STATISTICAL ANALYSIS PLAN

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Study Number:	Study 0167
Study Title:	A Phase 3b, 42-day, Randomized, Double-Blind, Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized Revefenacin and Nebulized Formoterol Fumarate [redacted] Administered in Sequence and as a Combined Solution in Subjects with Chronic Obstructive Pulmonary Disease
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CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

revefenacin, Study 0167

A Phase 3b, 42-day, Randomized, Double-Blind, Parallel Group Study to Evaluate the Safety and Tolerability of Nebulized Revefenacin and Nebulized Formoterol Fumarate (PERFOROMIST®) Administered in Sequence and as a Combined Solution in Subjects with Chronic Obstructive Pulmonary Disease

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Author: [redacted]
Theravance Biopharma US, Inc.

Reviewer: [redacted]
Theravance Biopharma US, Inc.

Reviewer: [redacted]
Theravance Biopharma US, Inc.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
ABS	absolute
ADaM	Analysis data model
AE	adverse event
ALB	albuterol
AUC	area under the curve
AR	autoregressive
BDI	Baseline Dyspnea Index
BID	twice-daily
BLQ	below level of quantification
BLS MEAN	Binomial least square mean reporting method
BMI	body mass index
BP	blood pressure
CAT	COPD Assessment Tool
CCQ	Clinical COPD Questionnaire
CEC	cardiovascular event committee
CFB	change from baseline
CI	confidence interval
C	continuous reporting method
COPD	chronic obstructive pulmonary disease
CRO	contract research organization
CSR	clinical study report
D	day(s)
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ePFM	electronic peak flow meter
F	frequency reporting method
FVC	forced vital capacity
FEV_1	forced expiratory volume in one second
GERD	gastrointestinal reflux disease
GOLD	Global initiative for chronic obstructive lung disease
H	hour(s)
HR	heart rate
ICS	inhaled corticosteroid
IPR	ipratropium
ITT	intent-to-treat
KDE	kernel density estimation
KM	Kaplan Meier reporting method

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LS	least-square
MAR	missing at random
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MIP	maximum inspiratory pressure
MF	multiple frequency reporting method
mL	milliliters
mMRC	Modified Medical Research Council Dyspnea Scale
MNAR	missing not at random
NC	non-calculable
NLS MEAN	normal least square mean reporting method
NQ	non-quantifiable
PD	pre-dose
PIFR	peak inspiratory flow rate
PK	pharmacokinetic
PP	per-protocol
QD	once-daily
REV	revefenacin
RMMM	repeated measures mixed effect model
SAE	serious adverse event
SAP	statistical analysis plan
SCR	screening
SOC	system organ class
TDI	Transitional Dyspnea Index
TEAE	treatment-emergent adverse event
UN	unstructured
WM	weighted mean
WHODD	World Health Organization Drug dictionary

1 INTRODUCTION

This document outlines the initial plan for the summarization and analysis of clinical data collected in the Phase 3b Study 0167 for revefenacin. This document describes the a priori plan for analysis. Once the analysis is in progress, it may become apparent from the data that the planned analysis should be modified. Any substantive modification to the original analysis plan will be identified in the clinical study report (CSR).

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is:

- To characterize the safety and tolerability of once-daily revefenacin inhalation solution when dosed sequentially with twice-daily formoterol inhalation solution [redacted] compared to monotherapy [redacted], in a population of patients with moderate to very severe COPD over 21 days.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To characterize the safety and tolerability of dosing a mixture of revefenacin inhalation solution and formoterol compared to dosing a mixture of placebo and formoterol in a population of patients with moderate to very severe COPD over 21 days.

2.3 Exploratory Objectives

The exploratory objectives of the study are:

- [redacted]

3 OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, active-controlled, parallel-group study. Each subject will receive treatment twice daily for a total of 42 days. There will be two main treatment periods (Period 1 – Day 1 to 21; Period 2 – Day 22 to 42) and each period will have two treatment groups (Figure 1):

Period 1 (Day 1 to 21):

Treatment Group 1 (Group 1-1): Placebo revefenacin and formoterol 20 mcg sequentially administered via nebulizer in the morning. Placebo will be administered first (as a 3 mL solution) and then formoterol will be administered (as a 2 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.

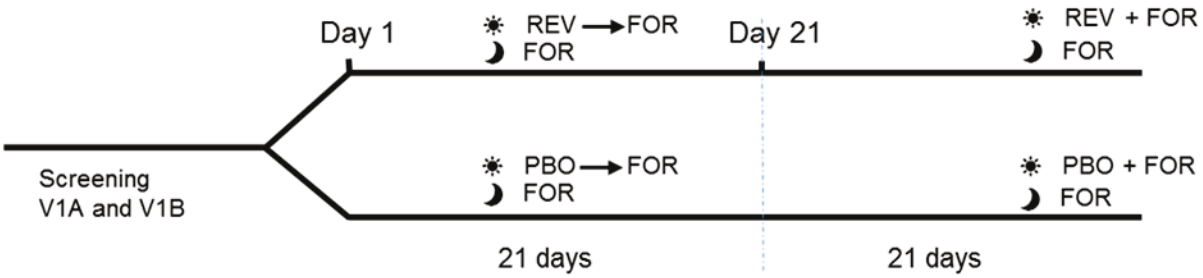
Treatment Group 2 (Group 1-2): Revefenacin 175 mcg and formoterol 20 mcg sequentially administered via nebulizer in the morning. Revefenacin will be administered first (as a 3 mL solution) and then formoterol will be administered (as a 2 mL solution). Formoterol will be administered again in the evening.

Period 2 (Day 22 to 42):

Treatment Group 1 (Group 2-1): After a 21 days period subjects on placebo revefenacin and formoterol 20 mcg will be dosed for 21 days with a combination of placebo revefenacin and formoterol 20 mcg administered as a combined solution and administered via a single nebulization (as a 5 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.

Treatment Group 2 (Group 2-2): After a 21 days period subjects on revefenacin 175 mcg and formoterol 20 mcg will be dosed for 21 days with a combination of revefenacin 175 mcg and formoterol 20 mcg administered as a combined solution and administered via a single nebulization (as a 5 mL solution). Formoterol 20 mcg will be administered (as a 2 mL solution) again in the evening.

Figure 1: Study Design Schematic



All treatments will be administered via a [redacted] jet nebulizer using the [redacted] compressor.

Subjects who are currently on a stable dose of inhaled steroids will continue the use of these medications throughout the course of the study. Subjects who are currently using LABA monotherapy (other than formoterol) will be switched to formoterol for the duration of the study. Those subjects on ICS/LABA fixed dose combinations must be able to switch to an identical dose of ICS monotherapy (or equivalent) to be eligible to enroll in the study.

Screening will involve either one or two visits, depending on whether a washout period is required. The first visit will be an Initial Screening Visit (Visit 1A) when informed consent will be obtained and the subject's existing COPD medication will be assessed to decide whether any adjustments are required to comply with the requirements of the protocol. The subject will start a washout period only after signing the informed consent form.

After completing the washout (if required), the subject will return for further screening assessments, including an Ipratropium Reversibility Visit (Visit 1B), ECGs and vitals. It is only necessary to conduct the Initial Screening Visit (Visit 1A) and Ipratropium Reversibility Visit (Visit 1B) as separate visits if a washout is required. If a washout period is not required, these two visits may be performed as one visit.

If a washout period is required, the time from the Initial Screening Visit (Visit 1A) to Visit 1B will be at least 48 hours and no longer than 7 days.

At the Ipratropium Reversibility Visit (Visit 1B), the FEV_1 response to a nebulized dose of ipratropium (500 mcg) will be tested to determine the subject's reversibility status and GOLD category for airflow limitation.

All remaining inclusion and exclusion criteria will be reviewed at this Visit 1B.

All subjects will be issued study-specific rescue medication (albuterol metered-dose inhaler (MDI) for use throughout the screening period. Subjects will be advised to avoid use of their rescue albuterol medication for at least 6 hours prior to each visit.

Subjects will come in 2 to 7 days after Screening for Visit 2 (Day 1 of dosing). Eligible subjects will be randomized to one of two treatment groups in the study.

The treatment period will involve 3 visits:

- Visit 2 (Day 1)
- Visit 3 (Day 21)
- Visit 4 (Day 42)

On visit days, subjects will attend the clinic for assessment of pre-dose vital signs, labs, ECGs, [redacted], and review of AEs and concomitant medications. Subjects will administer study medication under supervision at all clinic visits to assess nebulizer technique and to correct and retrain as required. ECGs and vital signs will be measured 60 minutes pre-dose and 10 minutes post-dose at these visits. [redacted] On all visits, subjects will return the unused vials of study medication and the study specific rescue medication they have been issued.

At Visit 3 (Day 21), subjects will return for in-clinic dosing [redacted]. Visit 3 will have a visit window of ±7 days. ECGs will be performed after the final supervised dose of the sequential administration of revefenacin (or placebo) and then formoterol at 10 minutes postdose, which should be near the peak plasma level of formoterol. The site will instruct the patient on how to mix the two solutions of study medication as a combined solution in the nebulizer. Subjects will administer the study drugs as a combined solution for the remainder of the treatment period (Day 22 to 42).

Subjects will return to clinic for Visit 4 (Day 42) for in-clinic supervised dosing [redacted]. Visit 4 will have a visit window of ±7 days. ECGs will be performed after the supervised final dose of the combined administration of revefenacin (or placebo) plus formoterol at 10 minutes postdose, which should be near the peak plasma level of formoterol.

Visit 5 will be a follow up phone call to take place 7 (±2) days after Visit 4 (Day 42) to assess the subject for any adverse events or changes in concomitant medications.

Subjects who experience moderate or severe acute exacerbations of COPD (AECOPD) will be not be allowed to continue the study and will be withdrawn from the study.

4 SAMPLE SIZE AND POWER

[redacted]

5 STUDY ENDPOINTS

All study endpoints and/or assessments include an evaluation type (i.e., absolute value, change from baseline), an ADAM Type, either derived from raw data (i.e., CRF or Lab-type data), an evaluation window (i.e., screening, Day 1, Days 1-42), and a summary type (i.e., continuous, frequency, normal least squares).

The primary endpoints of this study will assess the long-term safety and tolerability of revefenacin in the treatment of COPD:

- Frequency and severity of adverse events, including COPD exacerbations
- Vital signs
- Clinical laboratory evaluations
- 12-lead ECG changes from baseline
- Heart rate (as measured by ECG)
- [redacted]

5.1 Screening Endpoints

The following screening endpoints will be summarized. The screening endpoints will be summarized by two treatment groups in Period 1 (Group 1-1 and Group 1-2).

Table 1: Screening Endpoints

Endpoint	Evaluation Type	ADaM Type	Reporting Window	Summary Type(s)
ipratropium reversibility	[redacted]	[redacted]	[redacted]	[redacted]
ipratropium reversibility	[redacted]	[redacted]	[redacted]	[redacted]
post ipratropium predicted normal FEV_1	[redacted]	[redacted]	[redacted]	[redacted]
post ipratropium percent predicted FEV_1	[redacted]	[redacted]	[redacted]	[redacted]
post ipratropium predicted normal FVC	[redacted]	[redacted]	[redacted]	[redacted]
post ipratropium percent predicted FVC	[redacted]	[redacted]	[redacted]	[redacted]
post ipratropium FEV_1/FVC ratio	[redacted]	[redacted]	[redacted]	[redacted]

Note: SCR: screening, CFB: change from baseline, ABS: absolute value or observed value

Note: For summary types, see Appendix 1

Note: Reversible definition: CFB of ≥12% and ≥200 mL

5.2 General Endpoints

The following general endpoints will be summarized in the following table. The general endpoints will be summarized by two treatment groups in Period 1 (Group 1-1 and Group 1-2).

Table 2: Table of General Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window
age	[redacted]	[redacted]	[redacted]
sex	[redacted]	[redacted]	[redacted]
ethnicity	[redacted]	[redacted]	[redacted]
race	[redacted]	[redacted]	[redacted]
height	[redacted]	[redacted]	[redacted]
weight	[redacted]	[redacted]	[redacted]
BMI	[redacted]	[redacted]	[redacted]
smoking Status	[redacted]	[redacted]	[redacted]
Maximum number of packs per day	[redacted]	[redacted]	[redacted]
Number of years smoked	[redacted]	[redacted]	[redacted]
Number of pack-years	[redacted]	[redacted]	[redacted]
Age (≤65, >65)	[redacted]	[redacted]	[redacted]
concurrent ICS use	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
duration of COPD	[redacted]	[redacted]	[redacted]
subjects with a history of supplemental oxygen	[redacted]	[redacted]	[redacted]
subjects with a history of respiratory infections	[redacted]	[redacted]	[redacted]
Exacerbations in prior year	[redacted]	[redacted]	[redacted]
Exacerbations requiring hospitalization in prior year	[redacted]	[redacted]	[redacted]
Cardiovascular risk factor	[redacted]	[redacted]	[redacted]
GOLD category	[redacted]	[redacted]	[redacted]
GOLD severity of airflow limitation	[redacted]	[redacted]	[redacted]
primary reason for study drug discontinuation	[redacted]	[redacted]	[redacted]
subject disposition	[redacted]	[redacted]	[redacted]
subjects in Safety Group	[redacted]	[redacted]	[redacted]

Table 2: Table of General Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window
subjects in ITT Group	[redacted]	[redacted]	[redacted]
subjects in PP Group	[redacted]	[redacted]	[redacted]

Note: D: day, CFB: change from baseline, ABS: absolute value or observed value;
CAT: categorical/binary
Note: summary type, see Appendix 1

5.3 Safety Endpoints

Safety variables to be summarized include adverse events, vital signs, clinical laboratory evaluations (i.e., hematology and serum chemistry), 12-lead ECG changes from baseline, and heart rate (as measured by ECG). Vital signs will be summarized in terms of observed values and changes from baseline. The safety endpoints will be summarized by four treatment groups (Group 1-1, Group 1-2, Group 2-1, and Group 2-2).

5.4 Other Endpoints

[redacted]

Table 3: Table of Other Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6 GENERAL ANALYSIS CONSIDERATIONS

6.1 Global Definitions and Conventions

All data from scheduled and unscheduled visits will be presented in the subject listings; however, unless noted otherwise, only data from appropriately windowed visits (Section 6.3) will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.2 Baseline Definition

The following table indicates the baseline to be used in the analysis.

Table 4: Baseline Specifications for Specific Variables

Parameter	No Baseline	Visit 1B	Visit 2 (Day 1-PD)
[redacted]			[redacted]
[redacted]		[redacted]	
[redacted]		[redacted]	
Vital signs and ECG			X

[redacted]

6.3 Analysis Windows

All assessments will be summarized using analysis windows. The terminology of unscheduled will be applied to assessments that are outside an analysis window regardless, of the nominal label associated with the assessments in the EDC system.

All data (scheduled and unscheduled visits) will be presented in the subject listings; however, unless noted otherwise, only data from assessments within analysis windows will be included in the summaries, statistical analysis, and calculation of derived parameters.

Selection of Data in the Event of Multiple Records in an Analysis Window

In general, if multiple, valid, non-missing observations exist at a visit or collection time point then records will be chosen based on the following:

- The record closest to the nominal time point in question, or,
- The later record if the two visits are equidistant from the time point, or,
- The average (arithmetic mean) if there is more than one record at the time point (generally applies to assessments done in triplicate).

The following visit windows will be used in the summary of clinical data.

Table 5: Visit Analysis Windows

Nominal Visit	Nominal Day	Start (days)	Stop (days)
2	1	1	1
3	21	14	28
4	42	35	49

Safety Endpoints

The following windows summarize the definition of treatment-emergent.

Table 6: Analysis Windows: Treatment Emergent Events

Window	Start	Stop
Adverse events	Signing of ICF	Maximum of Follow-up visit or Last dose + 7 days
Treatment-emergent Adverse events, ECGs and Labs	Post first dose	Last dose + 7 days
Concomitant Medications	Post first dose	Last dose + 24 hours

Table 7: Analysis Windows: Vital Signs and ECGs

Window	Start	Stop
“60 minutes pre-dose” / “pre-dose”	-90	-30
“10 min post dose”	5	40

[redacted]

[redacted]

[redacted]

6.4 Missing Data

In general, it is not anticipated that there will be considerable missing data. In general, missing data will not be imputed. Missing data for the following specific endpoints will be handled as follows:

Adverse Events

For graded adverse event summaries, subjects with an AE and no grade on the CRF will be graded as severe.

For by relationship adverse event summaries, subjects with an AE and no relatedness on the CRF will be graded as "possibly/probably related".

Missing dates/time for Adverse Events and Concomitant Medications

Missing dates will be handled as follows:

- Complete missing start date will be imputed as the same as first dose date;
- Partial missing start date imputation:
  - Missing start day with same month as first dose: maximum day (1, first dose day);
  - Missing start day with different month as first dose: 1
  - Missing start month with same year as first dose: maximum (January, first dose month);
  - Missing start month with different year as first dose: January
- Complete missing stop date will be considered as ongoing and not imputed;
- Partial missing stop date imputation:
  - Missing stop day: last day of month;
  - Missing stop month with same year as last dose: minimum (December, last dose month);
  - Missing stop month with different year as last dose: December

Missing times will be handled as follows:

- If a start or stop time is missing, the start time is imputed as 1 minute after a.m. midnight (12:01) and stop time is imputed to be 1 min before p.m. midnight (23:59).

Laboratory Data

For laboratory data, a missing baseline value will be replaced with the last available assessment, generally the screening assessment. A retest value will be used if the first test is invalidated, e.g., specimen hemolyzed.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation/limit of detection (LOD) will be, in general, imputed as follows:

- A value that is 1 unit less than the LOD will be used for calculation of descriptive statistics if the data are reported in the form of "< x" (x is considered as the LOD). More specifically, x−1 is used for data summarization if the data are reported in the form of "< x"; and x.e where e = d−1, will be used for analysis if the data are reported in the form of "< x.d";
- The LOD will be used for calculation of descriptive statistics if the data is reported in the form of "≤x" or "≥x.

All Other Endpoints

In general, missing data will not be imputed. If a missing data method is used, it will be fully specified in the corresponding analysis section.

6.5 Adverse Events

Recorded adverse events will be mapped according to the MedDRA thesaurus by the data management CRO for this study, with Theravance Biopharma review and approval of the mappings. BioClinica will use MedDRA, version 18.1.

6.6 Medications

Recorded prior and concomitant medication names will be mapped according to the World Health Organization Drug Dictionary (WHODD) by the data management CRO for this study with Theravance Biopharma review and approval of the mappings.

For non-concomitant medication eCRFs that contain albuterol use information, e.g., study drug administration and in-clinic albuterol dosing forms, mapping will be conducted by Theravance Biopharma using the WHODD mapping.

The CRO will use the September 2015 version of the WHODD.

6.7 Medical History

Medical history will be mapped according to MedDRA version 18.1 and will be provided in listings. Select medical history will be summarized.

6.8 General Considerations for Summaries

Analyses and tabulations will generally be prepared using SAS®, version 9.4 or later.

Reporting Structures for Data Summary

Data will be summarized using the appropriate reporting structure as defined in Appendix 1.

Presenting Multiple Summaries on Same Table Summary

In summary tables where multiple single line frequency summaries are being presented, the "n line" can be suppressed in the individual summaries and presented at the top of the summary a single time.

Use of Evaluable N Terminology

The term "evaluable non-missing n" will only be used in summaries derived from model based analyses.

Ordering of Treatment Headers in Summary Tables

In General Analysis and Exposure Summaries, treatment headers in summary tables will be presented in the following order:

- Placebo – [redacted],
- Yupelri 175 mcg - [redacted]
- Total

In Safety and [redacted] Analysis Summaries, treatment groups will be presented in the following order (ordered as Group 1-1, Group 1-2, Group 2-1, Group 2-2):

- Placebo - [redacted], sequential,
- Yupelri 175 mcg - [redacted], sequential,
- Placebo + [redacted], combined
- Yupelri 175 mcg + [redacted], combined

Rounding

In general, the convention for rounding percentages is as follows:

- Values greater than or equal to x.x5 are rounded up,
- Values between 0 and less than x.x5 are rounded down,
- Values between –x.x5 and 0 are rounded up,
- Values less than or equal to –x.x5 are rounded down.

All rounding will occur in the last step of data summarization.

Significant Digits

Raw measurements will be reported the same as the data captured electronically or on the CRFs. Exceptions will be made for values reported with greater than 4 significant digits (round to 4 significant digits using a similar criterion as for percentages with the 5 in the last digit)).

The following significant digit convention will be used for the purposes of summarizing primarily lab data:

- Mean, median: +1 significant digit reported data,
- Standard deviation: +2 significant digits reported data,
- Minimum, maximum: 2 significant digits reported data,
- Percentages: +1 decimal place.

The following significant digit convention will be used for the purposes of summarizing spirometry data:

- Mean, median: 1 significant digit,
- Standard deviation: 2 significant digits,
- Minimum, maximum: 1 significant digit,
- Percentages: 1 decimal place.

P-values

No p-values will be reported in this study.

Colors in Figures

In figures that only contain the 4 treatment groups, the following colors will be used:

- Placebo – [redacted] sequential (grey),
- Yupelri 175 mcg – [redacted], sequential (dodgerblue- CX1E90FF),
- Placebo + [redacted] combined (orange),
- Yupelri 175 mcg + [redacted] combined (steelblue)

In figures that contain multiple subgroups on same figure (e.g., forest plots), no color (default black) will be used.

6.9 Tables, Figures and Listings (TFLs)

A line listing of tables, listings, and figures to be generated are in Appendix 3, respectively. Table titles will be denoted as underlined text in Section 9 of this SAP. Selected table, listing or figure mock-ups will be in a separate document.

7 ANALYSIS SETS

7.1 Safety

The Safety analysis set will include all subjects who

(1) Were randomized into the study, and,

(2) Received at least one dose of study drug (revefenacin, placebo or [redacted]

Treatment assignment will be based on **actual treatment**. The Safety analysis set is the primary analysis set for safety analyses.

7.2 Intent-to-Treat

The Intent-to-treat (ITT) analysis set will include all subjects who

(1) Were randomized into the study,

(2) Received at least one dose of study drug (revefenacin, placebo or [redacted] and,

(3) Have at least one recorded post-baseline spirometry assessment.

Treatment assignment will be based on the **treatment randomized**. [redacted]

7.3 Per-Protocol

The Per-protocol (PP) analysis set included all subjects in the ITT analysis set with no major analysis protocol deviations (Section 7.7).

Treatment assignment will be based on **actual treatment**.

7.4 Strata and Covariates

[redacted]

7.5 Examination of Subgroups

The following subgroups are pre-defined for the purposes of analyses:

1. Baseline smoking status: [redacted]
2. Age: [redacted];
3. Current ICS use: [redacted];
4. Reversibility to a short-acting bronchodilator: [redacted]
5. Sex: [redacted];

Selected analysis will be conducted using the subgroup analysis sets.

7.6 Inclusion and Exclusion Deviations

Deviations to inclusion and exclusion criteria will be identified prior to database lock and we be summarized in a listing with the deviation and the protocol version associated with the deviation.

7.7 Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the conclusions of the study will be identified prior to database lock. Major analysis protocol deviations may include, but are not limited to:

- [redacted]
- [redacted]

[redacted]

Subjects with major analysis protocol deviations will be identified before the database lock and provided in a listing.

In addition, a listing of all major deviations will be provided whether they impact analysis.

8 DEFINITION OF ANALYSIS VARIABLES

8.1 Demographic and Baseline Characteristics

Age

Age will be calculated as of the date of informed consent form (ICF) and truncated to its integer value. The following formula is used:

$$age = floor\left(\frac{ICF\ Signing - Date\ of\ Birth}{365.25}\right)$$

BMI

BMI will be calculated and converted to metric units by the following:

$$BMI\left(kg/m^2\right) = \frac{weight\left(kg\right)}{height\left(m\right)^2}.$$

Reversibility to a Short-Acting Bronchodilator

Reversibility (yes or no), to ipratropium, is defined as a post-bronchodilator (CFB) FEV_1 increase of at least (≥) 12% and at least (≥) a 200 mL increase, relative to the pre-bronchodilator FEV_1, at the relative screening visit.

Smoking Pack Years

Maximum number of packs multiplied by years smoked.

2017 GOLD Severity of Airflow Limitation Categories

Table 8: GOLD Severity of Airflow Limitation Categories

GOLD airflow category	Severity	FEV_1 threshold
GOLD 1	Mild	≥80% predicted
GOLD 2	Moderate	≥50%, <80% predicted
GOLD 3	Severe	≥30%, <50% predicted
GOLD 4	Very severe	<30% predicted

Note: Based on post-ipratropium values in patients with post-ipratropium FEV_1/ FVC <0.70

8.2 Safety Variables

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment. Unless otherwise specified, only treatment-emergent AEs will be summarized in the tables.

[redacted]

9 ANALYSES

Table, figures and listing titles are denoted in underlined text.

9.1 General Analyses

9.1.1 Subject Disposition

Subject disposition information will be summarized for all subjects by treatment group in Period 1. Summaries will include:

- Number of randomized subjects,
- Number and percentage of subjects randomized and treated with study drug (ITT Analysis set),
- Number and percentage of subjects completing the study,

- Number and percentage of subjects by reason discontinuing the study drug,
- Number and percentage of subjects by reason discontinuing the study.

A listing of subject disposition will include the ITT analysis set status, the date of informed consent signed, the date of first dose and last dose of study drug, primary reason for subject discontinuation of study medication, date of last visit, study completion status, primary reason for study termination, and the date of last contact.

9.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics (age, sex, race, ethnicity, height, weight, and BMI) will be summarized for ITT analysis set by treatment group in Period 1.

A listing will also be provided.

9.1.3 Reversibility Summaries

A post-bronchodilator screening reversibility summary taken during screening visits will be provided with the following parameters:

- Ipratropium reversibility (mL),
- Ipratropium reversibility (%),

In addition, a post-bronchodilator screening reversibility categorical summary will be provided in a separate summary:

- Not reversible to ipratropium,
- Reversible to ipratropium,

The ITT analysis set will be used for the summaries.

9.1.4 Screening Spirometry Summaries

A screening spirometry summary will be provided with the following parameters:

- Post-ipratropium predicted Normal FEV_1 (mL),
- Post-ipratropium percent predicted FEV_1 (%),
- Post-ipratropium FEV_1 (mL),
- Post-ipratropium FVC (mL),
- Post-ipratropium FEV_1 to FVC (ratio)

[redacted]

9.1.6 Baseline Clinical Characteristics Summaries

A summary of COPD clinical characteristics taken at baseline will be provided with the following parameters:

- Proportion of subject ≥65 years of age (%),
- Duration of COPD (years),
- Proportion of subjects with a history of supplemental oxygen use (%),
- Proportion of subjects with a history of respiratory infections (%)
- Number of exacerbations in past 12 months (%),
- Number of hospitalizations for an exacerbation in past 12 months (%),

A summary of smoking characteristics taken at baseline will be provided with the following parameters:

- Smoking history, current and former, (%),
- Number of years smoked (years),
- Maximum number of packs per day (packs),
- Pack years (packs).

A summary of ICS use will be provided with the following parameters using coded concomitant medication data:

- Concurrent ICS use (%),

The ITT analysis set will be used for the summaries.

9.1.7 GOLD Category Summary

A summary of GOLD categories will be provided with the following parameters:

- GOLD Severity of Airflow Limitation groups,

A listing will be provided. The ITT analysis set will be used for the summary.

9.2 Key Demographic and Baseline Characteristics Summary

A summary of key demographic and baseline characteristics will include the following with the following parameters on a single page:

- Age, mean(SD),
- Sex (male), %,
- Race (white), %,
- BMI, mean (SD),
- Current smoker (yes), %,
- Concurrent ICS use (yes), %,
- Post-ipratropium percent predicted FEV_1, mean (SD),
- Post-ipratropium FEV_1 to FVC (ratio), mean (SD),
- Baseline FEV_1 (in mL), mean (SD),
- Baseline FVC, mean (SD),
- Proportion of subjects with ≤1 exacerbations in prior year, %

For continuous summaries, only the "mean (SD)" will be displayed. As this data is summarized in listing format elsewhere, no listing is provided for this summary. The ITT analysis set will be used for the summary.

9.3 Safety Analyses

For all safety analyses, the safety analysis population will be used.

Safety variables to be summarized include vital signs, adverse events, clinical laboratory results (hematology and chemistry), and quantitative parameters from 12-lead ECGs. Vital signs will be summarized in terms of observed values and changes from baseline.

All safety analyses will be done by four treatment groups (Group 1-1, Group 1-2, Group 2-1, and Group 2-2).

9.3.1 Extent of Exposure

Study drug exposure (Number of doses and days) will be summarized using the 8-point descriptive summary. The source for exposure data is the drug accountability data domain.

Study drug compliance will be assessed using the following categories using the same source as the drug exposure data by treatment periods:

- 100%;
- 95%;
- 90%;
- 80%;
- < 80%.

Study drug administration (date/time and study day) will be provided in a data listing. The source for study drug administration is the diary data domain.

9.3.2 Adverse Events

Adverse events will be coded to the preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA®). Summaries will be presented by system organ class (SOC), preferred term (PT) and severity and/or relatedness, the frequency and percentage of subjects reporting each observed event.

A treatment-emergent adverse event (TEAE) will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from TEAEs.

All AEs and all TEAEs will be listed by subject.

Subjects who experienced treatment-limiting AEs will be listed. Treatment-limiting AEs are defined as any event that leads to permanent or temporary discontinuation from treatment, or a reduction in the treatment dose.

Summary of adverse events will be dependent on adverse events observed. If no adverse events meeting a specific table are observed, the summary table will not be completed. Blank summary tables will not be utilized.

The following is the list of adverse event tables:

Overall:

- Overall Summary of Adverse Events

By preferred term:

- Treatment-emergent Adverse Events by SOC and PT
- Treatment-emergent Adverse Events by PT
- Treatment-emergent Adverse Events by SOC and PT occurring in more than 1% of Study population

By severity:

- Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Treatment-emergent Adverse Events by SOC and PT
- Serious Adverse Events
- Deaths during Study

By relatedness:

- Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-Related Treatment-emergent Adverse Events by SOC, PT and Severity
- Moderate or Severe Drug-Related Treatment-emergent Adverse Events by SOC and PT
- Drug-related Serious Adverse Events

Other:

- Adverse events leading to premature study drug discontinuation
- Adverse events leading to temporary interruption of study drug

The overall summary of adverse events will include the following summary lines: Any AE, Moderate or severe AEs, Moderate or severe AEs related to Study Drug, Serious AEs, Serious AEs related to Study Drug, AEs leading to discontinuation, AEs leading to interruption, Deaths during Study.

9.3.2.1 Antimuscarinic Adverse Events

Antimuscarinic TEAEs are of interest as a common event in the drug class and will be summarized by preferred terms. The preferred terms for TEAEs considered antimuscarinic are as follows:

- Constipation
- Dry mouth
- Dysuria
- Worsening of urinary retention
- Worsening of narrow-angle glaucoma.

9.3.3 Vital Signs

For each nominal time point, vital signs will be summarized in terms of observed values and changes from Baseline. Outlier values of vital signs will be flagged in the listing.

Table 9: Vital Signs Outlier Thresholds

Heart Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
<40 >110	<85 >160	<45 >100

9.3.4 ECG

A summary of ECG parameters, parameters reported separately QTcF, PR interval, QT interval, QRS duration, RR, and HR, will be summarized in terms of observed values and change from baseline.

Subjects without post-baseline measurement for a given treatment period will be excluded from the summary statistic (e.g., denominator of the summary statistic) for that time point.

All recorded values by central reader at ECG core lab for the standard 12-lead electrocardiogram parameters will be presented in a by-subject listing.

Outlier Analysis

The number of subjects with absolute ECG values and change from baseline in the ranges shown in Table 10 will be presented in Electrocardiogram Outlier Summary by Visit and Time Point.

In addition in the same summary, QTcF will also be summarized by the following categories, Normal (males <430, females ≤450), Borderline (males (>430, ≤450); females (>450, ≤470)) and Prolonged (males >450, females >470).

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF > 500 msec or an increase > 60 msec will be provided, as necessary.

Figures

Cumulative distribution plots will be provided for maximum change in QTcF by day.

Investigator Assessment of ECG Readings

The investigators' assessment of ECGs as normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

Table 10: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
>120	>20	> 200	> 15	> 120	Males:	≤ 30
>130	>30	> 220	> 25		≤ 430	>30, ≤ 60
					> 430	> 60
					> 450	
					> 470	
					> 480	
					> 500	
					Females:	
					≤ 450	
					> 450	
					> 470	

Table 10: ECG Test Outlier Thresholds

Heart Rate (bpm)	Heart Rate Change from Baseline (bpm)	PR Interval (msec)	PR Percentage Change From Baseline (%)	QRS Interval (msec)	QT_cF (msec)	QT_cF change from Baseline (msec)
					≥ 480	
					≥ 500	

9.3.5 Clinical Laboratory Results

Laboratory data (hematology and serum chemistry) will be summarized in terms of observed values, and changes from baseline. In addition, changes from baseline relative to normal ranges (e.g., shifts from normal to abnormal high/low) will be summarized in hematology: shift from baseline, and serum chemistry: shift from baseline.

Listings will flag laboratory values that are outside of normal range.

A listing of all abnormal lab values will be provided.

9.3.6 Medical History

Medical history collected at screening will be provided in a data listing.

9.3.7 Prior and Concomitant Medications

Prior and concomitant Medications will be listed and summarized separately. Tables and listings will be provided for concomitant bronchodilators, concomitant corticosteroids, Concomitant NON-COPD medications, Post-treatment Bronchodilators. Coding logic for each group is in Appendix 2.

9.4 Other Analyses

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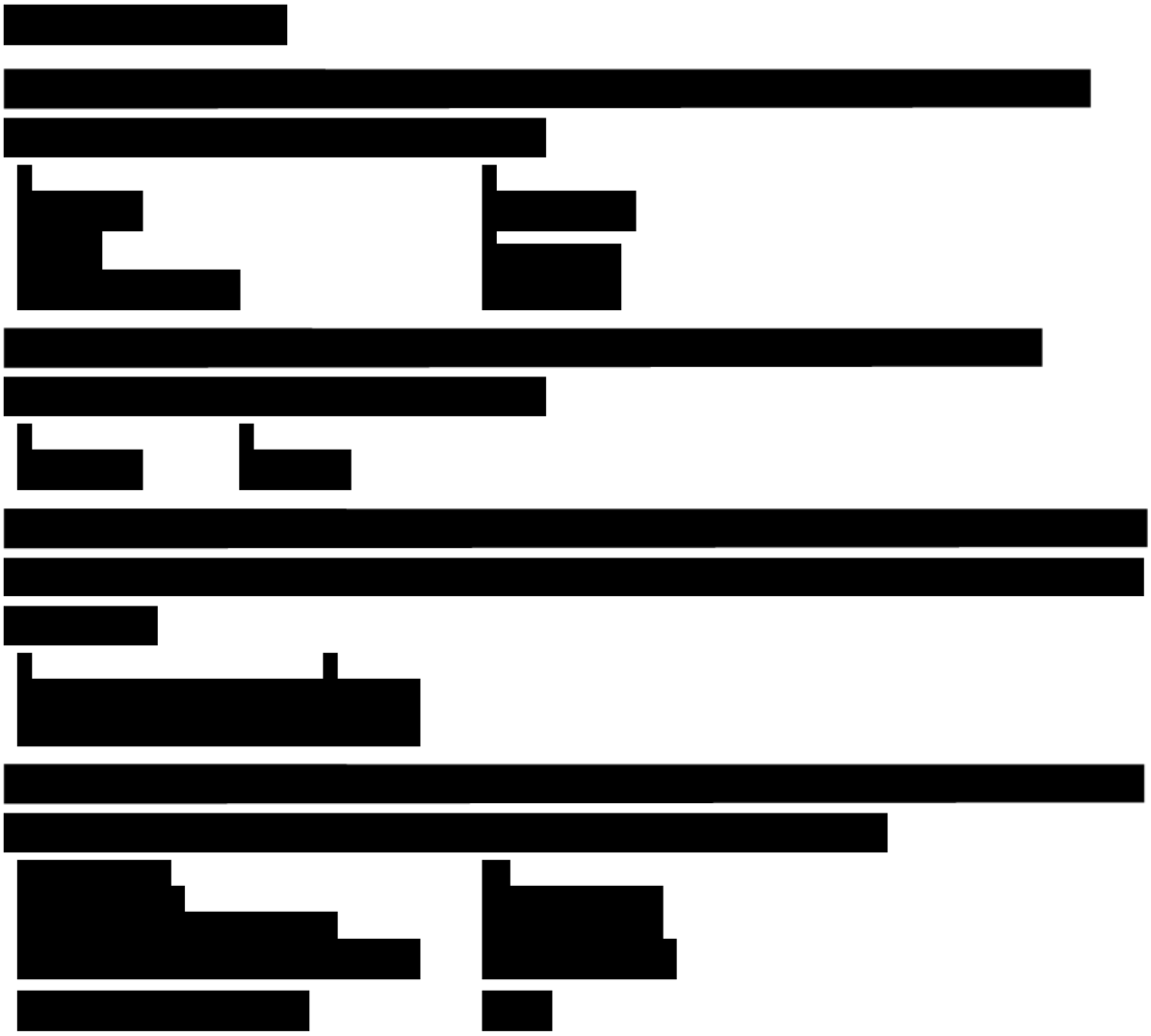
Appendix 1: Reporting Structures for Data Summary



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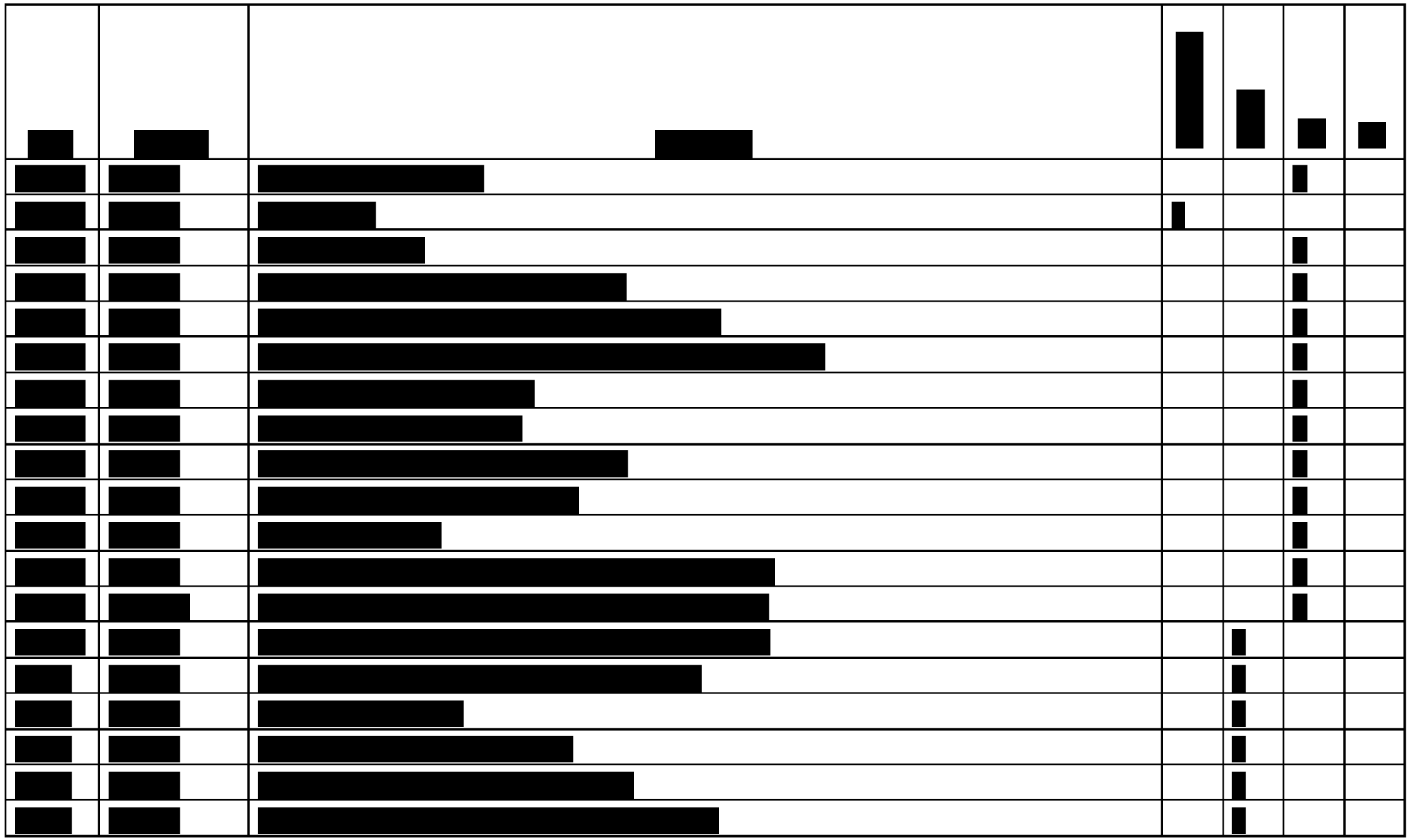

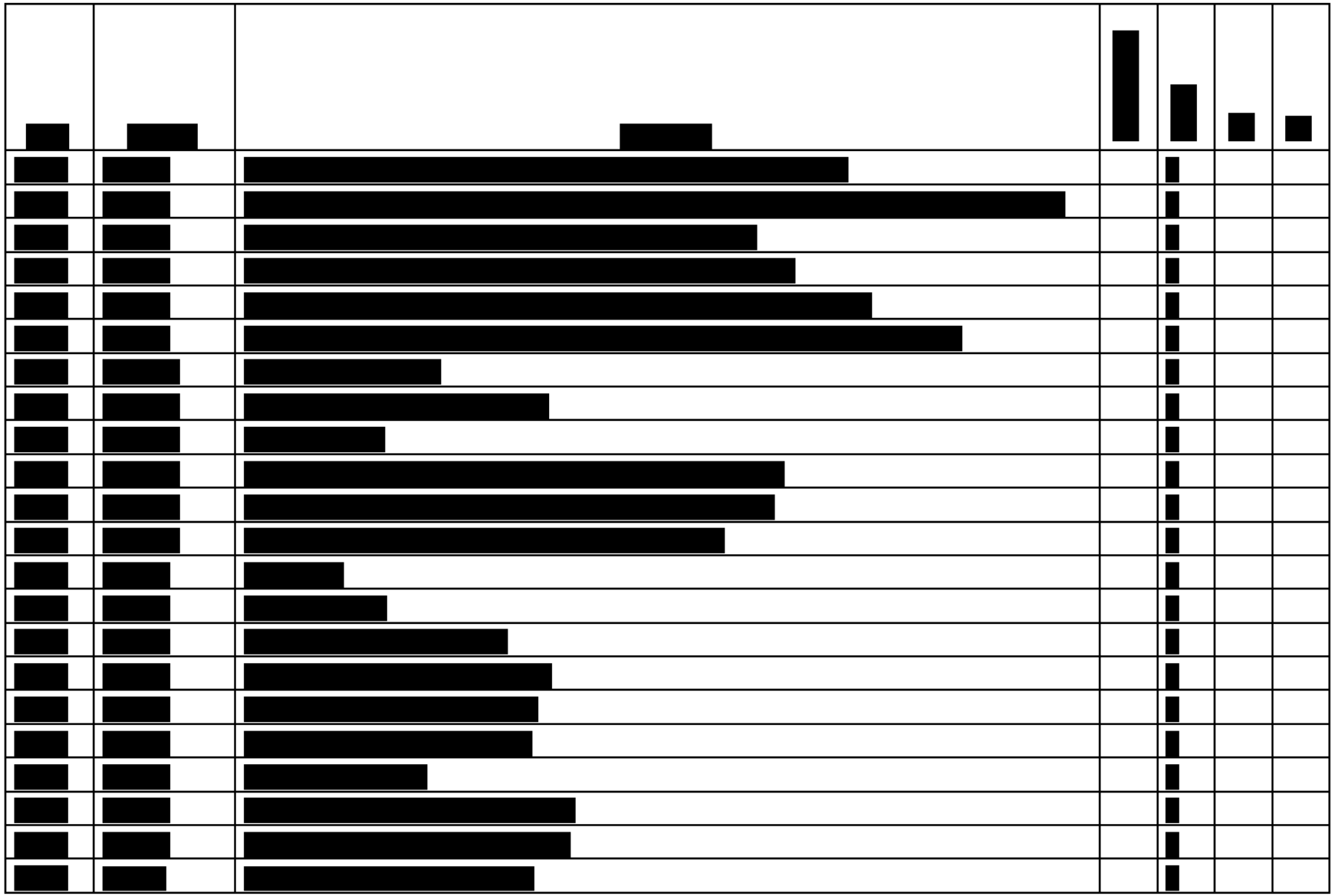

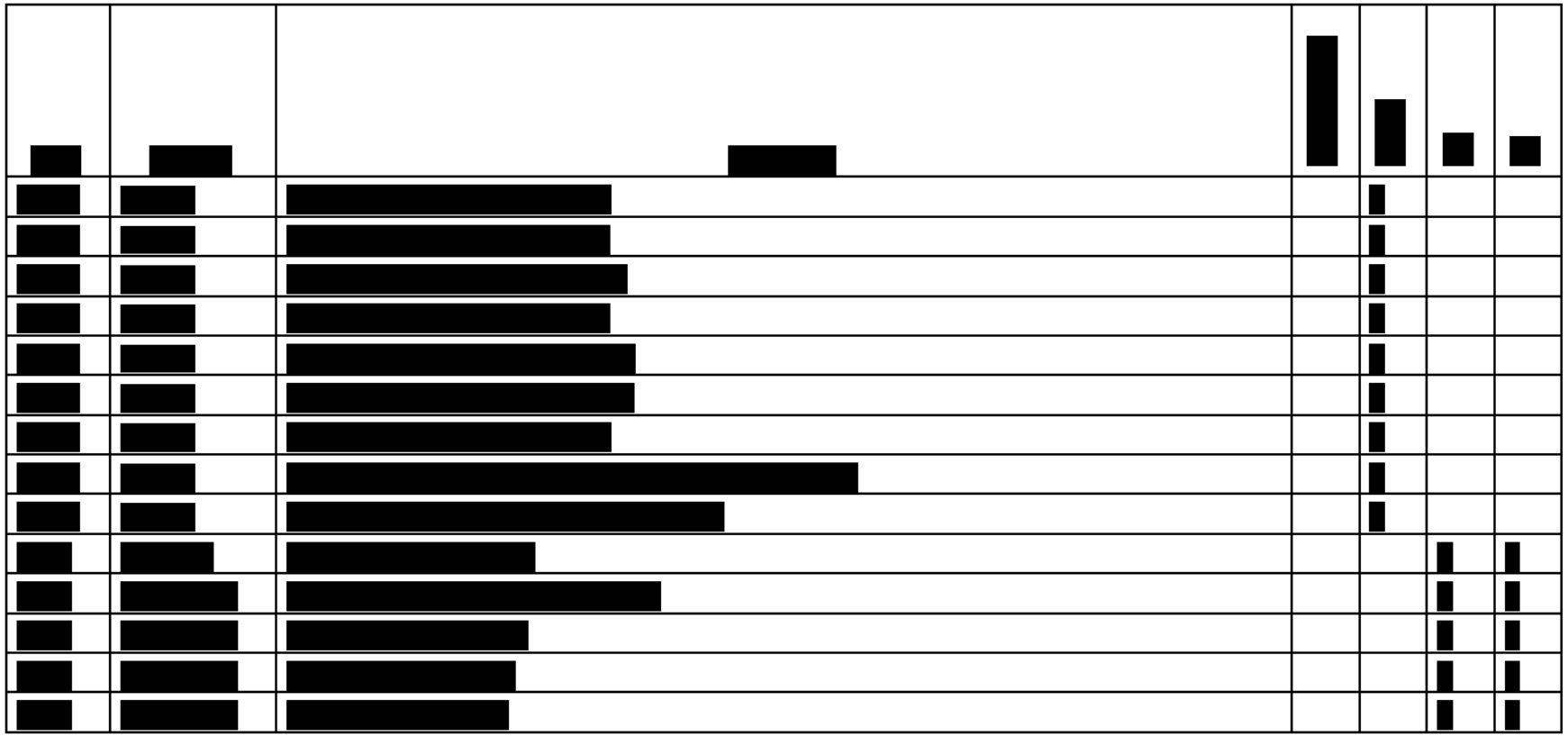

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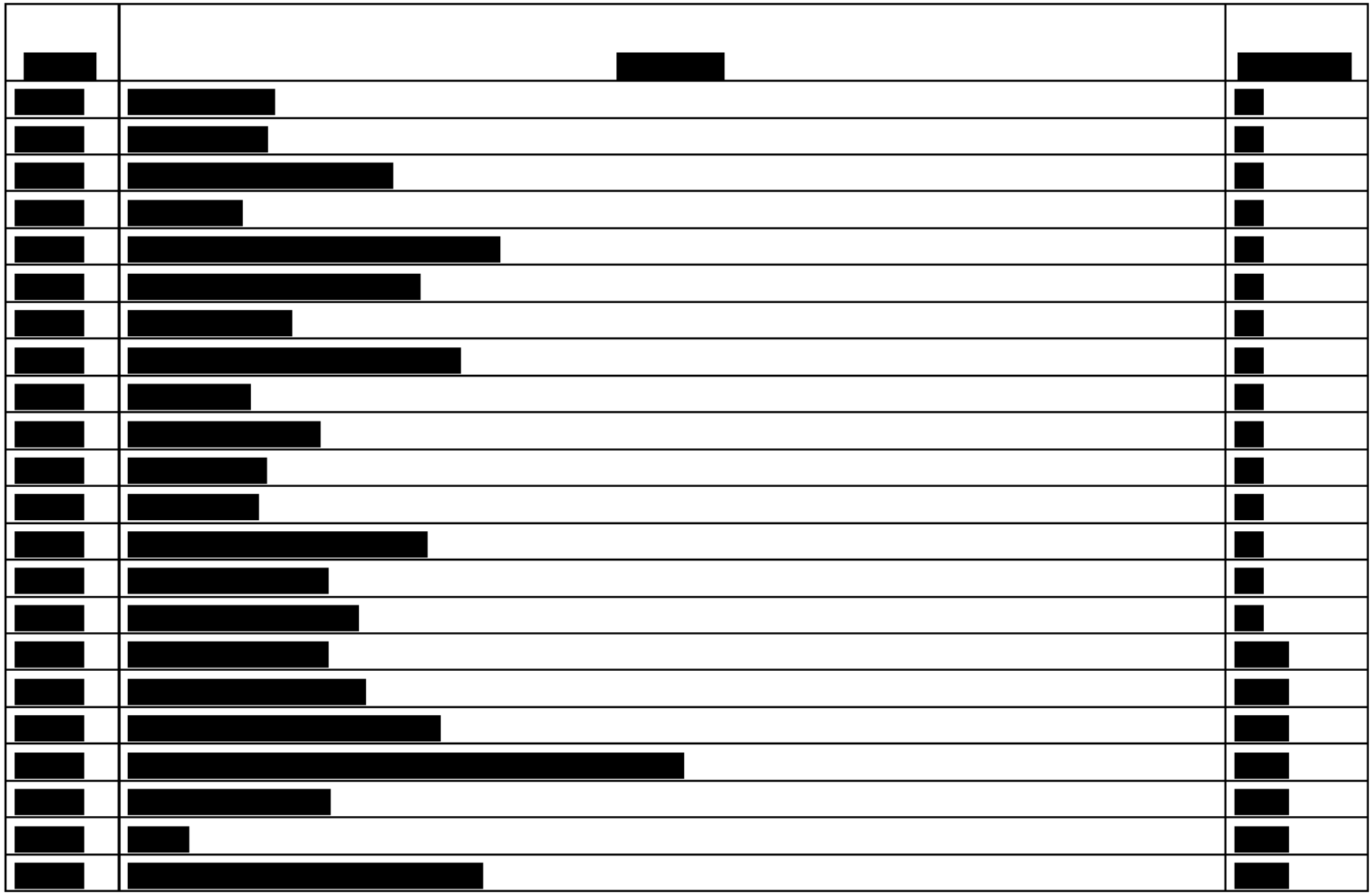

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