 (0.8%)
Chest discomfort	28 (0.7%)	0.447	33 (0.8%)	0.526	14 (0.5%)	0.330	75 (0.7%)

	Glycopyrronium bromide (N=4255)		LABA/LAMA fixed combination (N=4185)		Other anti-obstructive therapy (N=3001)		Total (N=11,441)
	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)	Event rate per 100 pt-yrs	n (%)
Chest pain	28 (0.7%)	0.461	28 (0.7%)	0.421	16 (0.5%)	0.349	72 (0.6%)
Cough	26 (0.6%)	0.382	28 (0.7%)	0.444	10 (0.3%)	0.275	64 (0.6%)
Prolonged expiration	24 (0.6%)	0.395	16 (0.4%)	0.257	13 (0.4%)	0.294	53 (0.5%)
Dyspnea	22 (0.5%)	0.382	44 (1.1%)	0.667	13 (0.4%)	0.257	79 (0.7%)
Wheezing	22 (0.5%)	0.329	20 (0.5%)	0.304	16 (0.5%)	0.367	58 (0.5%)
Bronchial carcinoma	20 (0.5%)	0.303	20 (0.5%)	0.316	11 (0.4%)	0.220	51 (0.4%)
Productive cough	20 (0.5%)	0.303	13 (0.3%)	0.164	7 (0.2%)	0.128	40 (0.3%)
Atrial fibrillation	19 (0.4%)	0.355	12 (0.3%)	0.175	13 (0.4%)	0.312	44 (0.4%)
Death	19 (0.4%)	0.303	35 (0.8%)	0.433	16 (0.5%)	0.294	70 (0.6%)
Grunting	18 (0.4%)	0.250	20 (0.5%)	0.304	15 (0.5%)	0.367	53 (0.5%)
Respiratory failure	17 (0.4%)	0.290	9 (0.2%)	0.105	4 (0.1%)	0.110	30 (0.3%)
Myocardial infarction	14 (0.3%)	0.237	14 (0.3%)	0.175	10 (0.3%)	0.183	38 (0.3%)
Cerebrovascular accident	13 (0.3%)	0.197	5 (0.1%)	0.058	2 (<0.1%)	0.037	20 (0.2%)
Hypertension	13 (0.3%)	0.237	12 (0.3%)	0.187	8 (0.3%)	0.147	33 (0.3%)
Coronary artery disease	12 (0.3%)	0.197	14 (0.3%)	0.222	10 (0.3%)	0.220	36 (0.3%)
Back pain	11 (0.3%)	0.184	2 (<0.1%)	0.023	1 (<0.1%)	0.018	14 (0.1%)
Sleep apnea syndrome	11 (0.3%)	0.158	8 (0.2%)	0.117	5 (0.2%)	0.092	24 (0.2%)
Weight decreased	11 (0.3%)	0.171	7 (0.2%)	0.082	5 (0.2%)	0.092	23 (0.2%)
Type 2 diabetes mellitus	8 (0.2%)	0.105	15 (0.4%)	0.175	6 (0.2%)	0.128	29 (0.3%)
Angina pectoris	4 (<0.1%)	0.092	11 (0.3%)	0.152	5 (0.2%)	0.092	20 (0.2%)

Source: Tables 3.1-3.1.3 (numbers and percentages), and 3.1-3.9 and 3.1-3.10 (event rates)

Data are sorted by percentage in the glycopyrronium bromide group. LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.

10.6.2.3 Suspected relationship of serious adverse events to the study

A slightly higher proportion of serious adverse events were considered related to the study in the LABA/LAMA fixed combination group than in either of the other two groups, with the differences predominantly due to a higher incidence of the events COPD, cough and dyspnea (Table 10-26).

Table 10-26 Most common (>/=0.1% in any treatment group) serious adverse events suspected related to the study or relationship not assigned - overall and by preferred term (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	57 (1.3%)	79 (1.9%)	23 (0.8%)	159 (1.4%)
Chronic obstructive pulmonary disease	18 (0.4%)	27 (0.6%)	8 (0.3%)	53 (0.5%)
Dyspnea at rest	8 (0.2%)	7 (0.2%)	2 (<0.1%)	17 (0.1%)
Exercise tolerance decreased	7 (0.2%)	2 (<0.1%)	4 (0.1%)	13 (0.1%)
Prolonged expiration	6 (0.1%)	7 (0.2%)	3 (<0.1%)	16 (0.1%)
Chest discomfort	5 (0.1%)	8 (0.2%)	4 (0.1%)	17 (0.1%)
Chest pain	5 (0.1%)	5 (0.1%)	4 (0.1%)	14 (0.1%)
Cough	5 (0.1%)	10 (0.2%)	2 (<0.1%)	17 (0.1%)
Dyspnea exertional	4 (<0.1%)	5 (0.1%)	0	9 (<0.1%)
Dyspnea	1 (<0.1%)	9 (0.2%)	1 (<0.1%)	11 (<0.1%)

Source 3.1-3.1.2

Data are sorted by percentage in the glycopyrronium bromide group

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.2.4 Outcome of serious adverse events

As mentioned in Section 10.6.1.4, the non-interventional nature of this study means that outcomes data are missing for many of the adverse events. Where data are available, the majority of patients recovered following a serious adverse event (Table 10-27).

Table 10-27 Serious adverse events (by patients) - outcomes (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Number (%) of patients with at least one event	579 (13.6%)	557 (13.3%)	364 (12.1%)
Condition improved	157 (3.7%)	160 (3.8%)	113 (3.8%)
Condition worsened	38 (0.9%)	25 (0.6%)	17 (0.6%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Fatal	110 (2.6%)	120 (2.9%)	72 (2.4%)
Not recovered	92 (2.2%)	95 (2.3%)	65 (2.2%)
Recovered	330 (7.8%)	269 (6.4%)	190 (6.3%)
Recovered with sequelae	14 (0.3%)	7 (0.2%)	9 (0.3%)
Unknown	93 (2.2%)	81 (1.9%)	56 (1.9%)
Missing values	31 (0.7%)	60 (1.4%)	14 (0.5%)
Not reported	5 (0.1%)	5 (0.1%)	3 (0.1%)

Source: Table 3.1-3.2.4
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.2.5 Deaths

A total of 302 patients died during the study, with a similar proportion of patients in each treatment group (Table 10-28). The MedDRA system organ class and preferred terms for the serious adverse events with a fatal outcome are shown in Table 10-28. Note that this table lists the events with a fatal outcome, not necessarily the cause of death.

Fatal serious adverse events were also captured in the Argus database, with reports limited to those from patients receiving one or more Novartis therapies (note that the 'other' group reports events in patients receiving Novartis therapies not in scope for this report, and therefore few events were reported for this group) ([Annex 1 Table 2-1]). Overall, the results for the glycopyrronium and LABA/LAMA fixed combination groups are similar in the two databases. Note that the percentages in the Argus results are calculated using the number of patients with an Argus report of at least one adverse event as the denominator, and not the overall exposed population, and so cannot be compared to the percentages in the safety set.

Fatal serious adverse events that were considered study related are shown in Table 10-29. However, no patient had a cause of death considered study related. Eight patients who died had the relationship of the event to study reported as 'non-assessable', either by the investigator or on subsequent assessment by Novartis (five receiving a regimen that included Ultibro Breezhaler, and three in the 'other' group).

Table 10-28 Fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Number (%) of patients with at least one fatal SAE	110 (2.6%)	120 (2.9%)	72 (2.4%)
Event rates per 100 patient-years	3.014	2.491	2.037

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Blood and lymphatic system disorders	1 (0.0%)	1 (0.0%)	2 (0.1%)
Anemia	0	1 (0.0%)	2 (0.1%)
Coagulopathy	1 (0.0%)	0	0
Cardiac disorders	36 (0.8%)	25 (0.6%)	13 (0.4%)
Acute myocardial infarction	2 (0.0%)	0	0
Angina pectoris	0	1 (0.0%)	0
Aortic valve stenosis	2 (0.0%)	0	0
Arrhythmia	1 (0.0%)	1 (0.0%)	1 (0.0%)
Atrial fibrillation	0	2 (0.0%)	1 (0.0%)
Cardiac arrest	4 (0.1%)	2 (0.0%)	2 (0.1%)
Cardiac failure	16 (0.4%)	5 (0.1%)	4 (0.1%)
Cardiac failure acute	1 (0.0%)	1 (0.0%)	0
Cardiac failure chronic	1 (0.0%)	0	0
Cardiogenic shock	2 (0.0%)	1 (0.0%)	1 (0.0%)
Cardiovascular insufficiency	0	1 (0.0%)	0
Cor pulmonale	1 (0.0%)	0	0
Cor pulmonale acute	1 (0.0%)	0	0
Coronary artery disease	1 (0.0%)	2 (0.0%)	0
Coronary artery insufficiency	0	1 (0.0%)	1 (0.0%)
Left ventricular failure	1 (0.0%)	2 (0.0%)	0
Myocardial infarction	6 (0.1%)	9 (0.2%)	4 (0.1%)
Palpitations	1 (0.0%)	1 (0.0%)	0
Right ventricular failure	2 (0.0%)	1 (0.0%)	0
Tachyarrhythmia	0	1 (0.0%)	0
Tachycardia	1 (0.0%)	0	0
Ventricular fibrillation	2 (0.0%)	0	0
Ventricular tachycardia	1 (0.0%)	0	0
Gastrointestinal disorders	5 (0.1%)	6 (0.1%)	1 (0.0%)
Abdominal pain	0	0	1 (0.0%)
Acute abdomen	1 (0.0%)	0	0
Anal incontinence	0	1 (0.0%)	0
Ascites	1 (0.0%)	0	0
Dysphagia	1 (0.0%)	0	0
Gastric hemorrhage	0	1 (0.0%)	0
Gastric perforation	0	1 (0.0%)	0
Intestinal ischemia	0	2 (0.0%)	0
Large intestine perforation	0	1 (0.0%)	0
Melena	1 (0.0%)	0	0
Mesenteric arterial occlusion	1 (0.0%)	0	0

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Nausea	1 (0.0%)	1 (0.0%)	0
Pancreatitis	0	1 (0.0%)	0
Vomiting	0	1 (0.0%)	0
General disorders and administration site conditions	34 (0.8%)	50 (1.2%)	26 (0.9%)
Adverse event	5 (0.1%)	3 (0.1%)	6 (0.2%)
Asthenia	1 (0.0%)	0	0
Cardiac death	1 (0.0%)	1 (0.0%)	0
Chest discomfort	1 (0.0%)	1 (0.0%)	0
Chest pain	1 (0.0%)	1 (0.0%)	0
Death	18 (0.4%)	33 (0.8%)	16 (0.5%)
Edema	0	0	1 (0.0%)
Edema peripheral	0	2 (0.0%)	0
Exercise tolerance decreased	1 (0.0%)	0	0
General physical health deterioration	3 (0.1%)	3 (0.1%)	0
Multimorbidity	1 (0.0%)	1 (0.0%)	0
Multiple organ dysfunction syndrome	5 (0.1%)	4 (0.1%)	2 (0.1%)
Organ failure	1 (0.0%)	1 (0.0%)	0
Pyrexia	2 (0.0%)	1 (0.0%)	0
Sudden cardiac death	0	2 (0.0%)	2 (0.1%)
Hepatobiliary disorders	3 (0.1%)	1 (0.0%)	0
Cholecystitis	0	1 (0.0%)	0
Hepatic cirrhosis	3 (0.1%)	0	0
Portal vein thrombosis	1 (0.0%)	0	0
Infections and infestations	17 (0.4%)	11 (0.3%)	10 (0.3%)
Abdominal sepsis	1 (0.0%)	0	0
Abdominal wall abscess	0	1 (0.0%)	0
Cardiac valve vegetation	0	0	1 (0.0%)
Clostridium difficile infection	1 (0.0%)	0	0
Infectious pleural effusion	0	0	1 (0.0%)
Infective exacerbation of chronic obstructive airways disease	1 (0.0%)	0	0
Peritonitis	1 (0.0%)	1 (0.0%)	1 (0.0%)
Peritonsillar abscess	0	1 (0.0%)	0
Pneumonia	5 (0.1%)	4 (0.1%)	4 (0.1%)
Pneumonia staphylococcal	1 (0.0%)	0	0
Post procedural sepsis	2 (0.0%)	0	0
Pseudomonas infection	0	0	1 (0.0%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Sepsis	6 (0.1%)	6 (0.1%)	2 (0.1%)
Septic shock	1 (0.0%)	0	1 (0.0%)
Upper respiratory tract infection	0	0	1 (0.0%)
Urinary tract infection	1 (0.0%)	0	0
Injury, poisoning and procedural complications	6 (0.1%)	4 (0.1%)	3 (0.1%)
Anastomotic leak	0	0	1 (0.0%)
Failure to anastomose	1 (0.0%)	0	0
Fall	1 (0.0%)	2 (0.0%)	1 (0.0%)
Fracture	1 (0.0%)	0	0
Overdose	1 (0.0%)	0	0
Postoperative renal failure	0	1 (0.0%)	0
Road traffic accident	0	0	1 (0.0%)
Subdural hematoma	0	0	1 (0.0%)
Thermal burn	1 (0.0%)	0	0
Tibia fracture	1 (0.0%)	0	0
Toxicity to various agents	0	1 (0.0%)	0
Investigations	1 (0.0%)	1 (0.0%)	1 (0.0%)
Ejection fraction decreased	1 (0.0%)	0	0
Glomerular filtration rate decreased	0	0	1 (0.0%)
Weight decreased	0	1 (0.0%)	0
Metabolism and nutrition disorders	4 (0.1%)	1 (0.0%)	1 (0.0%)
Cachexia	1 (0.0%)	0	1 (0.0%)
Dehydration	1 (0.0%)	0	0
Lactic acidosis	1 (0.0%)	0	0
Marasmus	1 (0.0%)	1 (0.0%)	0
Protein deficiency	0	0	1 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	20 (0.5%)	33 (0.8%)	20 (0.7%)
Adenocarcinoma	1 (0.0%)	2 (0.0%)	1 (0.0%)
B-cell lymphoma	0	0	1 (0.0%)
Bile duct cancer	0	0	1 (0.0%)
Bladder cancer recurrent	0	1 (0.0%)	0
Bladder neoplasm	0	2 (0.0%)	0
Breast cancer	0	1 (0.0%)	1 (0.0%)
Breast cancer metastatic	0	1 (0.0%)	1 (0.0%)
Bronchial carcinoma	4 (0.1%)	10 (0.2%)	6 (0.2%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Colon cancer	1 (0.0%)	1 (0.0%)	1 (0.0%)
Colon cancer metastatic	0	1 (0.0%)	1 (0.0%)
Gastric cancer	1 (0.0%)	0	0
Glioblastoma	0	0	1 (0.0%)
Glioblastoma multiforme	0	0	1 (0.0%)
Hepatic neoplasm	1 (0.0%)	0	0
Hepatocellular carcinoma	0	1 (0.0%)	0
Inflammatory carcinoma of the breast	0	1 (0.0%)	0
Lip and/or oral cavity cancer	0	1 (0.0%)	0
Lung adenocarcinoma	1 (0.0%)	3 (0.1%)	0
Lung cancer metastatic	1 (0.0%)	1 (0.0%)	0
Lung carcinoma cell type unspecified recurrent	1 (0.0%)	0	0
Lung neoplasm malignant	0	2 (0.0%)	1 (0.0%)
Malignant neoplasm of pleura	1 (0.0%)	0	0
Malignant neoplasm of unknown primary site	0	1 (0.0%)	0
Malignant neoplasm progression	0	0	1 (0.0%)
Metastases to abdominal wall	0	1 (0.0%)	0
Metastases to biliary tract	0	1 (0.0%)	0
Metastases to bone	1 (0.0%)	2 (0.0%)	0
Metastases to central nervous system	0	1 (0.0%)	0
Metastases to kidney	0	1 (0.0%)	0
Metastases to liver	0	4 (0.1%)	1 (0.0%)
Metastases to lung	0	1 (0.0%)	1 (0.0%)
Metastases to lymph nodes	1 (0.0%)	1 (0.0%)	0
Metastases to peritoneum	1 (0.0%)	0	0
Metastases to spine	0	1 (0.0%)	0
Metastatic bronchial carcinoma	3 (0.1%)	0	1 (0.0%)
Metastatic gastric cancer	0	1 (0.0%)	0
Neoplasm malignant	0	1 (0.0%)	0
Non-small cell lung cancer	1 (0.0%)	0	0
Oesophageal carcinoma	1 (0.0%)	0	0
Pancreatic carcinoma	3 (0.1%)	2 (0.0%)	0
Pancreatic carcinoma metastatic	0	0	1 (0.0%)
Plasma cell myeloma	0	0	1 (0.0%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Prostate cancer metastatic	0	1 (0.0%)	0
Rectal cancer	0	1 (0.0%)	1 (0.0%)
Renal cell carcinoma	0	1 (0.0%)	0
Small cell lung cancer	0	1 (0.0%)	0
Small intestine carcinoma	0	0	1 (0.0%)
T-cell lymphoma	0	1 (0.0%)	0
Thyroid cancer	0	0	1 (0.0%)
Transitional cell carcinoma	1 (0.0%)	0	0
Nervous system disorders	8 (0.2%)	6 (0.1%)	4 (0.1%)
Akinesia	1 (0.0%)	0	0
Amyotrophic lateral sclerosis	1 (0.0%)	0	0
Aphasia	1 (0.0%)	0	0
Basal ganglia haemorrhage	1 (0.0%)	0	0
Brain compression	1 (0.0%)	0	0
Brain injury	1 (0.0%)	1 (0.0%)	0
Brain stem ischemia	0	1 (0.0%)	0
Cerebral hemorrhage	0	0	1 (0.0%)
Cerebral infarction	2 (0.0%)	0	1 (0.0%)
Cerebrovascular accident	2 (0.0%)	2 (0.0%)	1 (0.0%)
Dementia	1 (0.0%)	0	0
Embolic stroke	1 (0.0%)	0	0
Hemiparesis	1 (0.0%)	0	0
Myasthenia gravis	0	1 (0.0%)	0
Paraparesis	0	1 (0.0%)	0
Syncope	0	0	1 (0.0%)
Psychiatric disorders	1 (0.0%)	0	1 (0.0%)
Completed suicide	1 (0.0%)	0	1 (0.0%)
Depression	1 (0.0%)	0	1 (0.0%)
Renal and urinary disorders	5 (0.1%)	10 (0.2%)	2 (0.1%)
Acute kidney injury	3 (0.1%)	4 (0.1%)	0
Chronic kidney disease	0	1 (0.0%)	1 (0.0%)
Renal failure	2 (0.0%)	4 (0.1%)	1 (0.0%)
Urinary incontinence	0	1 (0.0%)	0
Respiratory, thoracic and mediastinal disorders	28 (0.7%)	16 (0.4%)	8 (0.3%)
Acute respiratory failure	2 (0.0%)	1 (0.0%)	0
Asphyxia	0	0	1 (0.0%)
Bronchiectasis	1 (0.0%)	0	0
Chronic obstructive pulmonary disease	12 (0.3%)	5 (0.1%)	2 (0.1%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Cough	1 (0.0%)	0	0
Dyspnea	2 (0.0%)	3 (0.1%)	1 (0.0%)
Dyspnea at rest	1 (0.0%)	1 (0.0%)	0
Dyspnea exertional	1 (0.0%)	0	1 (0.0%)
Emphysema	1 (0.0%)	1 (0.0%)	0
Hypercapnia	1 (0.0%)	0	0
Hypoxia	1 (0.0%)	0	0
Pleural effusion	0	0	1 (0.0%)
Pneumonia aspiration	1 (0.0%)	0	0
Pneumothorax	0	0	1 (0.0%)
Pulmonary embolism	3 (0.1%)	2 (0.0%)	1 (0.0%)
Pulmonary fibrosis	1 (0.0%)	0	0
Pulmonary mass	1 (0.0%)	0	0
Pulmonary edema	0	2 (0.0%)	0
Respiratory failure	9 (0.2%)	2 (0.0%)	0
Skin and subcutaneous tissue disorders	0	1 (0.0%)	0
Cold sweat	0	1 (0.0%)	0
Surgical and medical procedures	0	0	1 (0.0%)
Chemotherapy	0	0	1 (0.0%)
Vascular disorders	4 (0.1%)	7 (0.2%)	0
Aortic aneurysm	1 (0.0%)	0	0
Aortic aneurysm rupture	0	2 (0.0%)	0
Circulatory collapse	0	3 (0.1%)	0
Granulomatosis with polyangiitis	1 (0.0%)	0	0
Hypertension	1 (0.0%)	0	0
Hypotension	1 (0.0%)	0	0
Pallor	0	1 (0.0%)	0
Peripheral arterial occlusive disease	0	1 (0.0%)	0

Sources: Tables 3.1-3.2.4 (numbers and percentages), and 3.1-4.2 (event rates)
LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

Table 10-29 Study related fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)
Number (%) of patients with at least one fatal SAE	4 (0.1%)	8 (0.2%)	4 (0.1%)
Cardiac disorders	2 (0.0%)	2 (0.0%)	0
Acute myocardial infarction	1 (0.0%)	0	0
Arrhythmia	0	1 (0.0%)	0
Cardiac failure	1 (0.0%)	0	0
Myocardial infarction	0	1 (0.0%)	0
Gastrointestinal disorders	1 (0.0%)	0	0
Ascites	1 (0.0%)	0	0
General disorders and administration site conditions	2 (0.0%)	5 (0.1%)	4 (0.1%)
Adverse event	0	1 (0.0%)	2 (0.1%)
Death	2 (0.0%)	4 (0.1%)	2 (0.1%)
Hepatobiliary disorders	1 (0.0%)	0	0
Hepatic cirrhosis	1 (0.0%)	0	0
Infections and infestations	1 (0.0%)	0	0
Sepsis	1 (0.0%)	0	0
Injury, poisoning and procedural complications	0	1 (0.0%)	1 (0.0%)
Fall	0	0	1 (0.0%)
Subdural hematoma	0	0	1 (0.0%)
Toxicity to various agents	0	1 (0.0%)	0
Renal and urinary disorders	1 (0.0%)	0	0
Acute kidney injury	1 (0.0%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.0%)	0	0
Acute respiratory failure	1 (0.0%)	0	0
Chronic obstructive pulmonary disease	1 (0.0%)	0	0
Hypercapnia	1 (0.0%)	0	0

Source: Table 3.1-3.2.3

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

10.6.2.6 Serious adverse events of special interest

The only serious adverse events of special interest for glycopyrronium bromide that occurred during the study was severe renal failure (Table 10-30). The incidence was similar in the two treatment groups, with no events considered related to the study. Similar results were reported for the glycopyrronium group in the Argus database ([Annex 1 Table 2-2]). As described earlier,

since the Argus database only includes reports on Novartis treatments, and the percentages are calculated on the number of patients with at least one Argus report, the 'other anti-obstructive therapy' data cannot be compared with those of the safety set.

Table 10-30 Serious adverse events of special interest (for glycopyrronium bromide) (by patients) - overall, and by MedDRA class and preferred term (>/=0.1% in any treatment group) (safety set)

	Glycopyrronium bromide (N=4255)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	4 (<0.1%)	5 (0.2%)	9 (0.1%)
Severe renal impairment	4 (<0.1%)	5 (0.2%)	9 (0.1%)
Renal failure	3 (<0.1%)	4 (0.1%)	7 (<0.1%)

Source: Table 3.1-3.4.3.1

The overall incidence of serious adverse events of special interest for Ultibro® Breezhaler® was lowest in the LABA/LAMA fixed combination group, and was similar in the glycopyrronium bromide and 'other' groups (Table 10-31). Few of these events were considered related to the study (Table 10-32). The number of patients with serious adverse events of special interest for Ultibro® Breezhaler® was slightly higher in the Argus database than the safety set (102 patients with at least one event in the LABA/LAMA fixed combination group), but overall the results for the two databases were similar ([Annex 1 Table 2-3]).

Table 10-31 Serious adverse events of special interest (for LABA/LAMA) (by patients) - overall, and by MedDRA class and preferred term (>/=0.1% in any treatment group) (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	133 (3.1%)	94 (2.2%)	83 (2.8%)	310 (2.7%)
Asthma/bronchospasm	1 (<0.1%)	1 (<0.1%)	2 (<0.1%)	4 (<0.1%)
Cardiac arrhythmia	32 (0.8%)	20 (0.5%)	23 (0.8%)	75 (0.7%)
Atrial fibrillation	19 (0.4%)	12 (0.3%)	13 (0.4%)	44 (0.4%)
Cardiac failure	47 (1.1%)	22 (0.5%)	26 (0.9%)	95 (0.8%)
Cardiac failure	33 (0.8%)	11 (0.3%)	22 (0.7%)	66 (0.6%)
Pulmonary edema	1 (<0.1%)	5 (0.1%)	0	6 (<0.1%)
Cerebrovascular events	26 (0.6%)	14 (0.3%)	9 (0.3%)	49 (0.4%)
Cerebrovascular accident	13 (0.3%)	5 (0.1%)	2 (<0.1%)	20 (0.2%)
Transient ischemic attack	5 (0.1%)	1 (<0.1%)	1 (<0.1%)	7 (<0.1%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Diabetes mellitus/hyperglycemia	17 (0.4%)	18 (0.4%)	9 (0.3%)	44 (0.4%)
Type 2 diabetes mellitus	8 (0.2%)	15 (0.4%)	6 (0.2%)	29 (0.3%)
Ischemic heart disease	20 (0.5%)	23 (0.5%)	16 (0.5%)	59 (0.5%)
Angina pectoris	4 (<0.1%)	11 (0.3%)	5 (0.2%)	20 (0.2%)
Coronary artery disease	12 (0.3%)	14 (0.3%)	10 (0.3%)	36 (0.3%)
Myocardial infarction	28 (0.7%)	19 (0.5%)	14 (0.5%)	61 (0.5%)
Acute myocardial infarction	9 (0.2%)	3 (<0.1%)	4 (0.1%)	16 (0.1%)
Myocardial infarction	14 (0.3%)	14 (0.3%)	10 (0.3%)	38 (0.3%)
Narrow angle glaucoma	2 (<0.1%)	1 (<0.1%)	1 (<0.1%)	4 (<0.1%)
QT prolongation	2 (<0.1%)	0	0	2 (<0.1%)

Source 3.1-3.4.3.2

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

Table 10-32 Serious adverse events of special interest with relationship to study suspected (for LABA/LAMA) (by patients) - overall, and by MedDRA class and preferred term (safety set)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Number (%) of patients with at least one event	7 (0.2%)	9 (0.2%)	4 (0.1%)	20 (0.2%)
Asthma/bronchospasm	0	1 (<0.1%)	0	1 (<0.1%)
Asthma	0	1 (<0.1%)	0	1 (<0.1%)
Cardiac arrhythmia	2 (<0.1%)	4 (<0.1%)	0	6 (<0.1%)
Arrhythmia	0	1 (<0.1%)	0	1 (<0.1%)
Atrial fibrillation	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Extrasystoles	0	2 (<0.1%)	0	2 (<0.1%)
Supraventricular extrasystoles	1 (<0.1%)	0	0	1 (<0.1%)
Ventricular extrasystoles	1 (<0.1%)	0	0	1 (<0.1%)
Cardiac failure	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)
Cardiac failure	1 (<0.1%)	0	1 (<0.1%)	2 (<0.1%)
Cerebrovascular events	1 (<0.1%)	0	2 (<0.1%)	3 (<0.1%)
Carotid artery stenosis	0	0	1 (<0.1%)	1 (<0.1%)
Cerebrovascular accident	1 (<0.1%)	0	0	1 (<0.1%)
Subdural hematoma	0	0	1 (<0.1%)	1 (<0.1%)

	Glycopyrronium bromide (N=4255)	LABA/LAMA fixed combination (N=4185)	Other anti-obstructive therapy (N=3001)	Total (N=11,441)
Diabetes mellitus/Hyperglycemia	0	2 (<0.1%)	0	2 (<0.1%)
Type 2 diabetes mellitus	0	2 (<0.1%)	0	2 (<0.1%)
Ischemic heart disease	2 (<0.1%)	3 (<0.1%)	2 (<0.1%)	7 (<0.1%)
Angina pectoris	2 (<0.1%)	2 (<0.1%)	0	4 (<0.1%)
Angina unstable	0	1 (<0.1%)	0	1 (<0.1%)
Coronary artery disease	1 (<0.1%)	2 (<0.1%)	2 (<0.1%)	5 (<0.1%)
Myocardial infarction	1 (<0.1%)	2 (<0.1%)	0	3 (<0.1%)
Acute myocardial infarction	1 (<0.1%)	0	0	1 (<0.1%)
Angina unstable	0	1 (<0.1%)	0	1 (<0.1%)
Myocardial infarction	0	1 (<0.1%)	0	1 (<0.1%)
Narrow angle glaucoma	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Glaucoma	1 (<0.1%)	0	0	1 (<0.1%)
Vision blurred	0	1 (<0.1%)	0	1 (<0.1%)

Source: Table 3.1-3.4.2.2

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

11 Discussion

11.1 Key results

The main aim of DACCORD was to generate data on the course of COPD under typical treatment conditions. Over 12,000 patients were recruited, with the study applying few inclusion or exclusion criteria and the choice of therapy made prior to entry; two-year follow-up data were analyzed from 6611 patients, all of whom received standard clinical care. The study therefore met this overall aim.

In terms of the baseline characteristics, there were few differences between the three treatment groups, and comorbid conditions were common (especially cardiovascular disease). The majority of patients had symptoms, whereas only approximately a quarter had experienced a COPD exacerbation, suggesting that the main factor resulting in a change in COPD therapy in this population is symptoms. There was a broad range of prior therapy, with no clear relationship between physician type and therapeutic regimen. However, on entry to DACCORD secondary care physicians were more likely to prescribe inhaled triple therapy and regimens containing theophylline or a PDE4-inhibitor, whereas primary care physicians were more likely to prescribe LAMA monotherapy.

Patients receiving a treatment regimen that included a LABA/LAMA fixed combination had the lowest risk of exacerbating over the two-year follow-up, both in terms of the percentage of patients who exacerbated and the annualized exacerbation rate. Consistent with a number of previous analyses, exacerbation history influenced subsequent exacerbation risk, with the risk of exacerbations being highest in the subgroup of patients who had experienced two or more

exacerbations during the six months prior to entering the study regardless of the treatment received during the follow-up period.

There was a clinically meaningful improvement from baseline in health status (assessed using mean CAT total score) in the glycopyrronium bromide and LABA/LAMA fixed combination groups, although not in the 'other' group. In contrast, pulmonary function (mean FEV_1) was similar across groups and did not change over the follow-up period. The most marked improvement in symptoms was in the glycopyrronium bromide group – with nearly one third of patients free of symptoms by the end of two years, compared with 10.5% in the LABA/LAMA fixed combination group and 21.9% in the 'other' group. However, given the majority of patients in the glycopyrronium group were receiving additional COPD maintenance therapy, it is difficult to ascribe any of these efficacy results to any particular treatment. It is notable that more than three quarters of the patients included in these analyses were persistent to their COPD maintenance therapy at the end of the second year.

Overall, the safety and tolerability profiles of the three treatment groups were similar. In particular, the adverse event profiles in the glycopyrronium and LABA/LAMA fixed combination groups were consistent with their known profiles, and so are unlikely to change the overall risk-benefit balance of either product.

Although serious adverse events of special interest for LABA/LAMA with relationship to study were more common in the glycopyrronium bromide and LABA/LAMA fixed combination groups than the 'other' group, the number of patients with these events were low. Further, the overall percentage of patients with adverse events of special interest for LABA/LAMA (regardless of relationship) was lowest in the LABA/LAMA fixed combination group.

11.2 Limitations

The study recruited a broad population from study centers across Germany. However, to be eligible all patients had to initiate or change their COPD maintenance medication, and so the results apply only to this population. In addition, as a non-interventional, observational study, the data available are only those collected from standard clinic visits, with a limited opportunity to follow-up on missing or implausible data.

11.3 Interpretation

Overall, DACCORD evaluated the impact and progression of COPD in a population newly initiating or switching COPD maintenance therapy in Germany. This population had a high symptom load, with a subset of patients also having an exacerbation history. A substantial proportion of patients also had comordidities (more than half having cardiovascular disease). This is therefore a population that is likely to consume a substantial proportion of healthcare resources (in particular primary and secondary care healthcare practitioner time).

There were few differences between the three treatment groups in terms of disease progression or symptoms – and the substantial use of concomitant COPD maintenance medication complicates the interpretation of the data. However, the study overall shows the efficacy benefits possible through switching medication, in particular the impact of a LABA/LAMA fixed combination on the risk of exacerbations, and of a glycopyrronium-containing regime on COPD symptoms.

Although there were some imbalances in the adverse event profiles between the groups, the open-label study design may have influenced the results. The one-year recruitment period into Phase 1 means that initiation of glycopyrronium bromide was, at most, no later than one year after glycopyrronium bromide first became commercially available in Germany, whereas the comparator 'other' group comprised a broad mixture of treatments, many of which have been available for decades. Similarly, recruitment into Phase 2 commenced shortly after Ultibro Breezhaler became commercially available in Germany. A number of researchers have described the 'Weber effect', in which spontaneous Adverse Drug Reaction (ADR) reports tend to reach a peak two years after approval, before declining (Weber 1984, Hartnell and Wilson 2004, Hoffman et al 2014); although there are high levels of under-reporting in general, this results in lower levels of underreporting (i.e., relatively higher levels of reporting) of ADRs from drugs that are more recently approved (Alvarez-Requejo et al 1998). While the adverse event reporting in CNVA237ADE01 was not completely spontaneous (since it took place at study visits, with data being reported in eCRFs), it is possible that the reporting was influenced by the Weber effect. The open-label nature of treatment may also have influenced reporting – not only by physicians but also by patients – with authors of a review suggesting that patients may research a new drug and its side effects in publications, and so be influenced in their reporting behavior (Beyer-Westendorf and Büller 2011). Theoretically the same factors should apply to the LABA/LAMA fixed combination group, since the 1.5-year recruitment into Phase 2 commenced shortly after the first LABA/LAMA fixed combination became commercially available in Germany. However, the most common adverse events in all three groups were related to poor control of COPD (such as decreased exercise tolerance, dyspnea and wheezing) – symptoms that would indicate the need for treatment escalation in clinical practice. It is possible, therefore, that the better safety profile (in terms of non-serious adverse events) of the LABA/LAMA fixed combination group indicates improved efficacy, rather than a difference in safety profiles.

A further major source of bias in this setting, which applies to all open-label studies, relates to follow-up. As manufacturer, Novartis is required to conduct a detailed follow-up of any reported serious adverse event or event of special interest (as defined in the Risk Management Plan) of their own products; this requirement does not apply to other manufacturers' products. During this detailed follow-up process, many additional adverse events (both serious and non-serious) can be identified which had not been reported by the investigator.

There was no clear pattern in the outcome of non-serious or serious adverse events. Of particular note is that none of the deaths (where it was possible to determine causality) was considered related to the study. Furthermore, the majority of individual preferred-term non-serious and serious adverse events were reported by small numbers of patients, again with no clear signal. Although in the current study the incidence of adverse events was higher in the glycopyrronium bromide group than the other two groups, the percentage of patients with an event was much lower than reported in randomized controlled trials. For example, over the 26 weeks of the GLOW 1 study, 57.5% of patients randomized to glycopyrronium bromide experienced an adverse event, compared with 65.2% of patients randomized to placebo; the equivalent values for serious adverse events were 8.4% and 9.0% (D'Urzo et al 2011). Although direct comparisons between such different studies should be avoided, the relative experience of non-serious and serious adverse events does suggest some degree of reporting bias in CNVA237ADE01, whereby in this observational setting adverse events are more likely to be

recalled by patients if they were serious; this is also consistent with studies on underreporting of ADRs in primary care, in which serious cases are more likely to be reported (Alvarez-Requejo et al 1998).

The final consideration when interpreting the data from this study, is that although the treatment groups are described as 'glycopyrronium bromide', 'LABA/LAMA fixed combination' and 'other anti-obstructive therapy', many patients in these groups (especially in the glycopyrronium group) were receiving multiple COPD maintenance therapies, and even when adverse events were considered related by the investigators, it is challenging to tease out whether the event was related to one specific treatment (which is why such events are described as related to the study, rather than related to study drug).

11.4 Generalizability

Given this study recruited a broad, geographically diverse population from primary and secondary care, the results can be generalized to patients with COPD across Germany who newly initiate COPD maintenance therapy, or who need a change in their maintenance therapy.

12 Other information

Not applicable

13 Conclusion

Overall, this study provides useful data on the course of COPD in Germany. The safety data do not change the overall benefit-risk profile of glycopyrronium or the glycopyrronium/indacaterol fixed-dose combination.

14 References

References are available upon request.

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Appendices

Annex 1 – List of stand-alone documents

1. Study investigators and other important participants.

2. Data from the Argus database

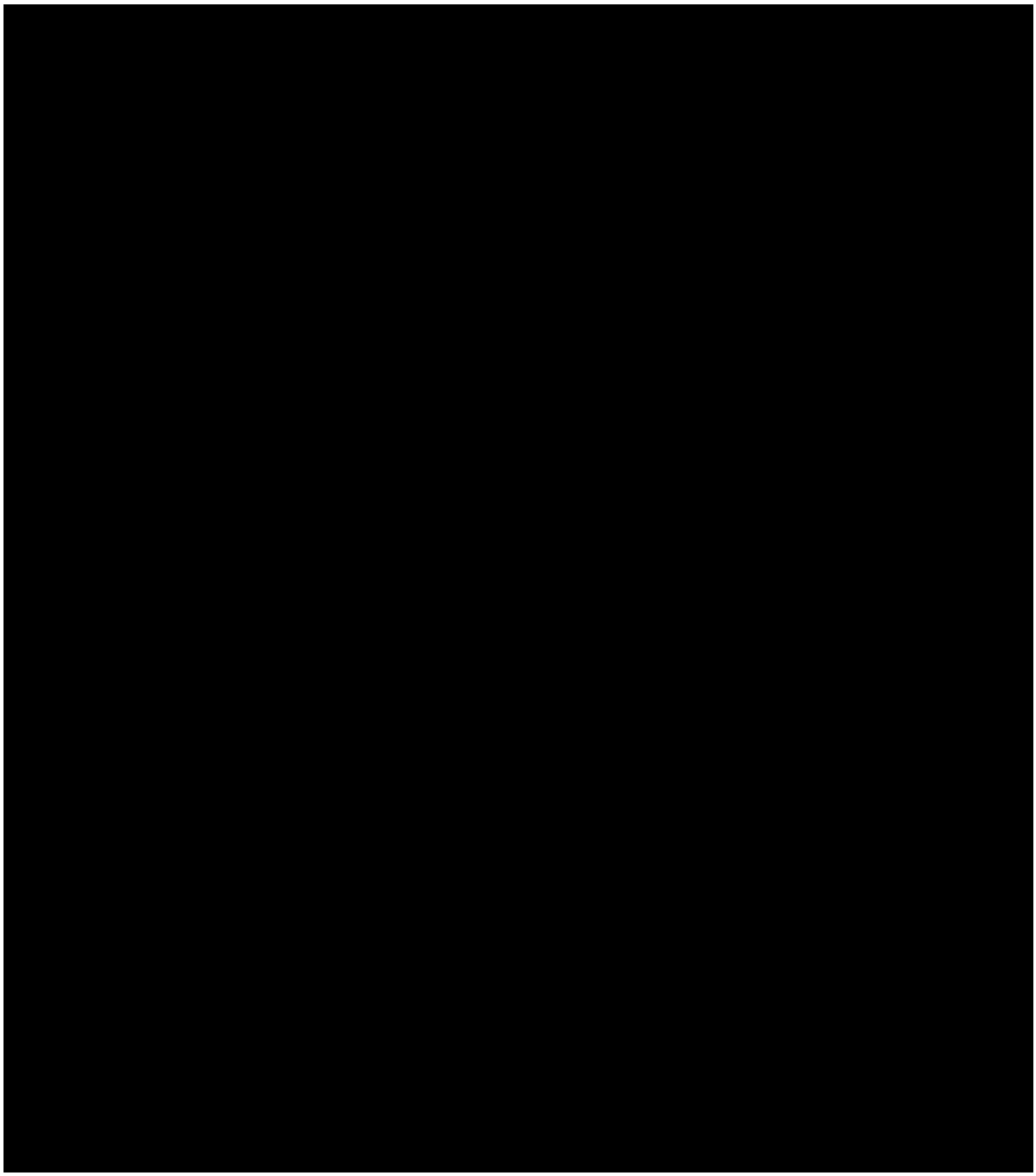
Table 2-1. Fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (Argus listing)

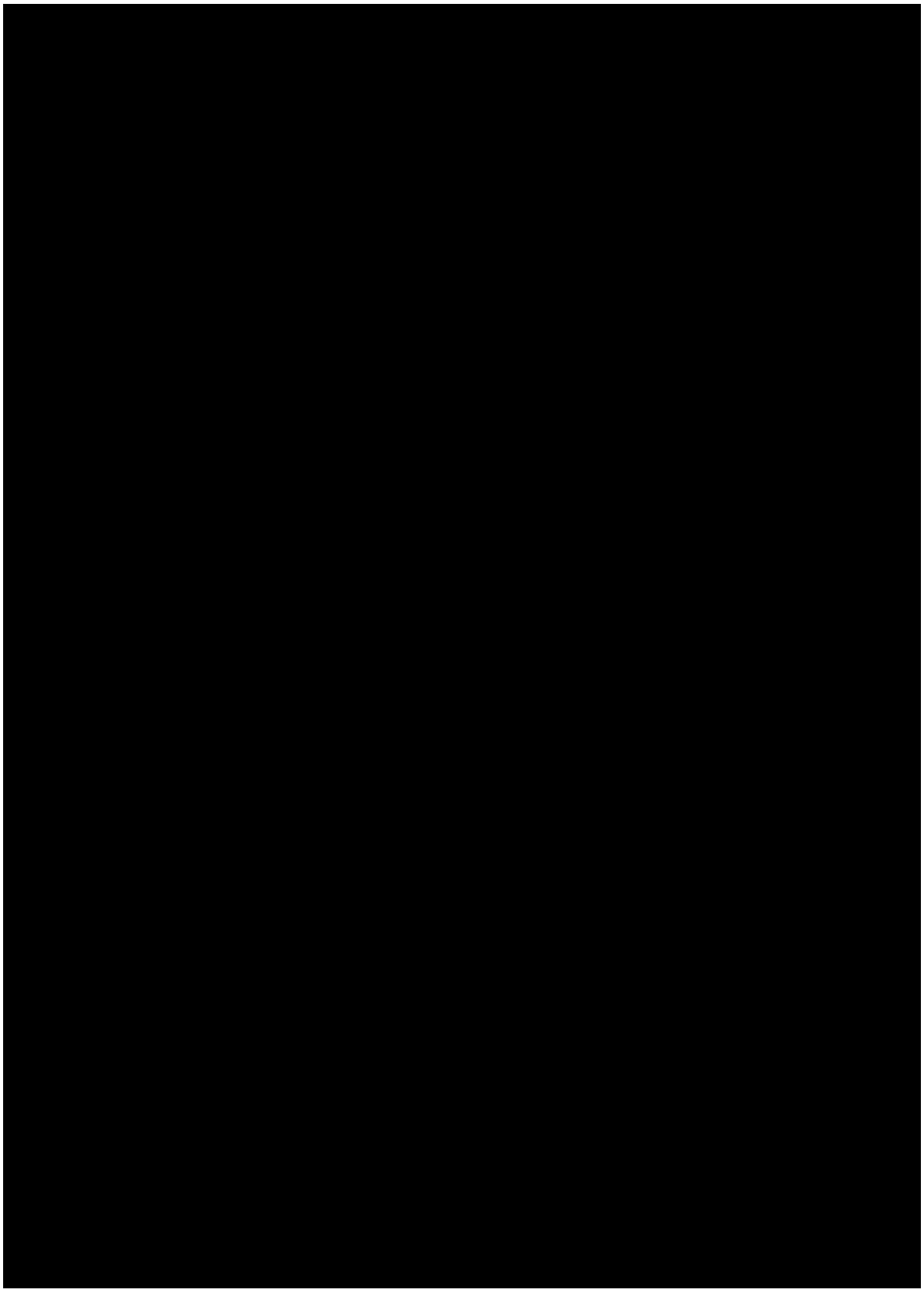
Table 2-2. Serious adverse events of special interest (for glycopyrronium bromide) (by patients) - overall, and by MedDRA class and preferred term (Argus listing)

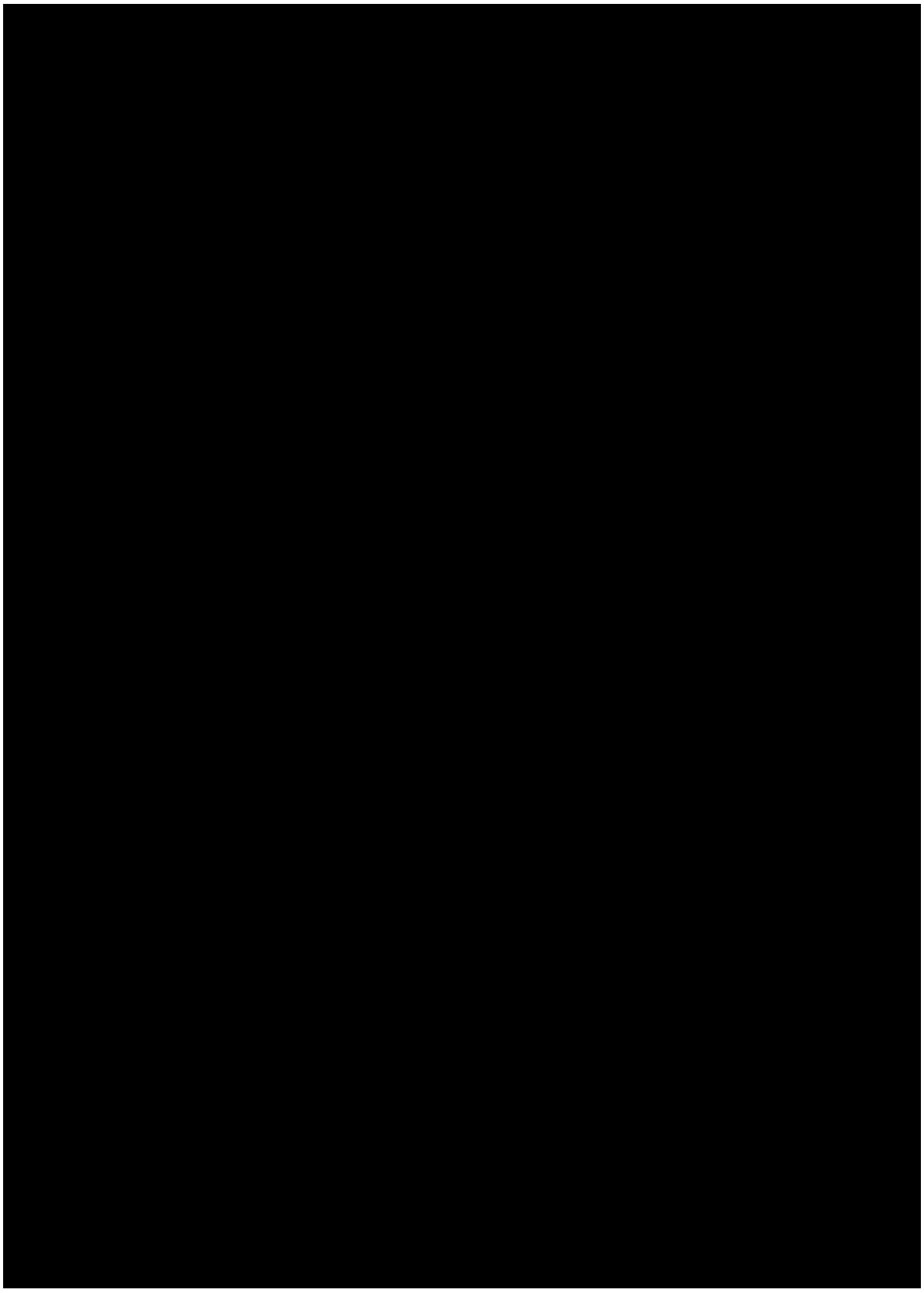
Table 2-3. Serious adverse events of special interest (for LABA/LAMA) (by patients) - overall, and by MedDRA class and preferred term (Argus listing).

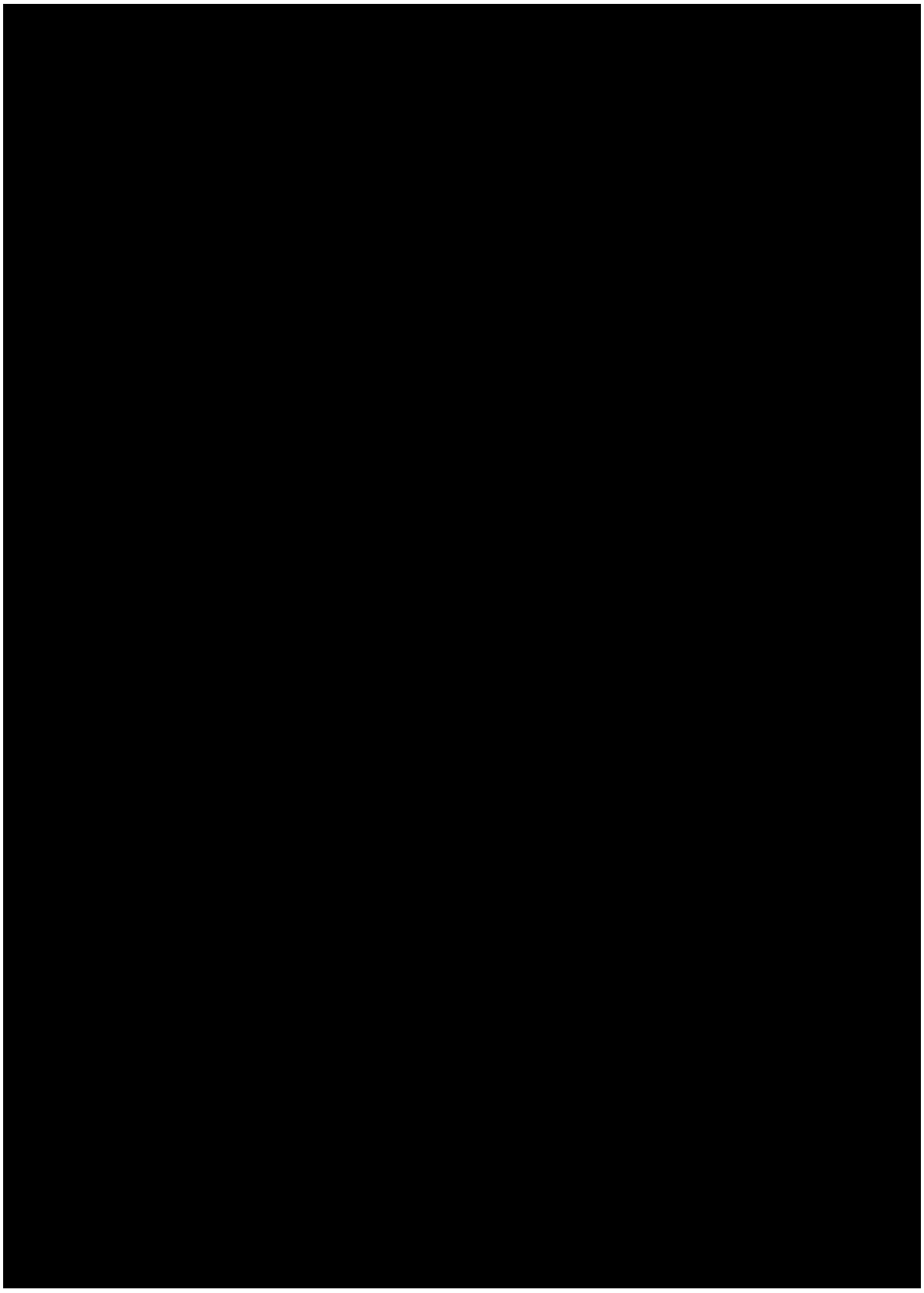
Annex 1 List and description of investigators and other important participants in the study, and data from the Argus database

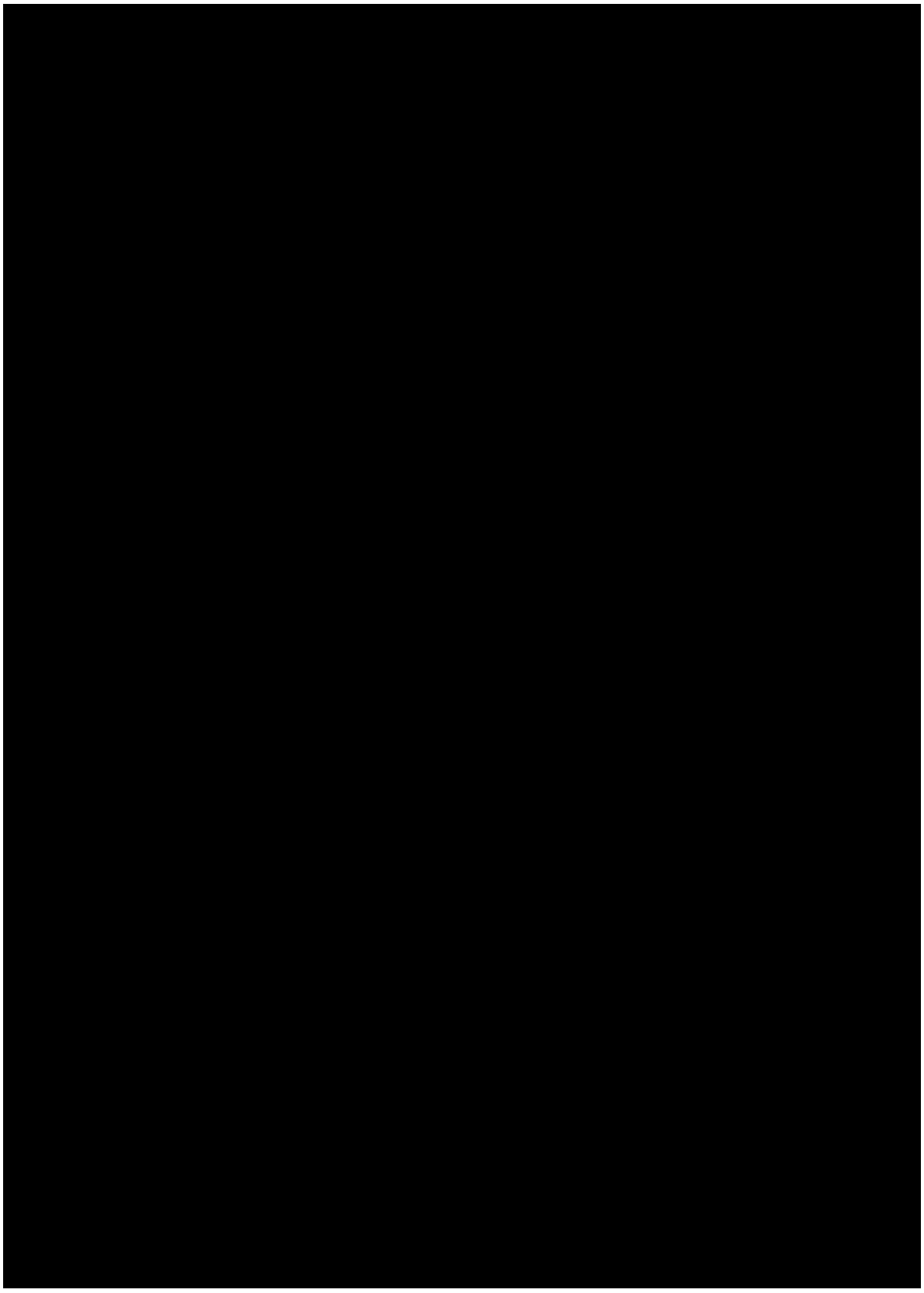
1 Study investigators and other important participants

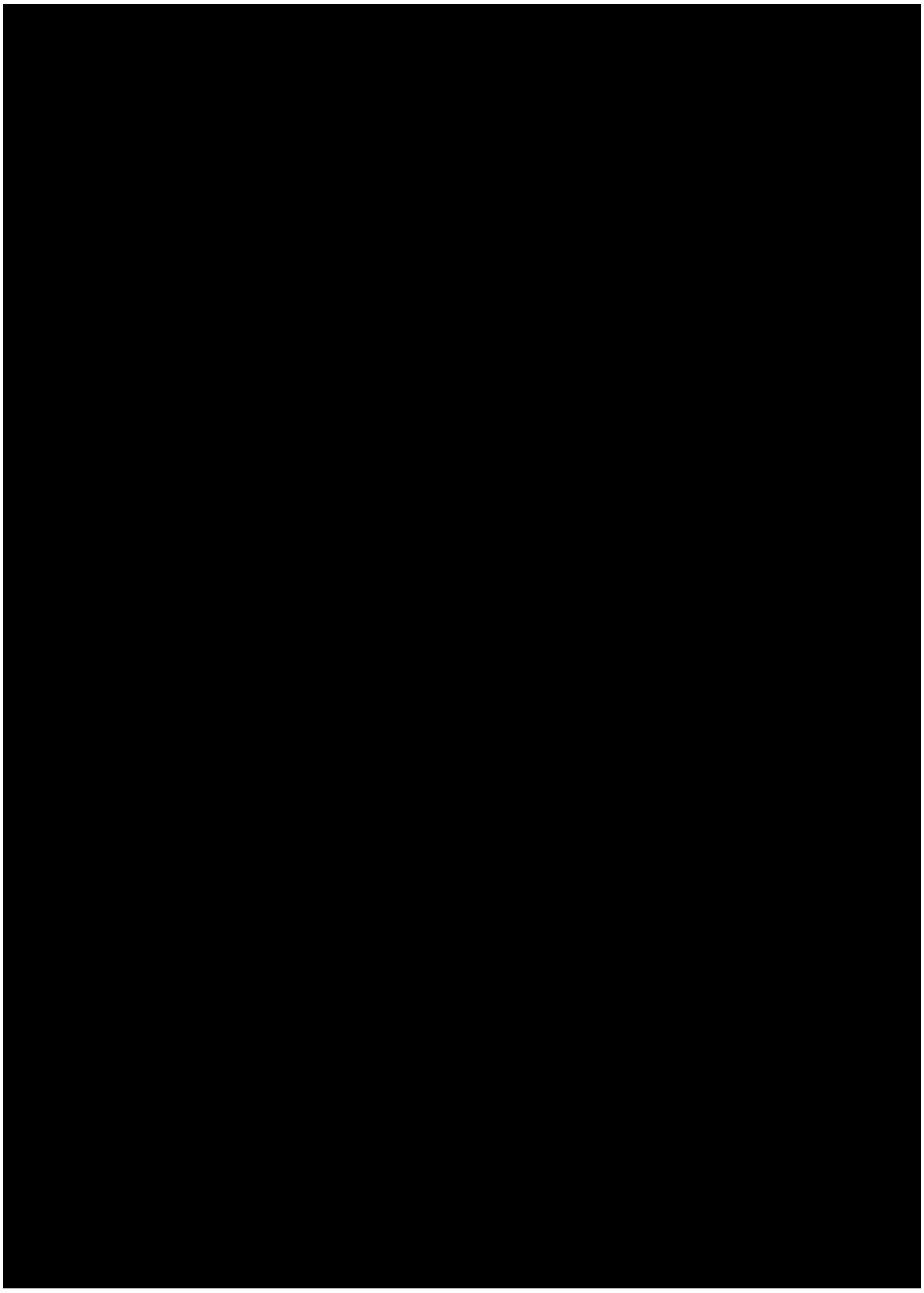


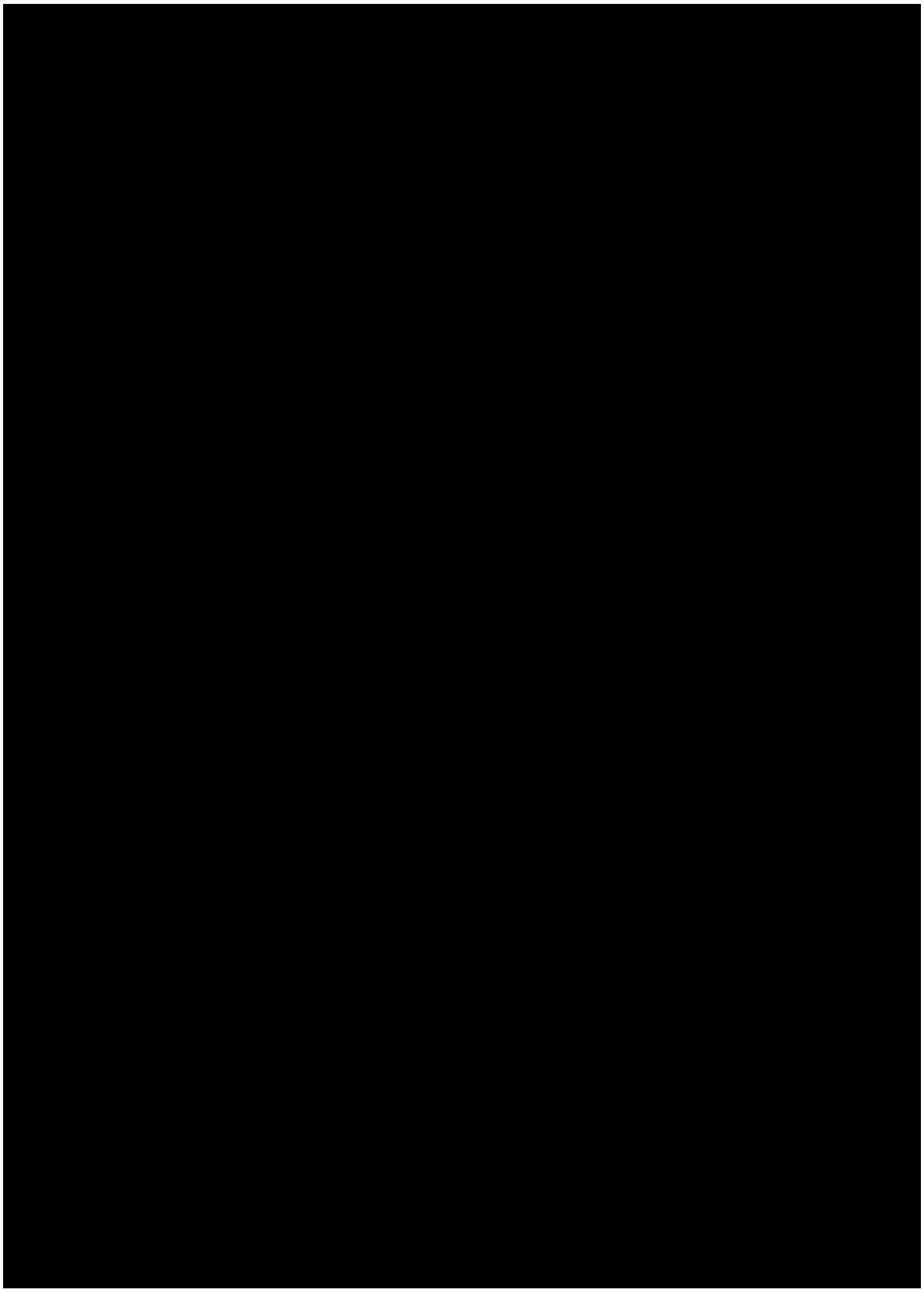


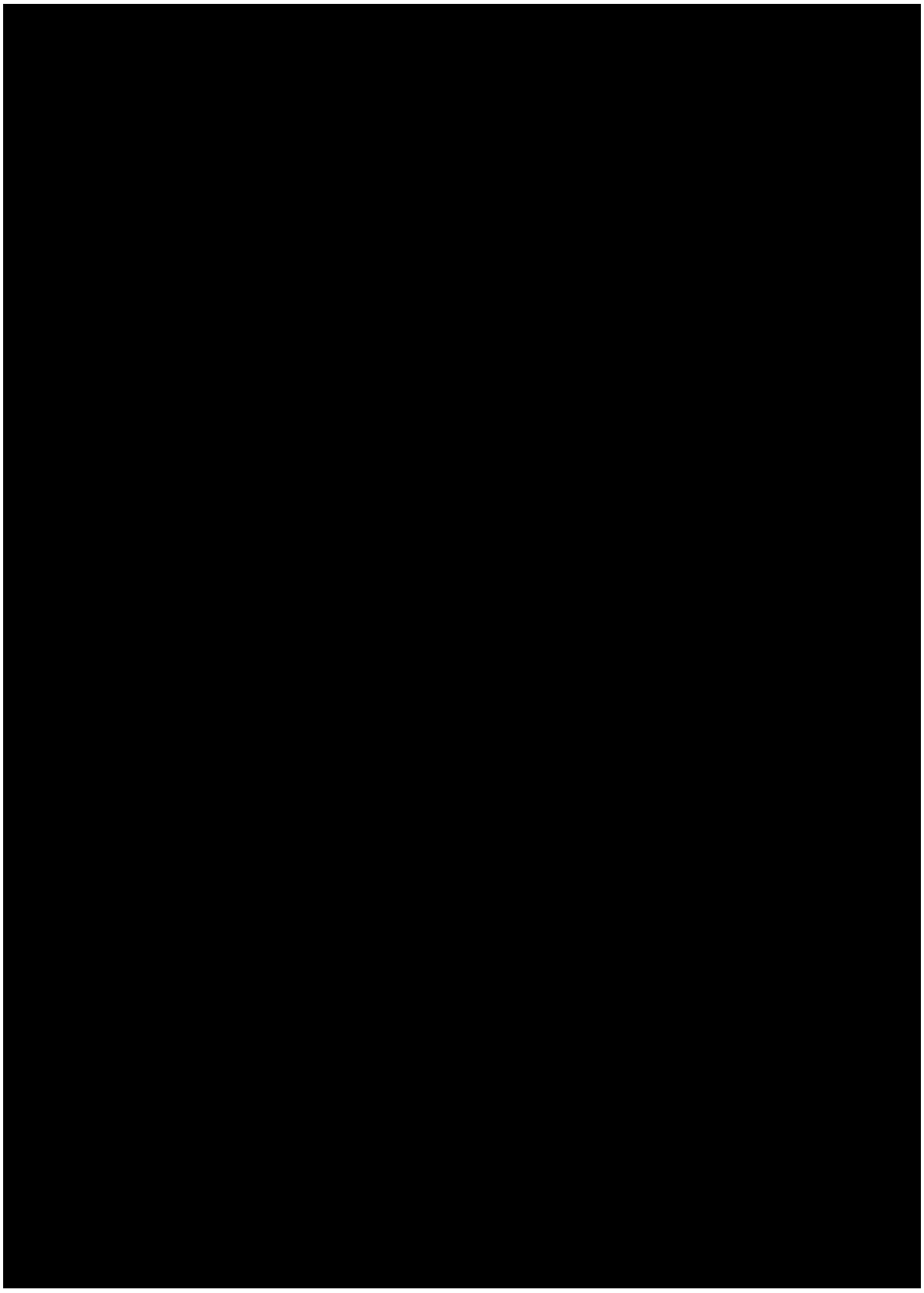


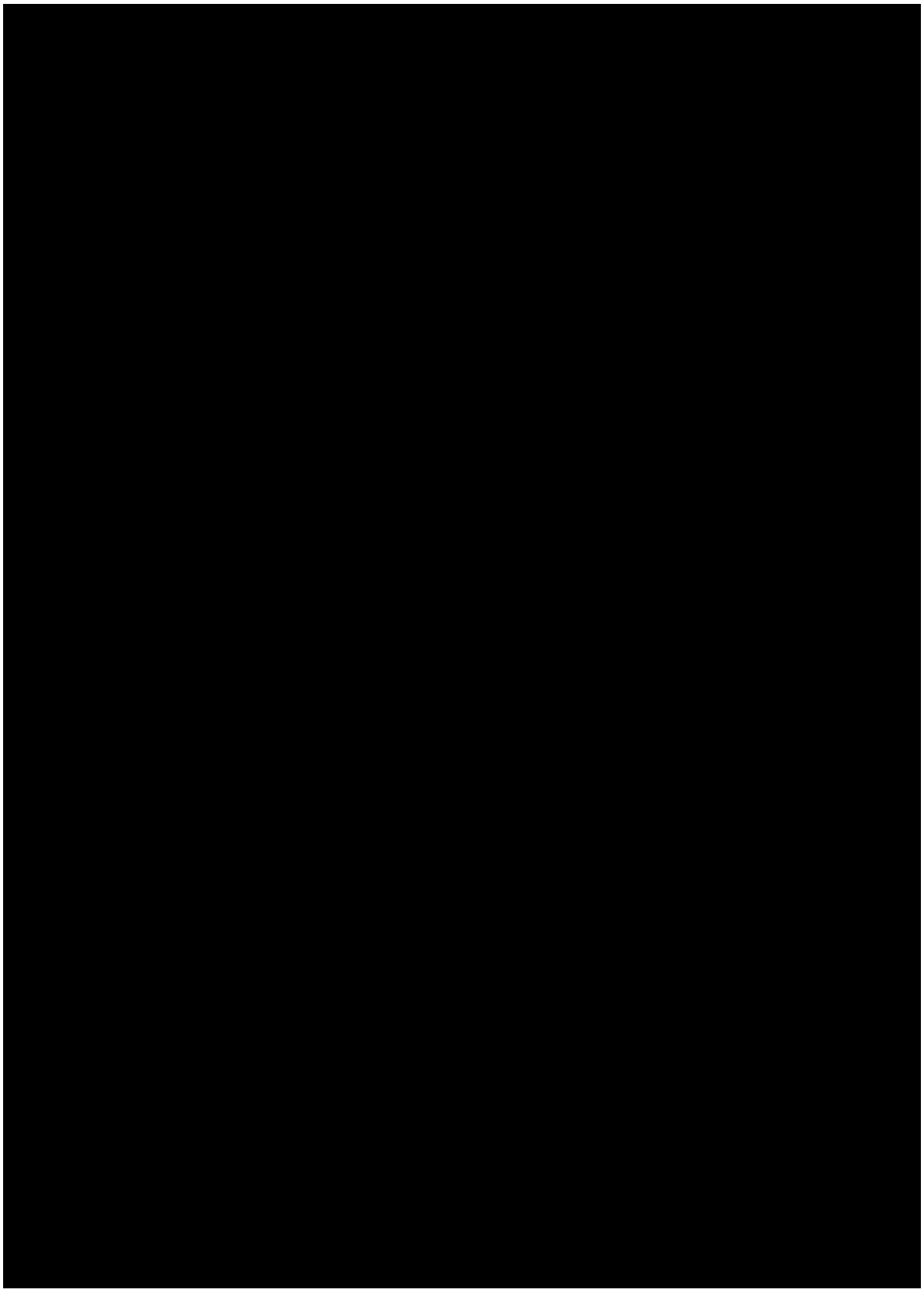


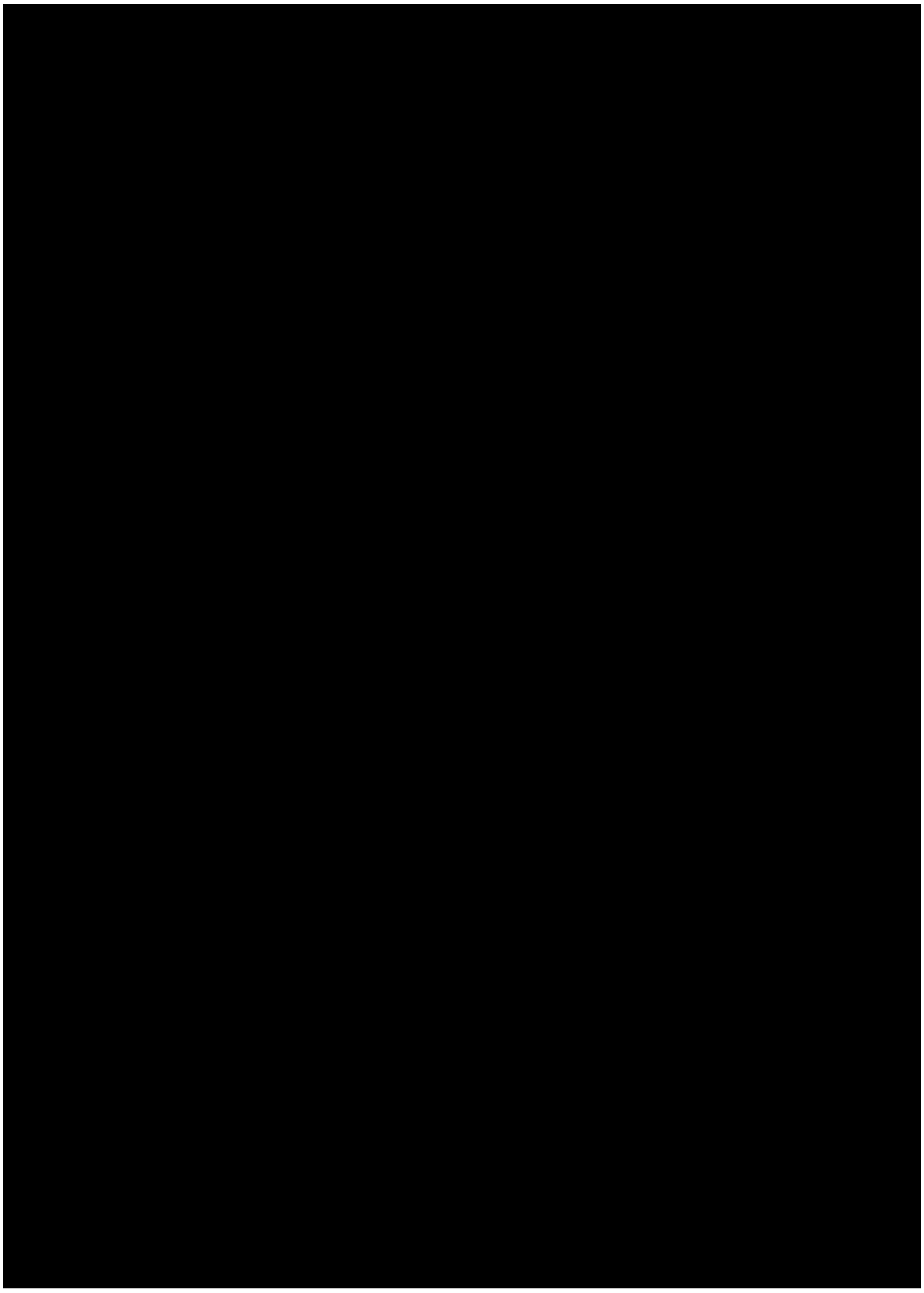


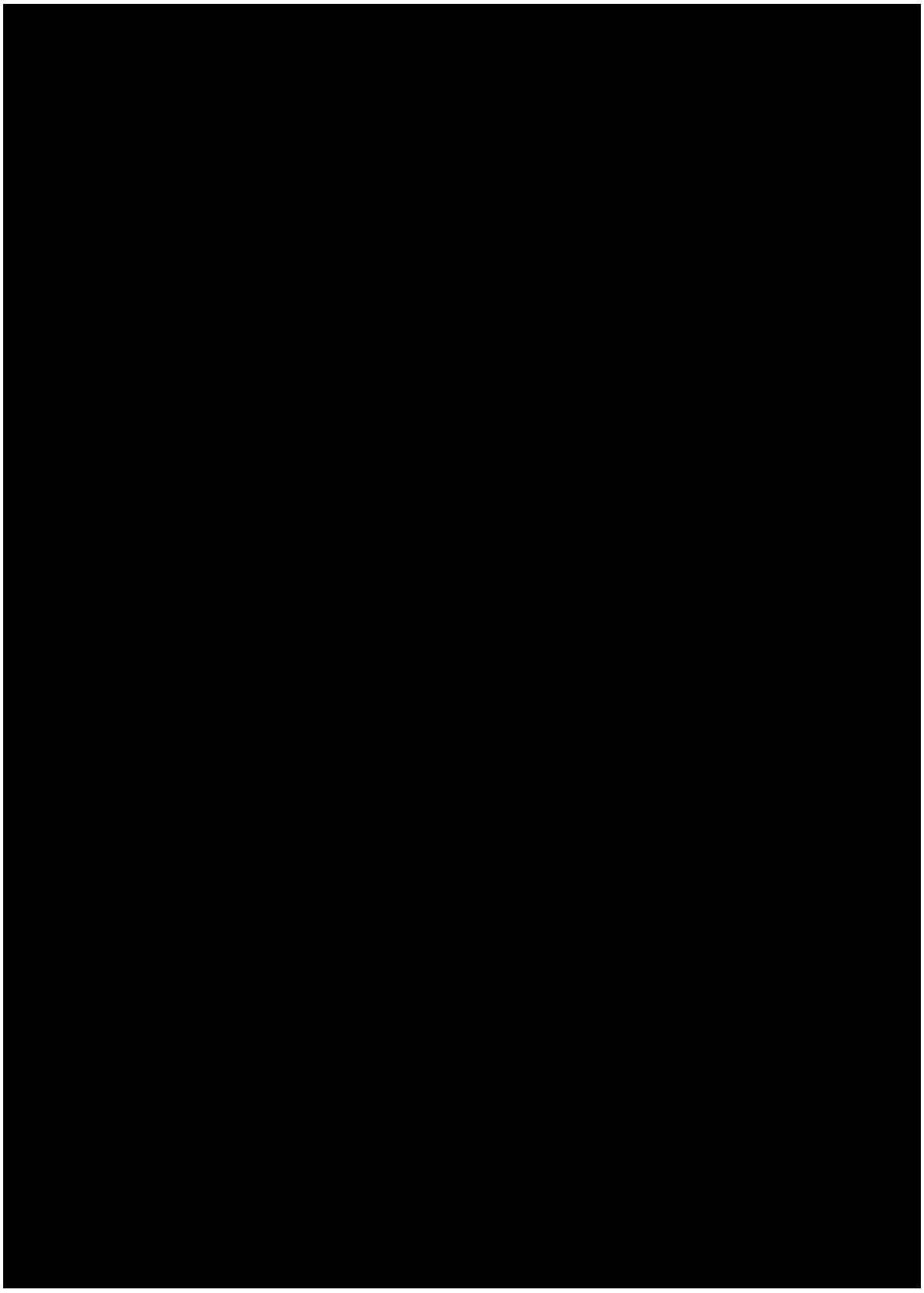


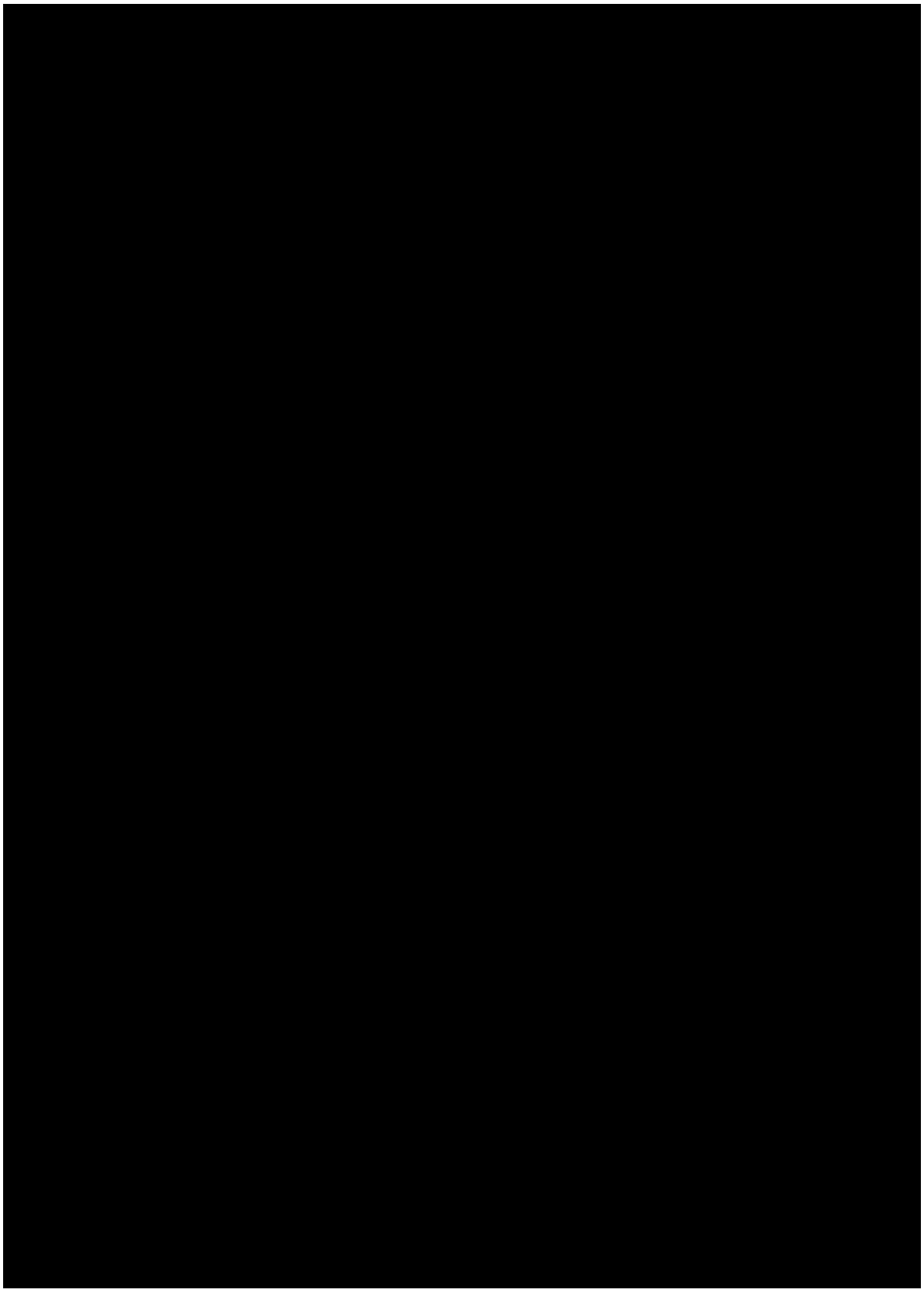


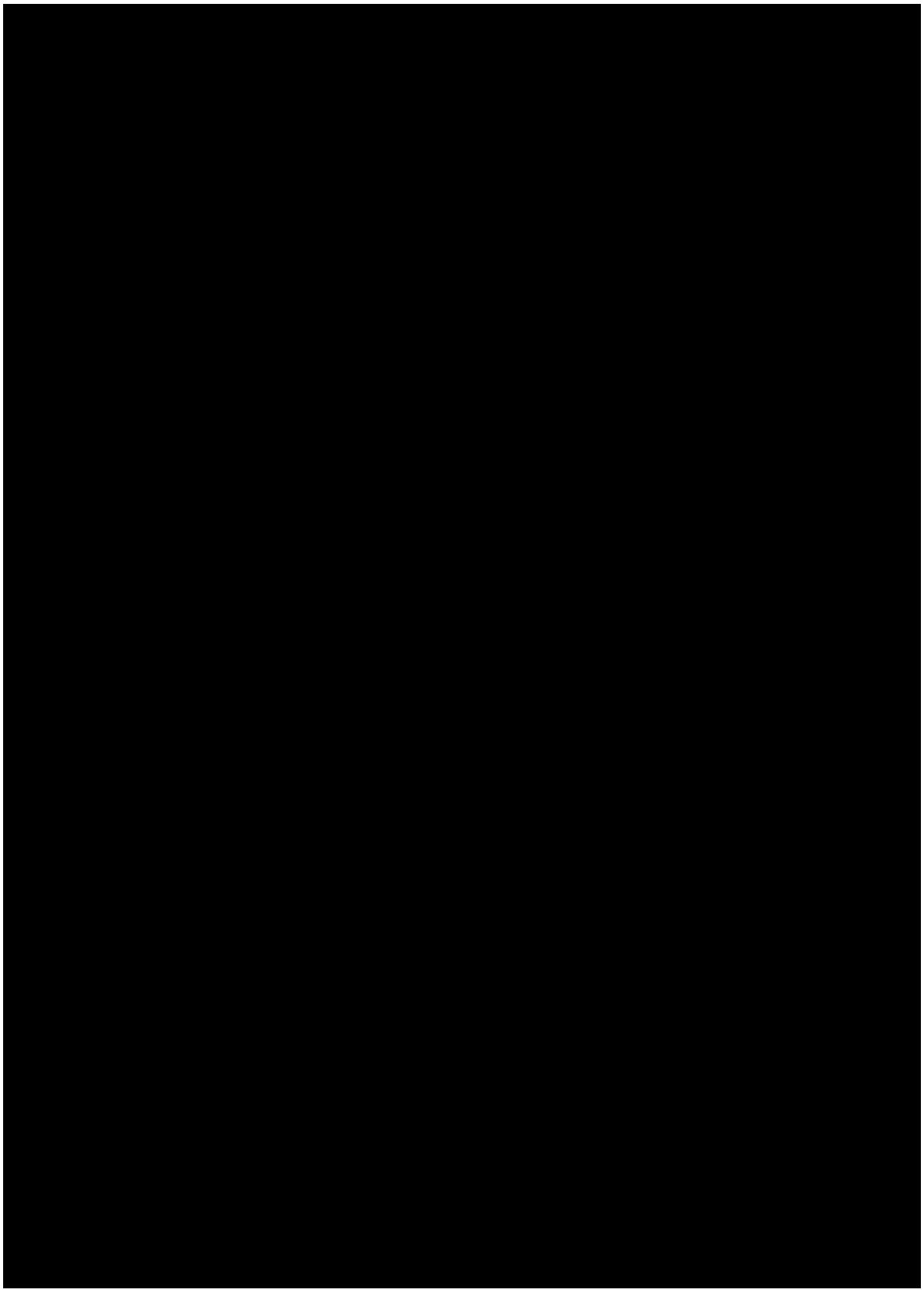


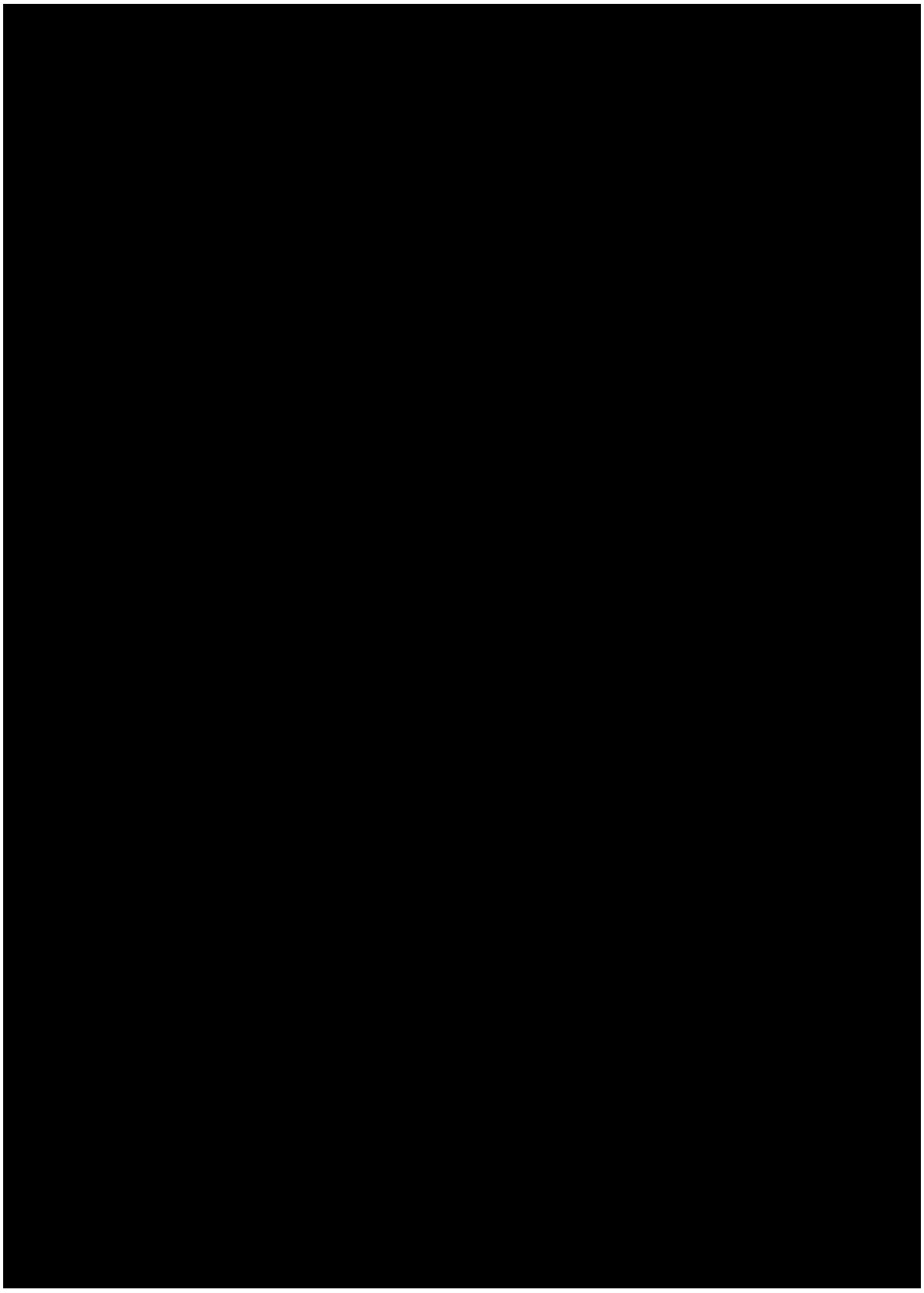


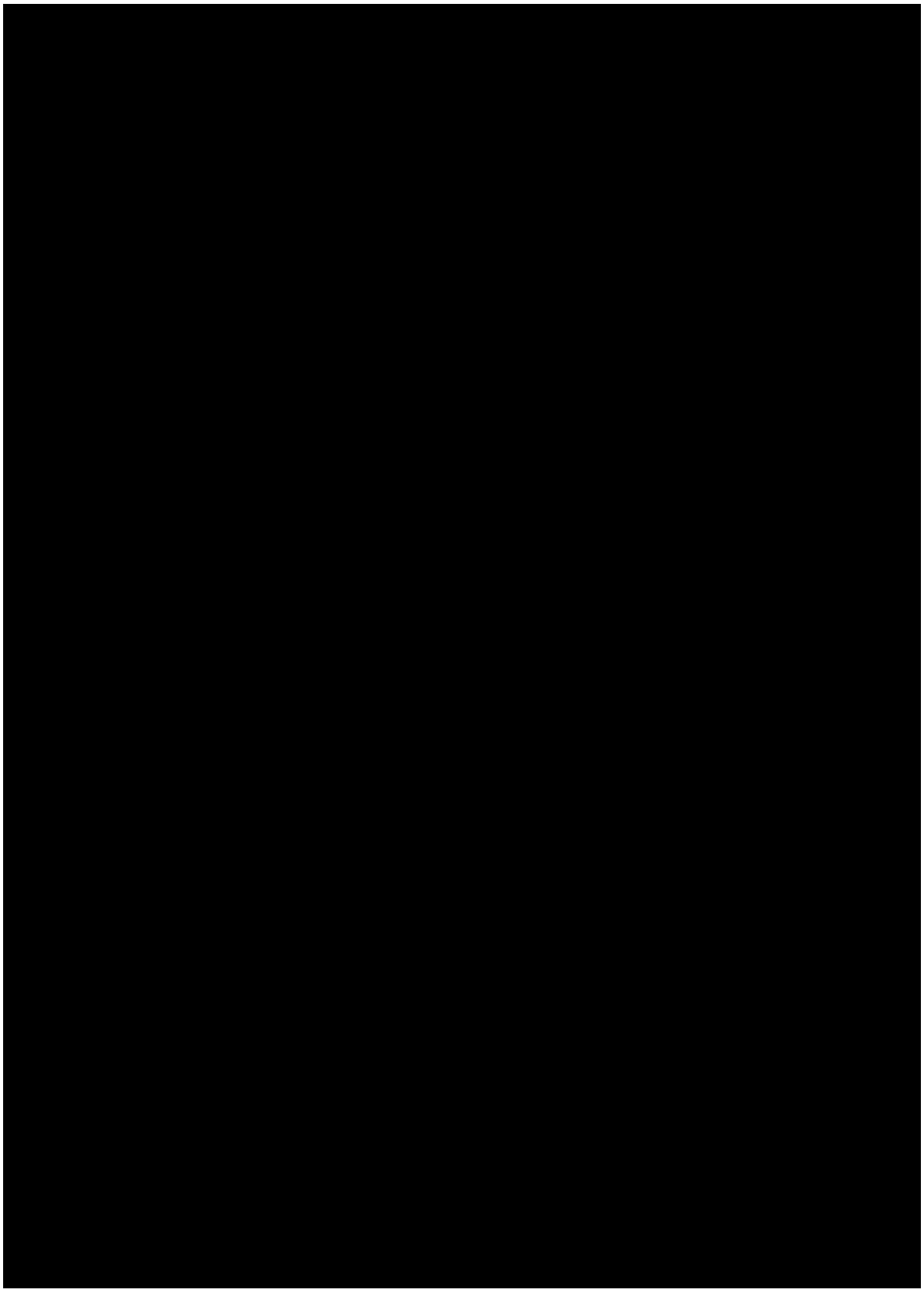


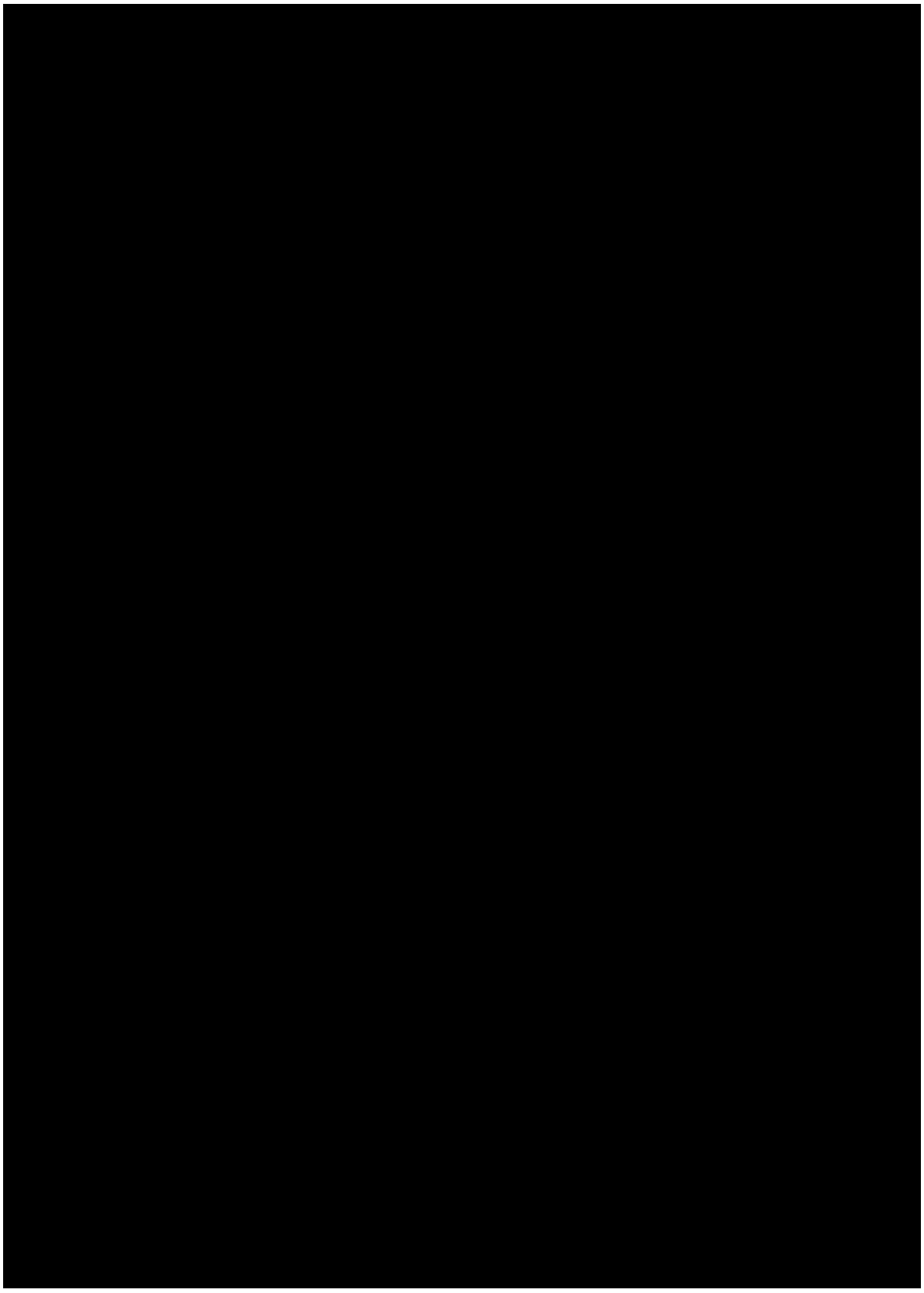


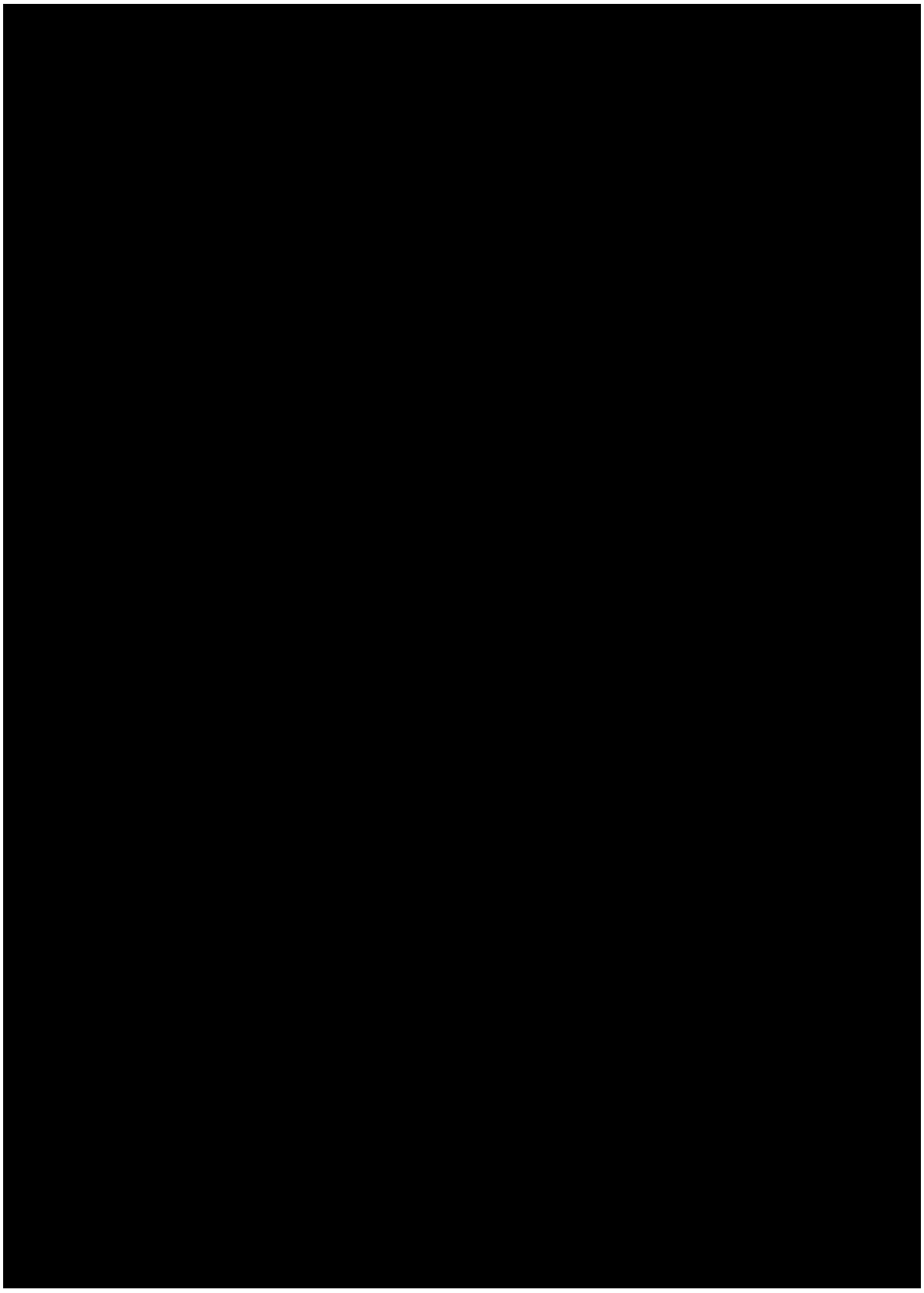


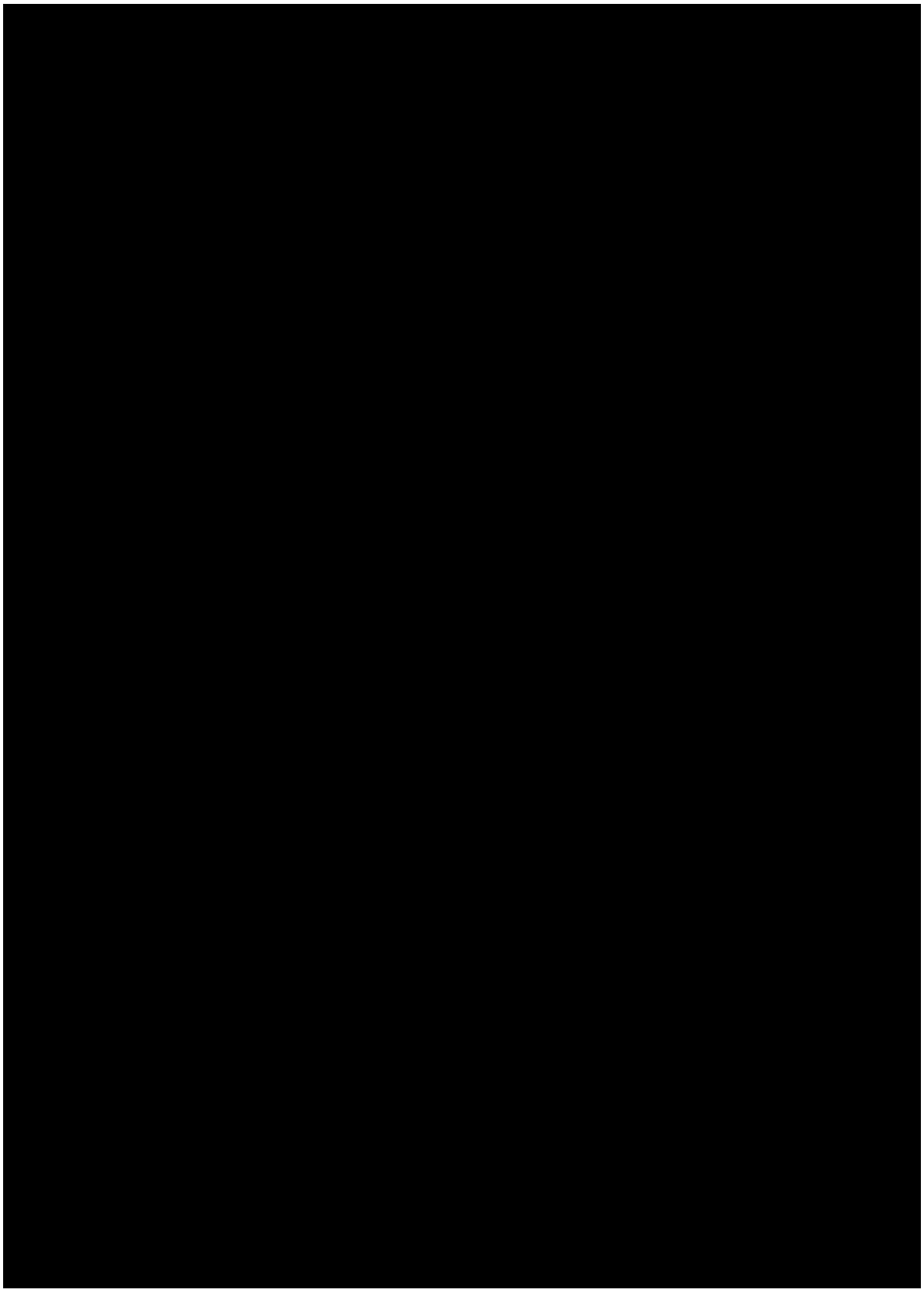


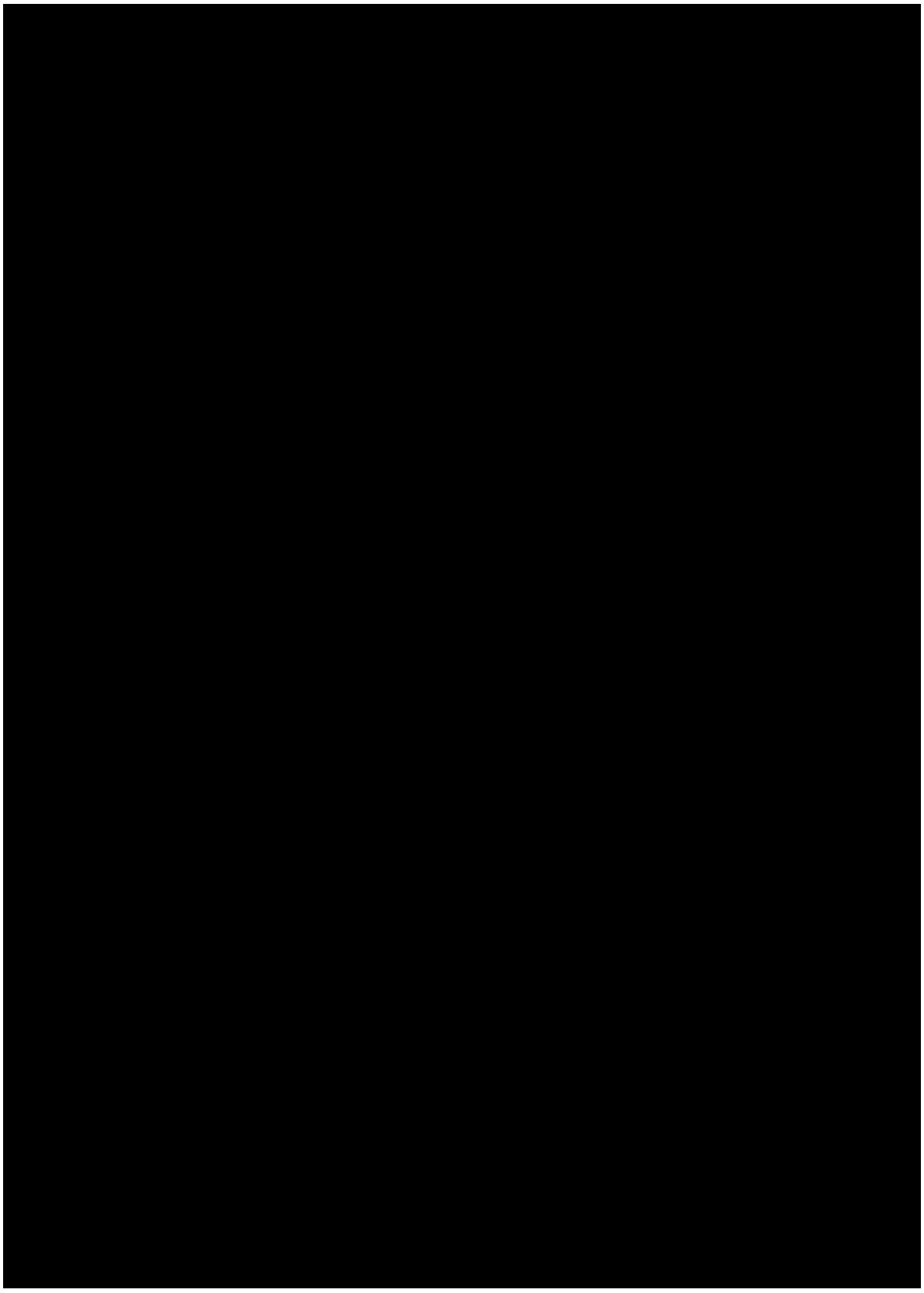


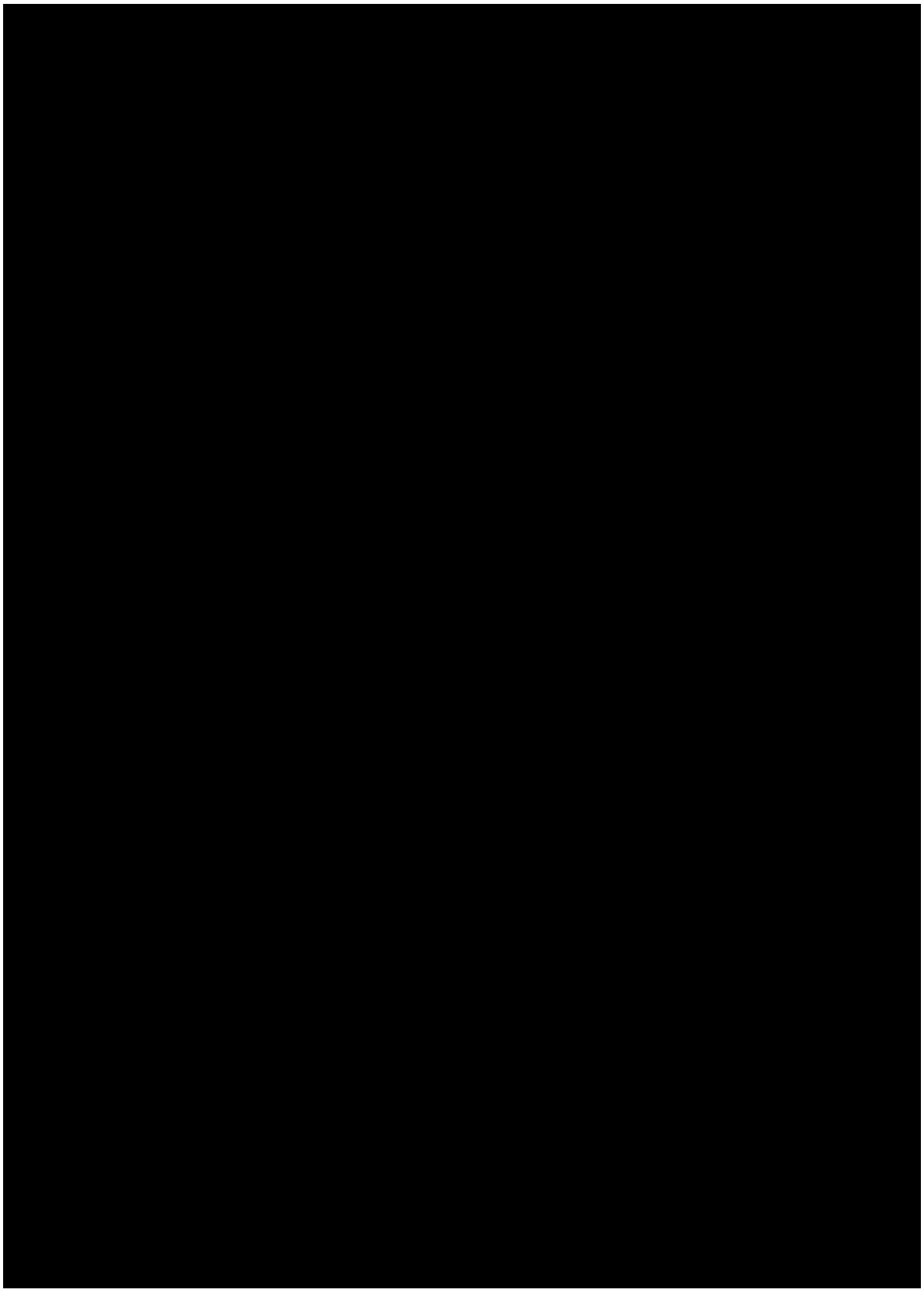


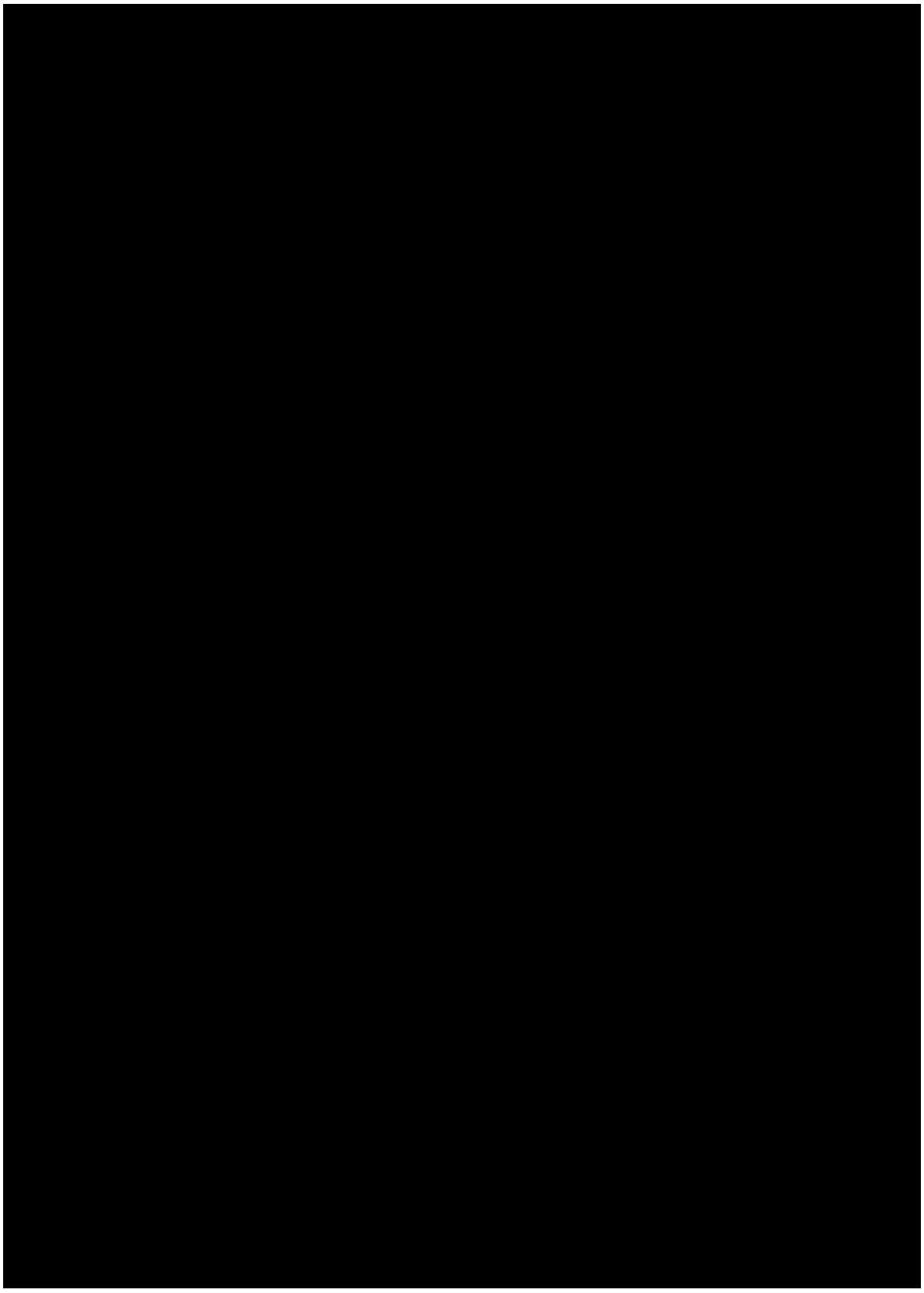


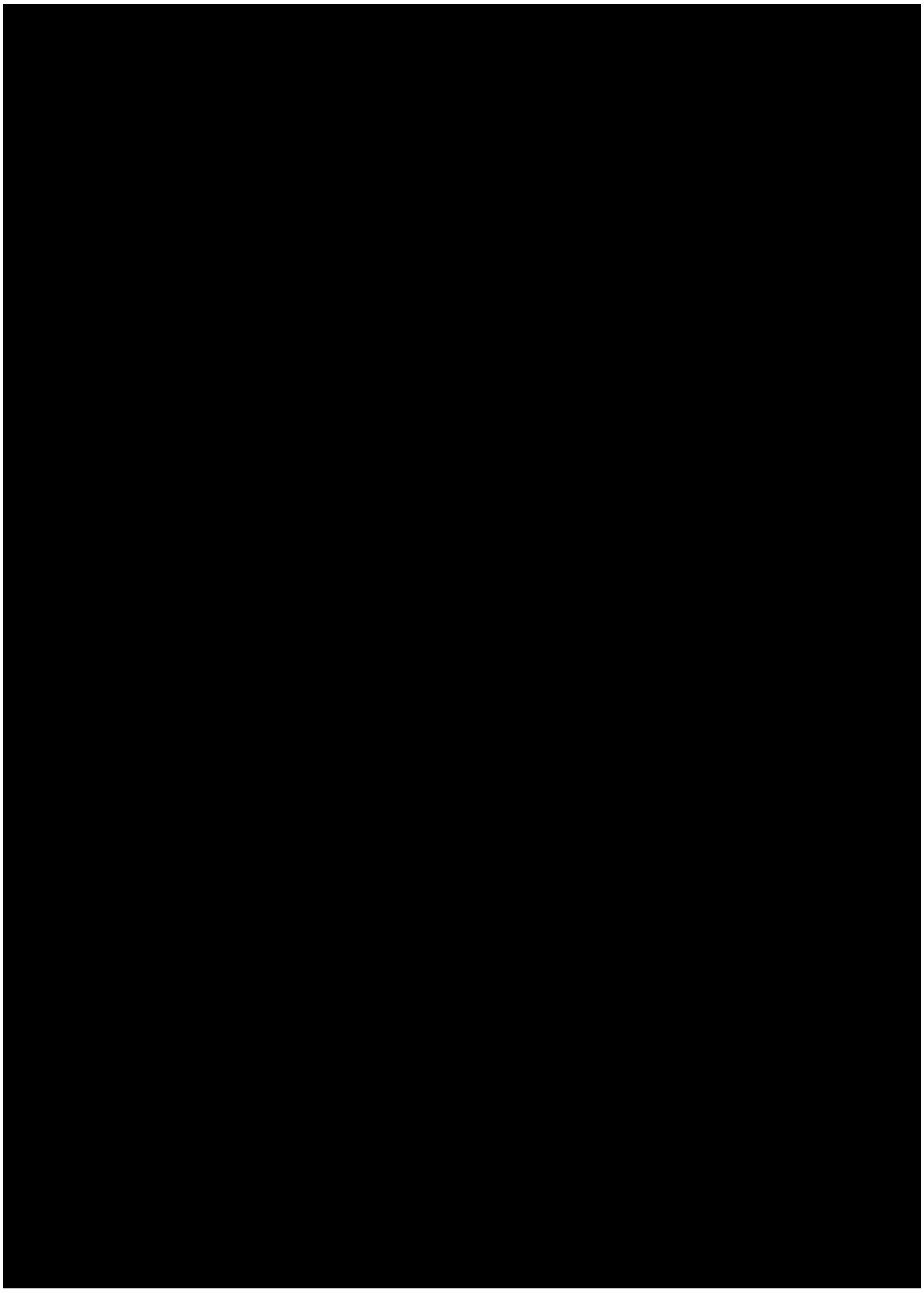


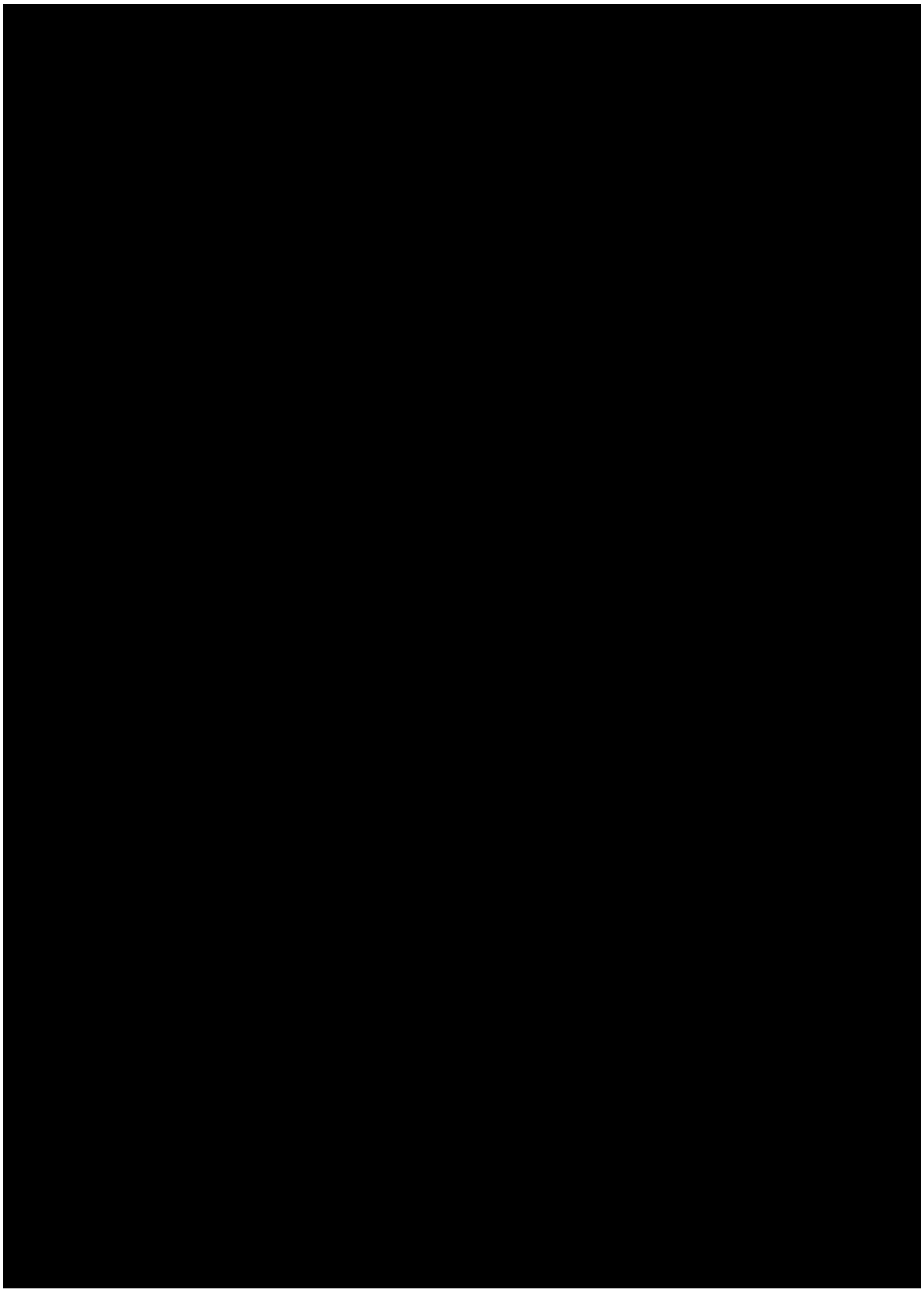












2 Data from the Argus database

2.1 Fatal adverse events

Table 2-1 Fatal serious adverse events (by patients) – overall, by MedDRA system organ class and preferred term (Argus listing)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Number (%) of patients with at least one fatal event	105 (6.9%)	125 (9.9%)	11 (10.8%)	232 (8.4%)
Blood and lymphatic system disorders	1 (<0.1%)	1 (<0.1%)	1 (1.0%)	3 (0.1%)
Anemia	0	1 (<0.1%)	1 (1.0%)	2 (<0.1%)
Coagulopathy	1 (<0.1%)	0	0	1 (<0.1%)
Leukocytosis	0	1 (<0.1%)	0	1 (<0.1%)
Cardiac disorders	36 (2.4%)	29 (2.3%)	2 (2.0%)	66 (2.4%)
Acute myocardial infarction	3 (0.2%)	0	0	3 (0.1%)
Angina pectoris	0	2 (0.2%)	0	2 (<0.1%)
Aortic valve stenosis	2 (0.1%)	0	0	2 (<0.1%)
Arrhythmia	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Atrial fibrillation	1 (<0.1%)	2 (0.2%)	1 (1.0%)	4 (0.1%)
Cardiac arrest	5 (0.3%)	3 (0.2%)	0	8 (0.3%)
Cardiac failure	15 (1.0%)	4 (0.3%)	1 (1.0%)	20 (0.7%)
Cardiac failure acute	0	1 (<0.1%)	0	1 (<0.1%)
Cardiac failure chronic	1 (<0.1%)	0	0	1 (<0.1%)
Cardiac failure congestive	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Cardiogenic shock	2 (0.1%)	1 (<0.1%)	0	3 (0.1%)
Cardiovascular insufficiency	0	1 (<0.1%)	0	1 (<0.1%)
Cor pulmonale	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Cor pulmonale chronic	1 (<0.1%)	0	0	1 (<0.1%)
Coronary artery disease	3 (0.2%)	1 (<0.1%)	0	4 (0.1%)
Coronary artery insufficiency	0	2 (0.2%)	0	2 (<0.1%)
Left ventricular failure	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Myocardial infarction	6 (0.4%)	9 (0.7%)	0	15 (0.5%)
Palpitations	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Right ventricular failure	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Tachyarrhythmia	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Tachycardia	1 (<0.1%)	0	0	1 (<0.1%)
Ventricular fibrillation	3 (0.2%)	0	0	3 (0.1%)
Ventricular tachycardia	1 (<0.1%)	0	0	1 (<0.1%)
Gastrointestinal disorders	8 (0.5%)	5 (0.4%)	1 (1.0%)	14 (0.5%)
Abdominal pain	1 (<0.1%)	0	1 (1.0%)	2 (<0.1%)
Abdominal pain upper	1 (<0.1%)	0	0	1 (<0.1%)
Acute abdomen	2 (0.1%)	0	0	2 (<0.1%)
Anal incontinence	0	2 (0.2%)	0	2 (<0.1%)
Ascites	3 (0.2%)	1 (<0.1%)	0	4 (0.1%)
Dysphagia	1 (<0.1%)	0	0	1 (<0.1%)
Gastrointestinal necrosis	1 (<0.1%)	0	0	1 (<0.1%)
Hematemesis	0	1 (<0.1%)	0	1 (<0.1%)
Ileal perforation	0	1 (<0.1%)	0	1 (<0.1%)
Intestinal ischemia	0	1 (<0.1%)	0	1 (<0.1%)
Large intestine perforation	1 (<0.1%)	0	0	1 (<0.1%)
Melena	1 (<0.1%)	0	0	1 (<0.1%)
Mesenteric arterial occlusion	1 (<0.1%)	0	0	1 (<0.1%)
Nausea	2 (0.1%)	2 (0.2%)	0	4 (0.1%)
Varices esophageal	1 (<0.1%)	0	0	1 (<0.1%)
Vomiting	0	1 (<0.1%)	0	1 (<0.1%)
General disorders and administration site conditions	36 (2.4%)	59 (4.7%)	2 (2.0%)	92 (3.3%)
Asthenia	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Brain death	1 (<0.1%)	0	0	1 (<0.1%)
Chest discomfort	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Chest pain	1 (<0.1%)	4 (0.3%)	0	5 (0.2%)
Concomitant disease aggravated	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Concomitant disease progression	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Condition aggravated	1 (<0.1%)	3 (0.2%)	0	4 (0.1%)
Death	14 (0.9%)	33 (2.6%)	1 (1.0%)	46 (1.7%)
Edema	1 (<0.1%)	1 (<0.1%)	1 (1.0%)	2 (<0.1%)
Edema peripheral	1 (<0.1%)	4 (0.3%)	0	5 (0.2%)
Exercise tolerance decreased	1 (<0.1%)	0	0	1 (<0.1%)
Fatigue	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
General physical health deterioration	4 (0.3%)	5 (0.4%)	0	8 (0.3%)
Inflammation	1 (<0.1%)	0	0	1 (<0.1%)
Mucous membrane disorder	1 (<0.1%)	0	0	1 (<0.1%)
Multimorbidity	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Multiple organ dysfunction syndrome	6 (0.4%)	3 (0.2%)	0	9 (0.3%)
Organ failure	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Pain	0	3 (0.2%)	0	3 (0.1%)
Pyrexia	2 (0.1%)	1 (<0.1%)	0	3 (0.1%)
Sudden cardiac death	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Hepatobiliary disorders	2 (0.1%)	2 (0.2%)	0	4 (0.1%)
Cholecystitis	0	1 (<0.1%)	0	1 (<0.1%)
Cholestasis	0	1 (<0.1%)	0	1 (<0.1%)
Hepatic cirrhosis	2 (0.1%)	0	0	2 (<0.1%)
Hepatomegaly	0	1 (<0.1%)	0	1 (<0.1%)
Jaundice	1 (<0.1%)	0	0	1 (<0.1%)
Portal vein thrombosis	1 (<0.1%)	0	0	1 (<0.1%)
Infections and infestations	19 (1.2%)	12 (1.0%)	2 (2.0%)	31 (1.1%)
Abdominal sepsis	1 (<0.1%)	0	0	1 (<0.1%)
Abdominal wall abscess	0	1 (<0.1%)	0	1 (<0.1%)
Candida infection	1 (<0.1%)	0	0	1 (<0.1%)
Clostridium difficile infection	1 (<0.1%)	0	0	1 (<0.1%)
Fungal infection	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Infective exacerbation of chronic obstructive airways disease	2 (0.1%)	1 (<0.1%)	0	2 (<0.1%)
Peritonitis	1 (<0.1%)	0	1 (1.0%)	2 (<0.1%)
Peritonsillar abscess	0	1 (<0.1%)	0	1 (<0.1%)
Pneumonia	7 (0.5%)	4 (0.3%)	0	11 (0.4%)
Pneumonia staphylococcal	1 (<0.1%)	0	0	1 (<0.1%)
Post procedural sepsis	1 (<0.1%)	0	0	1 (<0.1%)
Sepsis	5 (0.3%)	5 (0.4%)	1 (1.0%)	11 (0.4%)
Septic shock	2 (0.1%)	0	0	2 (<0.1%)
Upper respiratory tract infection	0	0	1 (1.0%)	1 (<0.1%)
Urosepsis	0	1 (<0.1%)	0	1 (<0.1%)
Injury, poisoning and procedural complications	6 (0.4%)	6 (0.5%)	1 (1.0%)	12 (0.4%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Anastomotic leak	1 (<0.1%)	0	1 (1.0%)	2 (<0.1%)
Fall	2 (0.1%)	4 (0.3%)	0	5 (0.2%)
Femur fracture	1 (<0.1%)	0	0	1 (<0.1%)
Fracture	1 (<0.1%)	0	0	1 (<0.1%)
Overdose	1 (<0.1%)	0	0	1 (<0.1%)
Poisoning	0	1 (<0.1%)	0	1 (<0.1%)
Postoperative renal failure	0	1 (<0.1%)	0	1 (<0.1%)
Subdural hematoma	0	1 (<0.1%)	0	1 (<0.1%)
Subdural hemorrhage	0	1 (<0.1%)	0	1 (<0.1%)
Thermal burn	1 (<0.1%)	0	0	1 (<0.1%)
Investigations	2 (0.1%)	3 (0.2%)	1 (1.0%)	6 (0.2%)
Blood creatinine increased	1 (<0.1%)	0	0	1 (<0.1%)
Body temperature increased	1 (<0.1%)	0	0	1 (<0.1%)
C-reactive protein increased	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Hemoglobin abnormal	0	1 (<0.1%)	0	1 (<0.1%)
Inflammatory marker increased	0	0	1 (1.0%)	1 (<0.1%)
Procalcitonin increased	1 (<0.1%)	0	0	1 (<0.1%)
Troponin T increased	1 (<0.1%)	0	0	1 (<0.1%)
Weight decreased	0	2 (0.2%)	0	2 (<0.1%)
Metabolism and nutrition disorders	5 (0.3%)	3 (0.2%)	1 (1.0%)	8 (0.3%)
Cachexia	1 (<0.1%)	1 (<0.1%)	1 (1.0%)	3 (0.1%)
Dehydration	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Hyponatremia	1 (<0.1%)	0	0	1 (<0.1%)
Lactic acidosis	1 (<0.1%)	0	0	1 (<0.1%)
Marasmus	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Protein deficiency	0	0	1 (1.0%)	1 (<0.1%)
Musculoskeletal and connective tissue disorders	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Back pain	1 (<0.1%)	0	0	1 (<0.1%)
Bone pain	0	1 (<0.1%)	0	1 (<0.1%)
Muscular weakness	0	1 (<0.1%)	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (1.2%)	30 (2.4%)	4 (3.9%)	51 (1.9%)
Adenocarcinoma	1 (<0.1%)	0	1 (1.0%)	2 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Bladder cancer	0	2 (0.2%)	0	2 (<0.1%)
Bladder cancer recurrent	0	1 (<0.1%)	0	1 (<0.1%)
Bronchial carcinoma	3 (0.2%)	12 (1.0%)	0	15 (0.5%)
Colon cancer	1 (<0.1%)	1 (<0.1%)	1 (1.0%)	3 (0.1%)
Esophageal cancer metastatic	1 (<0.1%)	0	0	1 (<0.1%)
Gastric cancer	1 (<0.1%)	0	0	1 (<0.1%)
Hepatic cancer	1 (<0.1%)	0	0	1 (<0.1%)
Hepatocellular carcinoma	0	1 (<0.1%)	0	1 (<0.1%)
Lip and/or oral cavity cancer	0	1 (<0.1%)	0	1 (<0.1%)
Lung adenocarcinoma	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Lung carcinoma cell type unspecified recurrent	1 (<0.1%)	0	0	1 (<0.1%)
Lung neoplasm malignant	1 (<0.1%)	3 (0.2%)	0	3 (0.1%)
Malignant neoplasm of pleura	1 (<0.1%)	0	0	1 (<0.1%)
Malignant neoplasm of unknown primary site	0	1 (<0.1%)	0	1 (<0.1%)
Malignant peritoneal neoplasm	1 (<0.1%)	0	0	1 (<0.1%)
Metastases to abdominal wall	0	1 (<0.1%)	0	1 (<0.1%)
Metastases to bone	0	2 (0.2%)	0	2 (<0.1%)
Metastases to central nervous system	0	1 (<0.1%)	1 (1.0%)	2 (<0.1%)
Metastases to kidney	0	1 (<0.1%)	0	1 (<0.1%)
Metastases to liver	1 (<0.1%)	3 (0.2%)	1 (1.0%)	5 (0.2%)
Metastases to lung	0	1 (<0.1%)	0	1 (<0.1%)
Metastases to lymph nodes	0	1 (<0.1%)	0	1 (<0.1%)
Metastases to spine	0	1 (<0.1%)	0	1 (<0.1%)
Metastasis	0	1 (<0.1%)	0	1 (<0.1%)
Metastatic bronchial carcinoma	2 (0.1%)	0	1 (1.0%)	3 (0.1%)
Metastatic gastric cancer	0	1 (<0.1%)	0	1 (<0.1%)
Non-small cell lung cancer	1 (<0.1%)	0	0	1 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Non-small cell lung cancer metastatic	0	0	1 (1.0%)	1 (<0.1%)
Oncologic complication	0	1 (<0.1%)	1 (1.0%)	2 (<0.1%)
Pancreatic carcinoma	3 (0.2%)	2 (0.2%)	0	5 (0.2%)
Prostate cancer metastatic	0	1 (<0.1%)	0	1 (<0.1%)
Rectal cancer	0	1 (<0.1%)	0	1 (<0.1%)
Renal cell carcinoma	0	1 (<0.1%)	0	1 (<0.1%)
Small cell lung cancer	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Small cell lung cancer metastatic	1 (<0.1%)	0	0	1 (<0.1%)
Small intestine carcinoma	0	0	1 (1.0%)	1 (<0.1%)
T-cell lymphoma	0	1 (<0.1%)	0	1 (<0.1%)
Urethral cancer metastatic	1 (<0.1%)	0	0	1 (<0.1%)
Nervous system disorders	9 (0.6%)	7 (0.6%)	0	16 (0.6%)
Akinesia	1 (<0.1%)	0	0	1 (<0.1%)
Amyotrophic lateral sclerosis	1 (<0.1%)	0	0	1 (<0.1%)
Aphasia	1 (<0.1%)	0	0	1 (<0.1%)
Basal ganglia hemorrhage	1 (<0.1%)	0	0	1 (<0.1%)
Brain compression	1 (<0.1%)	0	0	1 (<0.1%)
Brain injury	0	1 (<0.1%)	0	1 (<0.1%)
Brain stem ischemia	0	1 (<0.1%)	0	1 (<0.1%)
Cerebral infarction	2 (0.1%)	0	0	2 (<0.1%)
Cerebrovascular accident	2 (0.1%)	2 (0.2%)	0	4 (0.1%)
Cognitive disorder	1 (<0.1%)	0	0	1 (<0.1%)
Dementia	1 (<0.1%)	0	0	1 (<0.1%)
Hemiparesis	1 (<0.1%)	0	0	1 (<0.1%)
Hepatic encephalopathy	1 (<0.1%)	0	0	1 (<0.1%)
Myasthenia gravis	0	1 (<0.1%)	0	1 (<0.1%)
Paraparesis	0	1 (<0.1%)	0	1 (<0.1%)
Senile dementia	0	1 (<0.1%)	0	1 (<0.1%)
Somnolence	1 (<0.1%)	0	0	1 (<0.1%)
Syncope	1 (<0.1%)	0	0	1 (<0.1%)
Psychiatric disorders	2 (0.1%)	2 (0.2%)	0	3 (0.1%)
Completed suicide	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Depression	1 (<0.1%)	2 (0.2%)	0	2 (<0.1%)
Disorientation	1 (<0.1%)	0	0	1 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Renal and urinary disorders	5 (0.3%)	10 (0.8%)	1 (1.0%)	15 (0.5%)
Acute kidney injury	3 (0.2%)	2 (0.2%)	1 (1.0%)	5 (0.2%)
Chromaturia	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Chronic kidney disease	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Oliguria	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Renal failure	2 (0.1%)	4 (0.3%)	0	6 (0.2%)
Urinary incontinence	0	2 (0.2%)	0	2 (<0.1%)
Urinary retention	0	1 (<0.1%)	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	29 (1.9%)	25 (2.0%)	4 (3.9%)	54 (2.0%)
Acute respiratory distress syndrome	1 (<0.1%)	0	0	1 (<0.1%)
Acute respiratory failure	2 (0.1%)	2 (0.2%)	0	3 (0.1%)
Asphyxia	1 (<0.1%)	0	0	1 (<0.1%)
Asthma	1 (<0.1%)	0	0	1 (<0.1%)
Bronchospasm	1 (<0.1%)	0	0	1 (<0.1%)
Chronic obstructive pulmonary disease	13 (0.9%)	8 (0.6%)	1 (1.0%)	19 (0.7%)
Cough	2 (0.1%)	1 (<0.1%)	0	3 (0.1%)
Dyspnea	3 (0.2%)	8 (0.6%)	1 (1.0%)	11 (0.4%)
Dyspnea at rest	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Dyspnea exertional	2 (0.1%)	1 (<0.1%)	1 (1.0%)	4 (0.1%)
Emphysema	1 (<0.1%)	1 (<0.1%)	1 (1.0%)	3 (0.1%)
Hypercapnia	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Hypocapnia	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Hypoxia	3 (0.2%)	1 (<0.1%)	0	3 (0.1%)
Lung infiltration	1 (<0.1%)	0	0	1 (<0.1%)
Orthopnea	0	1 (<0.1%)	0	1 (<0.1%)
Pleural effusion	2 (0.1%)	0	0	2 (<0.1%)
Pneumonia aspiration	1 (<0.1%)	0	0	1 (<0.1%)
Pneumothorax	1 (<0.1%)	0	1 (1.0%)	2 (<0.1%)
Productive cough	0	1 (<0.1%)	0	1 (<0.1%)
Pulmonary embolism	3 (0.2%)	2 (0.2%)	0	5 (0.2%)
Pulmonary fibrosis	1 (<0.1%)	0	0	1 (<0.1%)
Pulmonary edema	2 (0.1%)	1 (<0.1%)	0	3 (0.1%)
Respiratory failure	9 (0.6%)	3 (0.2%)	0	11 (0.4%)
Rhonchi	1 (<0.1%)	0	0	1 (<0.1%)
Sputum discoloured	1 (<0.1%)	1 (<0.1%)	0	1 (<0.1%)
Wheezing	1 (<0.1%)	0	0	1 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Skin and subcutaneous tissue disorders	0	2 (0.2%)	0	2 (<0.1%)
Cold sweat	0	1 (<0.1%)	0	1 (<0.1%)
Hyperhidrosis	0	1 (<0.1%)	0	1 (<0.1%)
Vascular disorders	4 (0.3%)	7 (0.6%)	1 (1.0%)	12 (0.4%)
Aortic aneurysm rupture	0	2 (0.2%)	0	2 (<0.1%)
Aortic dissection	1 (<0.1%)	0	0	1 (<0.1%)
Circulatory collapse	0	2 (0.2%)	1 (1.0%)	3 (0.1%)
Granulomatosis with polyangiitis	1 (<0.1%)	0	0	1 (<0.1%)
Hypotension	1 (<0.1%)	0	0	1 (<0.1%)
Infarction	1 (<0.1%)	0	0	1 (<0.1%)
Pallor	0	2 (0.2%)	0	2 (<0.1%)
Peripheral arterial occlusive disease	0	1 (<0.1%)	0	1 (<0.1%)
Peripheral coldness	0	1 (<0.1%)	0	1 (<0.1%)

Source: Argus Table 2

N is the number of patients with at least one adverse event

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist. Note that the 'other' group reports events in patients receiving Novartis therapies not in scope for this report.

2.2 Serious adverse events of special interest

Table 2-2 Serious adverse events of special interest (for glycopyrronium bromide) (by patients) - overall, and by MedDRA class and preferred term (Argus listing)

	Glycopyrronium bromide (N=1527)	Other anti-obstructive therapy (N=102)	Total (N=1624)
Number (%) of patients with at least one event	6 (0.4%)	1 (1.0%)	7 (0.4%)
Severe renal impairment	6 (0.4%)	1 (1.0%)	7 (0.4%)
Blood urea increased	1 (<0.1%)	0	1 (<0.1%)
Oliguria	2 (0.1%)	0	2 (0.1%)
Renal failure	4 (0.3%)	1 (1.0%)	5 (0.3%)

Source: Argus Table 3.2-3.1

N is the number of patients with at least one adverse event. Note that the 'other' group reports events in patients receiving Novartis therapies not in scope for this report.

Table 2-3 Serious adverse events of special interest (for LABA/LAMA) (by patients) - overall, and by MedDRA class and preferred term (Argus listing)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Number (%) of patients with at least one event	122 (8.0%)	102 (8.1%)	8 (7.8%)	222 (8.1%)
Asthma/Bronchospasm	2 (0.1%)	0	0	2 (<0.1%)
Asthma	1 (<0.1%)	0	0	1 (<0.1%)
Bronchospasm	1 (<0.1%)	0	0	1 (<0.1%)
Cardiac arrhythmia	29 (1.9%)	22 (1.7%)	4 (3.9%)	54 (2.0%)
Arrhythmia	5 (0.3%)	3 (0.2%)	0	8 (0.3%)
Atrial fibrillation	14 (0.9%)	12 (1.0%)	3 (2.9%)	28 (1.0%)
Atrioventricular block	1 (<0.1%)	0	0	1 (<0.1%)
Atrioventricular block complete	0	1 (<0.1%)	0	1 (<0.1%)
Atrioventricular block first degree	0	1 (<0.1%)	0	1 (<0.1%)
Bradyarrhythmia	1 (<0.1%)	0	0	1 (<0.1%)
Bundle branch block left	2 (0.1%)	0	0	2 (<0.1%)
Conduction disorder	1 (<0.1%)	0	0	1 (<0.1%)
Heart rate irregular	0	1 (<0.1%)	0	1 (<0.1%)
Sinus bradycardia	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Sinus tachycardia	2 (0.1%)	1 (<0.1%)	1 (1.0%)	4 (0.1%)
Sudden cardiac death	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Supraventricular extrasystoles	2 (0.1%)	0	0	2 (<0.1%)
Supraventricular tachycardia	1 (<0.1%)	0	0	1 (<0.1%)
Tachyarrhythmia	2 (0.1%)	3 (0.2%)	0	5 (0.2%)
Ventricular extrasystoles	2 (0.1%)	0	0	2 (<0.1%)
Ventricular fibrillation	4 (0.3%)	0	0	4 (0.1%)
Ventricular tachycardia	3 (0.2%)	0	0	3 (0.1%)
Cardiac failure	43 (2.8%)	25 (2.0%)	1 (1.0%)	65 (2.4%)
Cardiac failure	32 (2.1%)	13 (1.0%)	1 (1.0%)	43 (1.6%)
Cardiac failure acute	0	1 (<0.1%)	0	1 (<0.1%)
Cardiac failure chronic	1 (<0.1%)	0	0	1 (<0.1%)
Cardiac failure congestive	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Cardiogenic shock	2 (0.1%)	1 (<0.1%)	0	3 (0.1%)
Cardiorenal syndrome	1 (<0.1%)	0	0	1 (<0.1%)
Cor pulmonale	3 (0.2%)	1 (<0.1%)	0	3 (0.1%)
Cor pulmonale chronic	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Left ventricular failure	2 (0.1%)	2 (0.2%)	0	4 (0.1%)
Pulmonary edema	3 (0.2%)	4 (0.3%)	0	7 (0.3%)
Right ventricular failure	2 (0.1%)	2 (0.2%)	0	4 (0.1%)
Cerebrovascular events	22 (1.4%)	16 (1.3%)	1 (1.0%)	38 (1.4%)
Basal ganglia hemorrhage	1 (<0.1%)	0	0	1 (<0.1%)
Brain stem infarction	1 (<0.1%)	0	0	1 (<0.1%)
Brain stem ischemia	0	1 (<0.1%)	0	1 (<0.1%)
Carotid artery stenosis	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
Cerebral infarction	3 (0.2%)	5 (0.4%)	0	8 (0.3%)
Cerebral ischemia	0	1 (<0.1%)	0	1 (<0.1%)
Cerebrovascular accident	9 (0.6%)	6 (0.5%)	1 (1.0%)	15 (0.5%)
Cerebrovascular disorder	0	1 (<0.1%)	0	1 (<0.1%)
Embolic cerebral infarction	0	1 (<0.1%)	0	1 (<0.1%)
Hemorrhagic stroke	0	1 (<0.1%)	0	1 (<0.1%)
Hypoxic-ischaemic encephalopathy	1 (<0.1%)	0	0	1 (<0.1%)
Lacunar infarction	1 (<0.1%)	0	0	1 (<0.1%)
Subarachnoid hemorrhage	1 (<0.1%)	0	0	1 (<0.1%)
Subdural hematoma	0	2 (0.2%)	0	2 (<0.1%)
Subdural hemorrhage	0	1 (<0.1%)	0	1 (<0.1%)
Thrombotic cerebral infarction	1 (<0.1%)	0	0	1 (<0.1%)
Transient ischemic attack	4 (0.3%)	1 (<0.1%)	0	5 (0.2%)
Diabetes mellitus/ hyperglycemia	13 (0.9%)	18 (1.4%)	2 (2.0%)	31 (1.1%)
Blood glucose increased	3 (0.2%)	2 (0.2%)	0	4 (0.1%)
Diabetes mellitus	4 (0.3%)	3 (0.2%)	0	6 (0.2%)
Diabetes mellitus inadequate control	1 (<0.1%)	0	0	1 (<0.1%)
Ketoacidosis	0	1 (<0.1%)	0	1 (<0.1%)
Type 2 diabetes mellitus	6 (0.4%)	13 (1.0%)	2 (2.0%)	21 (0.8%)
Ischemic heart disease	20 (1.3%)	24 (1.9%)	0	42 (1.5%)
Angina pectoris	3 (0.2%)	13 (1.0%)	0	15 (0.5%)
Angina unstable	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Arteriosclerosis coronary artery	3 (0.2%)	0	0	3 (0.1%)
Coronary artery disease	15 (1.0%)	14 (1.1%)	0	28 (1.0%)

	Glycopyrronium bromide (N=1527)	LABA/LAMA fixed combination (N=1262)	Other anti-obstructive therapy (N=102)	Total (N=2756)
Coronary artery insufficiency	0	2 (0.2%)	0	2 (<0.1%)
Coronary artery restenosis	1 (<0.1%)	0	0	1 (<0.1%)
Coronary artery stenosis	1 (<0.1%)	3 (0.2%)	0	3 (0.1%)
Myocardial ischemia	0	1 (<0.1%)	0	1 (<0.1%)
Stress cardiomyopathy	0	1 (<0.1%)	0	1 (<0.1%)
Myocardial infarction	30 (2.0%)	20 (1.6%)	0	49 (1.8%)
Acute coronary syndrome	1 (<0.1%)	0	0	1 (<0.1%)
Acute myocardial infarction	11 (0.7%)	3 (0.2%)	0	14 (0.5%)
Angina unstable	1 (<0.1%)	2 (0.2%)	0	3 (0.1%)
Blood creatine phosphokinase MB increased	1 (<0.1%)	0	0	1 (<0.1%)
Coronary artery occlusion	0	1 (<0.1%)	0	1 (<0.1%)
Coronary bypass thrombosis	1 (<0.1%)	0	0	1 (<0.1%)
Myocardial infarction	14 (0.9%)	14 (1.1%)	0	27 (1.0%)
Troponin T increased	1 (<0.1%)	0	0	1 (<0.1%)
Narrow angle glaucoma	3 (0.2%)	2 (0.2%)	0	4 (0.1%)
Glaucoma	2 (0.1%)	1 (<0.1%)	0	2 (<0.1%)
Intraocular pressure increased	1 (<0.1%)	0	0	1 (<0.1%)
Vision blurred	1 (<0.1%)	1 (<0.1%)	0	2 (<0.1%)
QT prolongation	3 (0.2%)	0	0	3 (0.1%)
Ventricular tachycardia	3 (0.2%)	0	0	3 (0.1%)

Source: Argus 3.2-3.2

N is the number of patients with at least one adverse event.

LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist. Note that the 'other' group reports events in patients receiving Novartis therapies not in scope for this report.