STATISTICAL ANALYSIS PLAN

Compound:	revefenacin
Study Number:	Study 0149
Study Title:	A Phase 3b, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Study to Compare Once Daily Nebulized Revefenacin with Spiriva Once Daily Delivered via the HandiHaler® on Lung Function in Subjects with Chronic Obstructive Pulmonary Disease and a Low Peak Inspiratory Flow Rate
Protocol Version:	[redacted]
Sponsor:	Theravance Biopharma R&D, Inc. c/o Theravance Biopharma US, Inc. 901 Gateway Boulevard South San Francisco, CA 94080
Plan Version:	27 November 2017 – Version 1.0
Plan History:	No prior versions
Plan Prepared by:	[redacted] Theravance Biopharma US, Inc.

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revefenacin, Study 0149

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Plan Version: 27 November 2017 – Version 1.0

Reviewed: 27 November 2017

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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 0149 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

- To characterize the relative efficacy on trough FEV_1 of revefenacin administered once daily via nebulization compared to tiotropium administered once daily via [redacted] in a population of subjects with moderate to very severe COPD and suboptimal PIFR.

2.2 Exploratory Objectives

The exploratory objectives of the study are:

[redacted]

3 OVERVIEW OF STUDY DESIGN

This is a randomized, double-blind, double-dummy, parallel group study.

Each subject will receive study treatment once daily in the morning for the length of study duration, up to 29 days and all subjects will be allowed to continue on their current regimen of concomitant ICS/LABA therapy of their choice, either QD or BID administration. There will be two treatment groups (revefenacin 175 mcg and tiotropium 18 mcg). Revefenacin solution for inhalation (3 mL) will be administered using the [redacted] jet nebulizer. Tiotropium will be administered using the [redacted] device with the drug and placebo capsules blinded using precedent blinding methods.

Subjects will be assessed during screening for low PIFR using the [redacted] device to measure PIFR set to [redacted] resistance for inclusion to the study and set to the [redacted] resistance for descriptive purposes. Subjects with PIFR lower than 60 L/min set to the [redacted] resistance defined in this study as suboptimal PIFR, and who meet all eligibility criteria will be randomized.

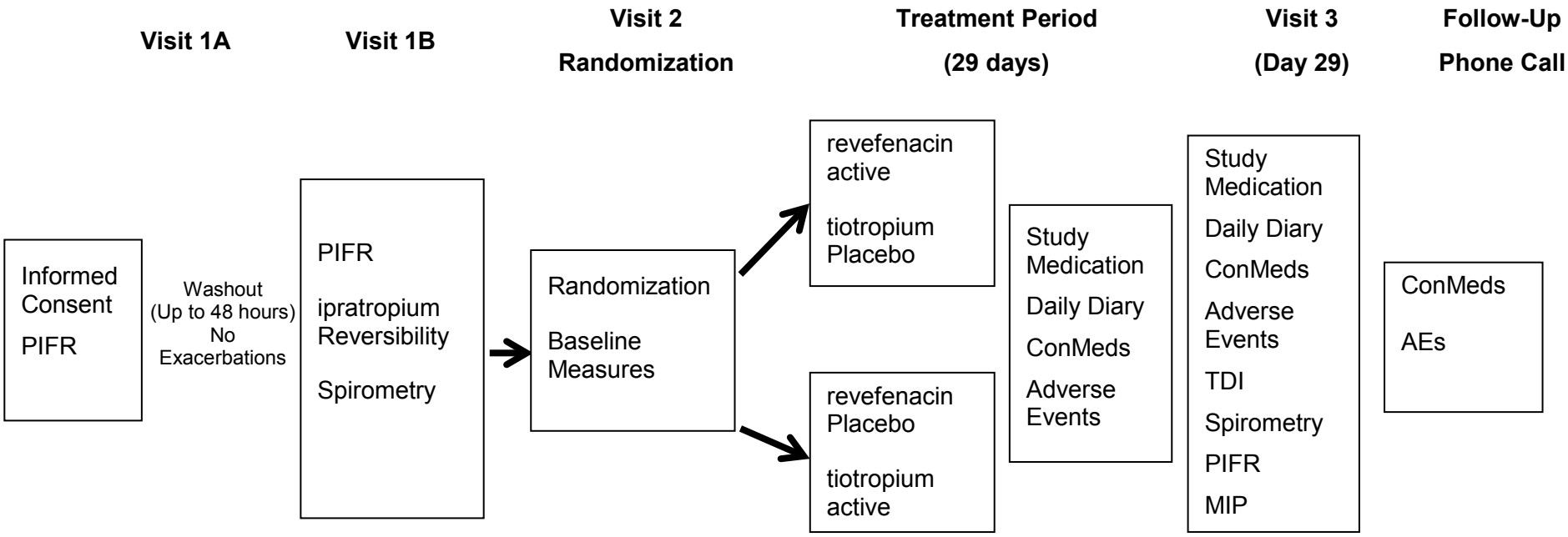
Once screening criteria have been met, subjects will have baseline characteristics and medical history collected. At Visit 1B reversibility to ipratropium will be evaluated and PIFR measurements will be collected set to both the [redacted] and to Handihaler® resistance.

At Visit 2 (Day 1), eligible subjects will be randomized to one of two groups in the study. Spirometry, including FVC and FEV_1, will be assessed at baseline (-45 and -15 minutes predose), 1 hour, 2 hour, and 4 hour post dosing. Hyperinflation, as measured by inspiratory capacity (IC) will also be assessed at -45 mins predose. This will be done by a Slow Vital Capacity (SVC) maneuver immediately after the FVC maneuver. Maximal Inspiratory Pressure (MIP) will be performed following the SVC.

At Visit 3 (Day 29), subjects will return for final in-clinic dosing and spirometry assessments. Safety assessments, including collection of adverse events will be performed at every visit.

A supply of rescue medication (albuterol MDI or nebulized) for use in the study and a 28-day supply of study medication will be provided for each subject.

Figure 1: Study Schematic



4 SAMPLE SIZE AND POWER

[redacted] approximately 100 subjects will be randomized per treatment group (N=200 subjects in total).

[redacted]

A total of 50 or more subjects with GOLD airflow limitation category 4 will be enrolled.

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 or raw data, i.e., CRF or Lab-type data, an evaluation window, i.e., screening, Day 1, Days 1-29, and a summary type, i.e., continuous, frequency, normal least squares.

The primary study endpoint is trough FEV_1 post the 28th dose on Day 29

The secondary endpoints are:

- Trough FVC and IC post 28th dose on Day 29
- Peak FEV_1, FVC on Day 29 (0-4 hours)
- Rescue albuterol use (incidence of albuterol use)

The safety endpoints are:

- Exposure
- Adverse events
- Vital signs
- Concomitant medications

The exploratory endpoints will be characterized:

[redacted]

5.1 General Endpoints

The following general endpoints will be summarized in the following table.

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]
concurrent LABA use	[redacted]	[redacted]	[redacted]
concurrent QD/BID/NO LABA	[redacted]	[redacted]	[redacted]
concurrent ICS/LABA use	[redacted]	[redacted]	[redacted]
Baseline FEV_1	[redacted]	[redacted]	[redacted]
predicted normal FEV_1	[redacted]	[redacted]	[redacted]
percent predicted FEV_1	[redacted]	[redacted]	[redacted]
Baseline FVC	[redacted]	[redacted]	[redacted]
FEV_1 to FVC ratio	[redacted]	[redacted]	[redacted]
Baseline PIFR	[redacted]	[redacted]	[redacted]
Baseline IC	[redacted]	[redacted]	[redacted]
Baseline MIP	[redacted]	[redacted]	[redacted]
duration of COPD	[redacted]	[redacted]	[redacted]
subjects with a history of supplemental oxygen	[redacted]	[redacted]	[redacted]
Cardiovascular risk factor	[redacted]	[redacted]	[redacted]
GOLD category	[redacted]	[redacted]	[redacted]
GOLD severity of airflow limitation	[redacted]	[redacted]	[redacted]
Indicator: mMRC score ≥2	[redacted]	[redacted]	[redacted]

Endpoint	Evaluation Type	ADAM Type	Reporting Window
primary reason for study drug discontinuation	[redacted]	[redacted]	[redacted]
subject disposition	[redacted]	[redacted]	[redacted]
subjects in Safety Group	[redacted]	[redacted]	[redacted]
subjects in ITT Group	[redacted]	[redacted]	[redacted]
subjects in PP Group	[redacted]	[redacted]	[redacted]1

Note: D: day, PD: pre-dose, SCR: screening, ABS: absolute value, EOS: end of study

5.2 Efficacy Endpoints

The efficacy endpoints will be summarized in Table 1.

Table 1: Efficacy Endpoints

Endpoint	Evaluation Type	ADAM Type	Reporting Window	Summary Type(s)
trough FEV_1	ABS, CFB	derived	D29	NLS MEAN
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: D: day, CFB: change from baseline, ABS: absolute value

Note: For summary types, see Appendix 1)

5.3 Safety Endpoints

Safety variables to be summarized include exposures, vital signs, and adverse events. Vital signs will be summarized in terms of observed values and changes from baseline.

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 6.1.2) will be included in the summaries, statistical analysis, and calculation of derived parameters.

6.1.1 Baseline Definition

The Table 2 indicates the timing of the baseline assessment to be used in the analysis of specific parameters.

Table 2: Baseline Assessment for Specific Parameters

Parameter	No Baseline	Visit 1B	Visit 2 (Day 1-PD)
PIFR		X	
FEV_1			X[1]
[redacted]	[redacted]		
[redacted]		[redacted]	
[redacted]		[redacted]	
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
[redacted]			[redacted]
Vital signs			X

1 mean of -45 and -15 min PD assessments; PD: pre-dose

6.1.2 Analysis Windows

All assessments will be summarized using analysis windows.

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

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

Table 3: Analysis Windows: Visits

Nominal Visit	Nominal Day	Start (days)	Stop (days)
2	1	1	1
3	29	14	44

Safety Endpoints

The following windows summarize the definition of treatment-emergent.

Table 4: 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	Post first dose	Last dose + 7 days

General Selection Process for 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 same time point (generally applies to assessments done in triplicate).

Multiple Spirometry Records

[redacted]

6.1.3 Missing Data

[redacted]

Primary Efficacy Endpoints

[redacted]

Rescue Medication Use Question

[redacted]

Rescue Medication Accountability

Screening albuterol kits

No imputation for missing data will be done for albuterol kits dispensed prior to Day 1.

Post-screening albuterol kits

For post-screening albuterol kit (i.e., dispensed on or after Day 1) with missing end counts at the end of study, the number of puffs used will be imputed as the starting count.

Albuterol kits dispensed on the day of last dose or early termination visit will not be included in summary analyses.

All Other Efficacy Endpoints

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

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”.

6.2 Adverse Events

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

6.3 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.

6.4 Medical History

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

6.5 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 summary table treatment headers, reverencing will be abbreviated as REV and will be presented in the following order:

- Tiotropium,
- REV 175 mcg,
- Total (Applicable to General Analysis and Exposure summaries).

In safety summaries by LABA subgroup, treatment groups will be presented in the following order:

- Tiotropium,
- REV 175 mcg,

Rounding

In general, the convention for rounding 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 four significant digits (round to four significant digits using a similar criterion as for percentages with the five in the last digit).

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.

The following significant digit convention will be used for the purposes of summarizing non-efficacy data (primarily lab data) 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.

P-values

P-values will be reported with four significant digits, e.g., 0.xxxx, except when reporting p-values less than 0.0001, reported as <0.0001.

Colors in Figures

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

- Tiotropium (orange),
- revefenacin 175 mcg (dodgerblue- CX1E90FF).

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

6.6 Tables, Figures and Listings (TFLs)

A line listing of tables, listings, and figures to be generated are in Appendix 6.

Table titles will be denoted as underlined text in Section 9 of this SAP.

Unique 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 or tiotropium).

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 or tiotropium), and,

(3) Have at least one recorded post-baseline FEV_1 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 7.5).

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

7.4 Examination of Subgroups

7.4.1 Study-Specific Subgroups

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

1. Baseline PIFR baseline PIFR [redacted]
2. Baseline smoking status: [redacted]
3. Age: [redacted]
4. Current LABA or ICS/LABA use: [redacted]
5. Reversibility to a short-acting bronchodilator:

   [redacted]
6. Baseline post bronchodilator % predicted FEV_1: [redacted]

7.5 Major Analysis Protocol Deviations

Major analysis protocol deviations that could potentially affect the efficacy 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]
- [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 or not they impact the analysis.

8 DEFINITION OF ANALYSIS VARIABLES

8.1 General Variables

Age

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

$$Baseline\ Age = floor\left(\frac{Date\ of\ Informed\ Consent - Date\ of\ Birth}{365.25}\right).$$

BMI

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

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

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.

LABA Use and Type of LABA Use

Two variables will be used in the analysis models to identify if a subject was on a concurrent LABA or ICS/LABA medication and whether the concurrent LABA or ICS/LABA was administered QD or BID:

- Concurrent LABA: yes (1) or no (0)
- LABA Type: none (0), QD (1) or BID (2)

LABA flags will be derived using concomitant medication data, i.e., presence or absence of a record matching the logic for LABA use, to ensure accuracy.

GOLD Severity of Airflow Limitation Categories

Table 5: 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 FEV1/ FVC <0.70

GOLD Categories (2011 Definition)

Table 6: GOLD Categories

GOLD Category	GOLD Airflow Severity Category	Exacerbations	mMRC
A	GOLD 1-2	≤1	0-1
B	GOLD 1-2	≤1	≥2
C	GOLD 3-4	≥2	0-1
D	GOLD 3-4	≥2	≥2

GOLD Categories (2017 Definition)

Table 7: GOLD Grade

Airflow Limitation	GOLD Grade	Exacerbations	mMRC
>80	1, A	≤1	0-1
	1, B	≤1	≥2
	1, C	≥2	0-1
	1, D	≥2	≥2
50-79.9	2, A	≤1	0-1
	2, B	≤1	≥2
	2, C	≥2	0-1
	2, D	≥2	≥2
30-49.9	3, A	≤1	0-1
	3, B	≤1	≥2
	3, C	≥2	0-1
	3, D	≥2	≥2
<30	4, A	≤1	0-1
	4, B	≤1	≥2
	4, C	≥2	0-1
	4, D	≥2	≥2

Screening data will be used to categorize subjects. For the purposes of categorization, GOLD categories (using 2011 definition to ensure consistency between the efficacy and safety studies in the phase 3 program) will use the GOLD airflow severity category and mMRC scores as the primary method to determine GOLD Category. If GOLD airflow severity is missing, then exacerbations will be used.

In addition, GOLD grade using 2017 definition will also be used for categorizing the subjects.

8.2 Efficacy Variables

[redacted]

[redacted]

[redacted]his analysis plan where the weighted mean (WM) is the AUC/total time, nominally, 4 H.

[redacted]

8.3 Safety Variables

Adverse Events

Adverse events (AEs) are recorded from signing of the informed consent form through the final follow-up assessment. Non-treatment-emergent AEs and treatment-emergent AEs (defined in Section 9.3.2) will be summarized separately.

Bronchodilators by Drug Class

Appendix 2 contains coding logic for determination of specific drug classes for bronchodilators.

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. Summaries will include the following parameters:

- Number of randomized subjects,
- Number and percentage of subjects randomized and treated with study drug (ITT Analysis set),
- Number of subjects randomized, but not dosed
- 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, the 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 set.

A listing of demographics and baseline characteristics 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,

Separate listings will also be provided. The ITT analysis set will be used for the summaries.

9.1.4 Screening and Baseline 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),

A Baseline spirometry summary will be provided in a separate table with the following parameters:

- Baseline FEV_1 (mL)
- Baseline FVC (mL)
- Baseline PIFR (L/min)
- Baseline PIFR by Category (≤40, > 40)
- Baseline IC (L)
- Baseline MIP (cm H_2O)
- Baseline FEV_1 to FVC (ratio)
- Baseline predicted Normal FEV_1 (mL)
- Baseline percent predicted FEV_1 (mL)

A single listing that includes screening, baseline and post-baseline spirometry will be provided. The ITT analysis set will be used for the summaries.

9.1.5 Baseline Clinical Characteristics Summaries

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

- Proportion of subject with baseline PIFR ≥ 40 L/min
- Proportion of subject ≥65 years of age (%),
- Duration of COPD (years),
- Proportion of subjects with a history of supplemental oxygen use (%),

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 LABA and ICS use will be provided with the following parameters using coded concomitant medication data:

- Concurrent ICS use (%),
- Concurrent LABA use (%),
- Subgroup: Concurrent QD LABA use (%),
- Subgroup: Concurrent BID LABA use (%),
- Concurrent ICS/LABA use (%).

Three listings will also be provided. The ITT analysis set will be used for the summaries.

9.1.6 GOLD Category Summary

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

- GOLD Severity of Airflow Limitation groups,
- 2011 GOLD Categories,
- 2017 GOLD Categories

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

9.1.7 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), %,
- Concurrent LABA use (yes), %,
- Concurrent ICS/LABA 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),
- Baseline IC, mean(SD)
- Baseline PIFR (L/min), mean (SD),
- Baseline PIFR (≥40 L/min), %
- Baseline MIP (cm H_2O), mean (SD)
- Baseline MIP, mean (SD)
- Proportion of subjects with baseline mMRC ≥2, %
- Proportion of subjects with ≤1 exacerbations in prior year, %
- BDI score, LS mean (SE)

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.

9.2 Efficacy Analysis

9.2.1 General Considerations for Efficacy Analyses

Analysis Set for Efficacy Analyses

For all efficacy data analyses, the ITT analyses set will be used unless otherwise specified.

9.2.2 Primary Efficacy Evaluation: Trough FEV1

Hypothesis

The null hypothesis will be that there is no difference between revefenacin (175 mcg) and tiotropium (18 µg) in change from baseline trough FEV_1 on Day 29.

Symbolically, this is expressed as follows:

$$H_0: \mu_{REV} = \mu_{TIO}$$
$$H_1: \mu_{REV} \neq \mu_{TIO}$$

Analysis and Summary Tables

[redacted]

[redacted]

Figures

[redacted]

9.2.3 Secondary Efficacy Evaluation: Trough FVC and Trough IC

Hypothesis

The null hypothesis will be that there is no difference between revefenacin (175 mcg) and tiotropium (18 µg) in change from baseline trough FVC and trough IC on Day 29, respectively.

Symbolically, this is expressed as follows:

$$H_0: \mu_{REV} = \mu_{TIO}$$
$$H_1: \mu_{REV} \neq \mu_{TIO}$$

Analysis and Summary Tables

Similar approach used for the primary efficacy endpoint of change from baseline trough FEV_1 will apply for Trough FVC and trough IC, respectively.

Similar code used for primary analysis will be used for trough FVC and trough IC.

[redacted]

9.2.4 Secondary Efficacy Evaluation: Peak FEV1 and Peak FVC (0−4 hours)

Hypothesis

The null hypothesis will be that there is no difference between revefenacin (175 mcg) and tiotropium (18 µg) in change from Baseline peak FEV1 and peak FVC on Day 1 and Day 29.

Analysis and Summary Tables

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Figures

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9.2.6 Exploratory Efficacy Evaluation: [redacted]

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9.2.7 Exploratory Efficacy Evaluation: [redacted]

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A summary of TDI Responders (≥1 units) will include observed counts and proportions (using frequency reporting format) and observed least-square proportions and odd ratios on the differences between treatment groups (using BLS MEAN format). Nominal p values and multiplicity adjusted p values will be reported.

9.2.8 Exploratory Efficacy Evaluation: [redacted]

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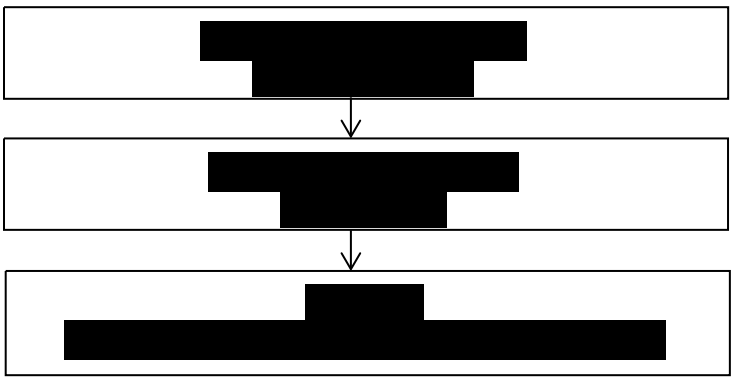

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9.3 Safety Analyses

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

Safety variables to be summarized include exposures, concomitant medication, vital signs and adverse events. Vital signs will be summarized in terms of observed values and changes from baseline.

9.3.1 Extent of Exposure

Study drug exposure (Number of Doses and Days) will be summarized using the eight-point descriptive summary by study periods. 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 study 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 present 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 7 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. Treatment-limiting AEs are defined as any event that leads to permanent or temporary discontinuation from treatment.

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
- Treatment-emergent Adverse Events by SOC, PT and LABA Use

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 LABA Use
- 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. Vital signs outliers will be flagged in the listing.

Table 8: Vital Signs Outlier Thresholds

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

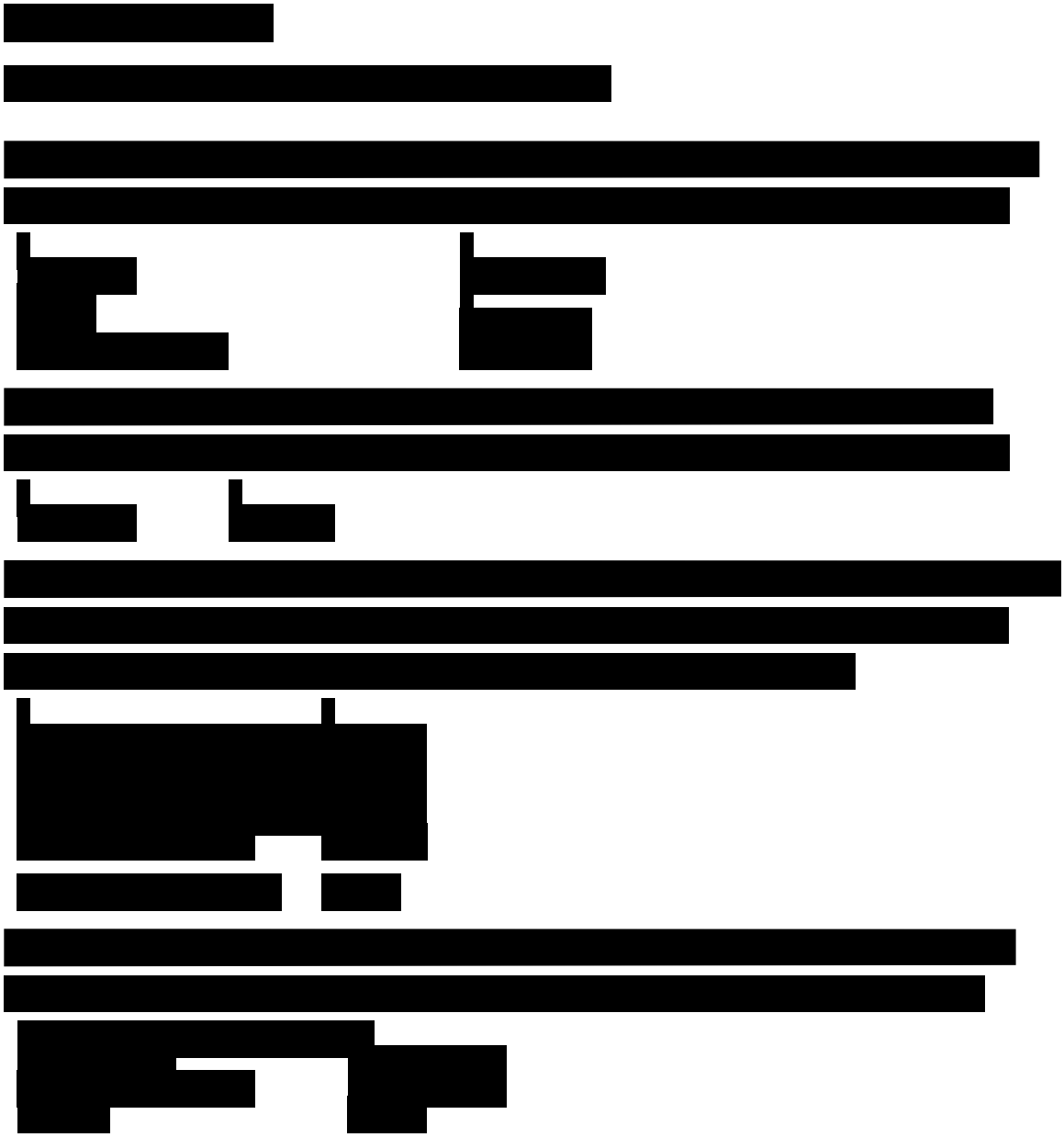
9.3.4 Medical History

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

9.3.5 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.

Appendix 1: [redacted]



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Appendix 3: [redacted]

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Appendix 4: [redacted]

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Appendix 5: [redacted]

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Appendix 6: [redacted]

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Type	Number	Table Title	Randomized	Safety	ITT	PP
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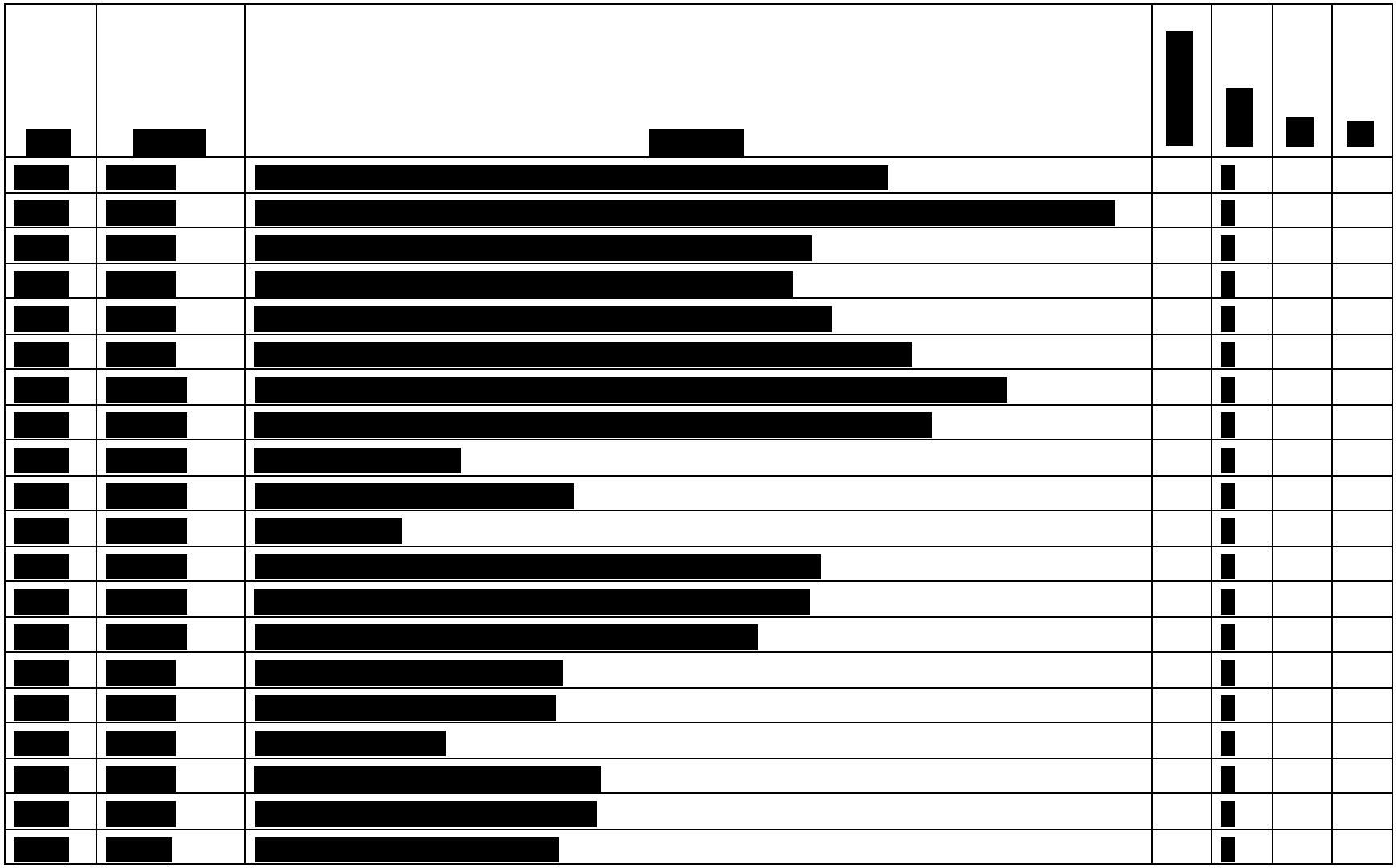

Listings

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