Statistical Analysis Plan	
Study Code	AV005
Edition Number	1.0
Date	07/08/2020

A Randomized, Double-blind, Single-Dose, 2-Period, Crossover Study to Assess the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult and Adolescent Subjects with Asthma (TYREE)

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A Randomized, Double-blind, Single-Dose, 2-Period, Crossover Study to Assess the Efficacy of PT027 Compared with Placebo on Exercise-Induced Bronchoconstriction in Adult and Adolescent Subjects with Asthma (TYREE)

Study Statistician [redacted]

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Avillion Statistician [redacted]

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
$AUC_{0\text{-}30\ minutes}$	Area under the curve from 0 to 30 minutes
BDA MDI (PT027)	Budesonide/albuterol metered-dose inhaler
BMI	Body mass index
ECG	Electrocardiogram
ECT	Exercise challenge test
eCRF	Electronic case report form
EOT	End-of-treatment
[redacted]	[redacted]
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
GINA	Global Initiative for Asthma
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IP	Investigational product
IPD	Important protocol deviation
MAR	Missing at random
MDI	Metered-dose inhaler
OAE	Other significant adverse event
PDV	Premature discontinuation visit
SABA	Short/rapid-acting β2-adrenoreceptor agonist
SAE	Serious adverse events
SDTM	Study Data Tabulation Model
TC	Telephone contact

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AMENDMENT HISTORY

Date	Brief description of change
	N/A

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1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of a single dose of BDA MDI (160/180 µg) compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*The maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge*

1.1.2 Secondary objective

Secondary Objectives:	Outcome Measures:
To further assess the efficacy of a single dose of BDA MDI compared with placebo MDI on EIB in adult and adolescent subjects with asthma	*Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of $\geq 10\%$*

1.1.3 Safety objective

Safety Objective:	Outcome Measures:
To evaluate the safety and tolerability of BDA MDI relative to placebo MDI on EIB in adult and adolescent subjects with asthma	*Incidence of AEs/SAEs*

1.1.4 Exploratory objective

Exploratory Objective:	Outcome Measures:
To characterize the effect of BDA MDI 160/180 µg administered as a single-dose on bronchoconstriction compared with placebo	1. *Percentage of subjects with a maximum percentage fall in FEV_1 post-exercise challenge of $<20\%$* 2. *Time to recovery, defined as the time from completion of the exercise challenge to the first measured post-exercise challenge FEV_1 value within 10% of the post-dose, pre-exercise challenge baseline FEV_1* 3. *The percentage fall from baseline in FEV_1 at each time point within 60 minutes post-exercise challenge* 4. *Post-exercise FEV_1 area under the curve from 0 to 30 minutes ($AUC_{0\text{-}30min}$)*

1.2 Study design

This is a multicenter, double-blind, randomized, placebo-controlled, 2-period, single-dose, crossover study. The study will consist of a screening period (Visit 1 and Visit 2) and 2

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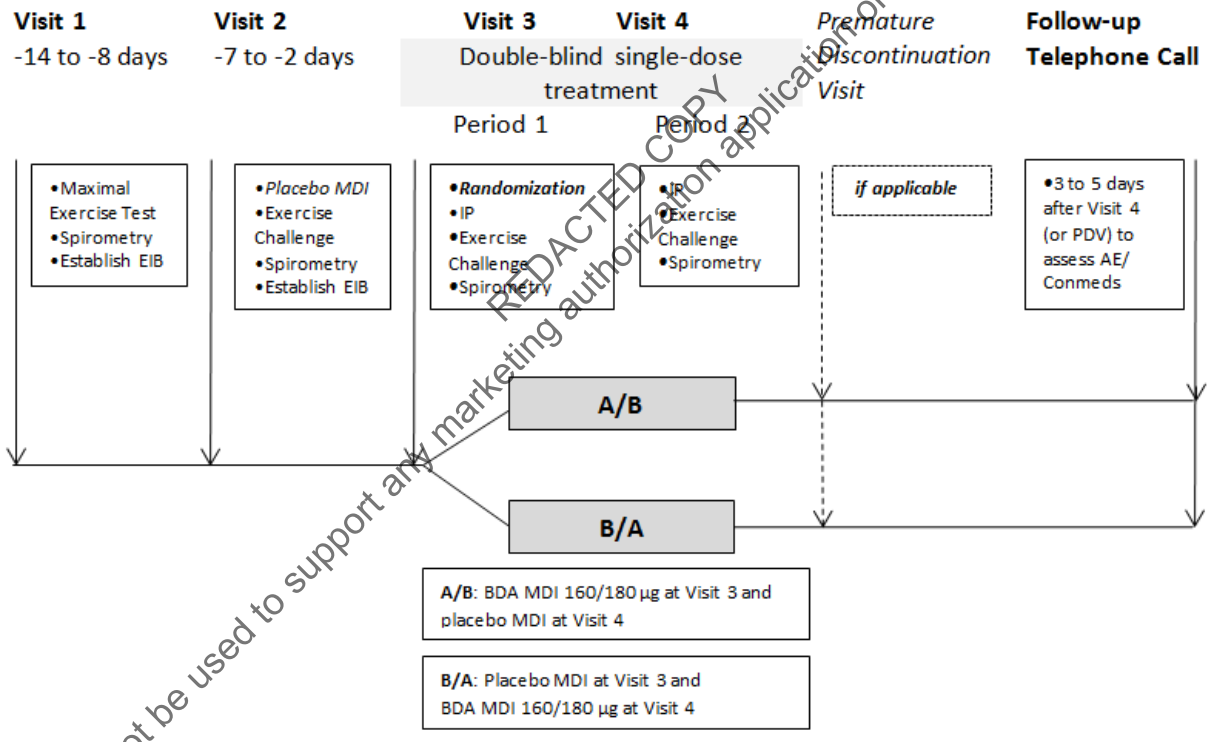
treatment visits (Visit 3 and Visit 4). A final follow-up visit will be conducted via a telephone call (TC) 3 to 5 days after the final in-clinic visit.

During the study, standardized exercise challenge tests (ECTs) are conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. At each visit, standard FEV_1 spirometry assessments will be performed relative to ECT and dosing, (before and after) as applicable. All spirometry and testing procedures are in accordance with current guidelines. A centralized spirometry data collection system incorporating a quality control program is used to reduce FEV_1 variability between and within subjects, and between study sites.

See Figure 1 for a graphical presentation of the study schema and Table 2 for a list of study assessments, and Table 3 and Table 4 for a list of the spirometry procedures conducted at the site, as per protocol.

Figure 1: Study design



Abbreviations: AE=adverse event; BDA=budesonide/albuterol; Conmeds=concomitant medication; EIB=exercise-induced bronchoconstriction; MDI=metered-dose inhaler; IP=investigational product; PDV=premature discontinuation visit.

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Approximately 60 subjects will be randomized 1:1 to 1 of 2 treatment sequences (ie, A/B or B/A) as specified in Table 1 Treatment sequences

Table 1 Treatment sequences

Treatment sequence	***Visit 3/Period 1***	***Visit 4/Period 2***
A/B	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*	*Placebo MDI (given as 2 actuations)*
B/A	*Placebo MDI (given as 2 actuations)*	*BDA MDI 160/180 µg (given as 2 actuations of BDA MDI 80/90 µg)*

Abbreviations: BDA=budesonide/albuterol; MDI metered-dose inhaler.

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Table 2 Study Assessments and Procedures

Visit	Screening [a]		Double-blind Treatment Phase		Unscheduled Visit or PDV [b] (if applicable)	Follow up
	1	2	3	4		TC (3 to 5 days after V4 or PDV)
			Period 1	Period 2		
Day	-14 to -8 [a]	-7 to -2 [a]	1	8(±6)		
Informed consent/assent	X					
Eligibility criteria	X [c]	X [c]				
Verify randomization criteria			X [d]			
Routine clinical procedures						
Medical/surgical history	X					
Demography	X					
Alcohol consumption and smoking history	X					
Physical examination	X			X	X	
Height and BMI	X					
Weight	X			X	X	
Concomitant medications	X	X	X	X	X	X
Routine safety measurements						
Pregnancy test [e]	X		X	X	X	
Laboratory assessments [f]	X					
Adverse events	X	X	X	X	X	X
Seated vital signs (blood pressure and heart rate) [g]	X	X	X	X		
12-lead ECG [g, h]	X	X	X	X		
Efficacy measurements						
Spirometry (FEV_1) [g]	X	X	X	X		
Maximal exercise test [h]	X [i]					
ECT with Treadmill [h]		X [i, j]	X [i, j]	X [i, j]		
Confirm FEV_1 stability [k]		X [k]	X [k]	X [k]		
Study treatment						
Randomization			X [d]			
IP		*(placebo MDI)*	X	X		

Abbreviations: *β-hCG=beta-human chorionic gonadotropin; BMI=body mass index; ECG=Electrocardiogram; ECT=Exercise Challenge Test; EIB=exercise-induced bronchoconstriction; FEV_1=Forced expiratory volume in 1 second; IP=Investigational Product; PDV=Premature discontinuation visit; TC=Telephone call; V=Visit.*

Notes:

[a] *The run-in periods at Screening are suggestions which can be shortened; the Screening and Double-blind Treatment Phase period must include at least 1 non-exercise test day between visit days.*

[b] *Subjects who prematurely withdraw from the study will undergo a PDV.*

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[c] *Eligibility criteria: At V2 pre-dose FEV_1 best value not exceeding ±20% of the best value measured at V1 pre-exercise; pre-exercise FEV_1 ≥70% of predicted at V1 and V2; demonstration of EIB (at both V1 and V2). One retest will also be allowed for a lack of FEV_1 drop (ie, negative EIB outcome) at V1 only if the FEV_1 drop is between 15% and <20%. Those subjects not meeting criteria will be considered screen failed.*

[d] *Subjects will be randomized at V3 to treatment if they demonstrate (at V3) a pre-exercise challenge FEV_1 ≥70% of predicted and a best pre-dose, pre-exercise challenge FEV_1 that does not exceed ±20% of the best pre-exercise challenge FEV_1 at V1.*

[e] *A serum pregnancy test (β-hCG) will be performed at V1, V4 and PDV; and a urine β-hCG test will be performed at V3 (for women of childbearing potential only).*

[f] *Laboratory assessments (clinical chemistry, hematology and urinalysis).*

[g] *The spirometry (and related safety) assessments to be performed in association with the exercise challenge at V1 to V4 are described in detail in Table 3 and Table 4 for details.*

[h] *Heart rate to be monitored continuously during the exercise challenge and until 60 minutes after completion.*

[i] *After V1, every attempt should be made to have subsequent ECTs started ±2 hours of the timing of the maximal exercise test done at V1.*

[j] *At V2, V3, and V4, an ECT will be conducted 30 (±5) minutes after IP administration.*

[k] *The pre-dose, pre-exercise challenge best FEV_1 value measured at each denoted visit (performed before exercise challenge) should not exceed ±20% of the pre-dose, pre-exercise challenge best FEV_1 value measured at V1.*

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Table 3 Spirometry assessments relative to the maximal exercise test at Visit 1

	Pre-exercise challenge			Maximal exercise test	Post-exercise challenge							
Time (minutes) / Assessments	-50 (±15)	-35 (±5)	-5 (±3)	0	5 (±3)	10 (±3)	15 (±3)	20 (±5)	30 (±5)	40 (±5)	45 (±5)	60 (±5)
Seated vital signs (BP and HR)	X [a]							X		X		X [b]
12-lead ECG	X [c]										X	
Spirometry [d]		X	X		X	X	X		X			X
Exercise challenge [e]				X								
HR monitoring [f]				X ----------	----------	----------	----------	----------	----------	----------	----------	----------X
Concomitant medication monitoring	X ----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------X
AE monitoring	X ----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------	----------X

Abbreviations: *ACQ-7=Asthma Control Questionnaire 7, AQLQ+12= Asthma Quality of Life Questionnaire for 12 years and older; ECG=electrocardiogram; FEV_1= forced expiratory volume in 1 second; IP=investigational product; min=minute; PAQLQ=Pediatric Asthma Quality of Life Questionnaire*

a. ***Notes***:

b. [a] *Vital signs should be recorded with the subject in the seated position and after 10 minutes of rest.*

c. [b] *Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes AFTER the last PFT (ie, 65 minutes [±5 minutes]).*

d. [c] *12-lead ECG recording at the pre-exercise challenge time point should be conducted after 10 minutes of rest.*

e. [d] *Every attempt should be made to perform the first pre-exercise (and pre-dose at Visits 2 to 4) spirometry measurement prior to 11:00 AM consistently across Visits 1 through 4 visit (ie, ±1 hour of the timing of the initial assessment at Visit 1).*

f. [e] *After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.*

g. [f] *Heart rate will be monitored continuously during the maximal exercise test and intermittently after maximal exercise test until 60 minutes after completion of the exercise challenge (ie, intermittently during PFTs).*

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Table 4 Spirometry assessments relative to the exercise challenge test and dosing at Visits 2, 3, and 4

	Pre-dose		***Dose***	***Post-dose***		***Post-exercise challenge***							
Time (minutes) / *Assessments*	*-50 (±15)*	*-5 (±3)*	*0*	*30 (±5)*	***ECT***	*5 (±3)*	*10 (±3)*	*15 (±3)*	*20 (±5)*	*30 (±5)*	*40 (±5)*	*45 (±5)*	*60 (±5)*
Seated vital signs (BP and HR)	*X* [a]								*X*		*X*		*X* [b]
12-lead ECG	*X* [c]											*X*	
Spirometry [d, e]		*X* [d, e]		*X*		*X*	*X*	*X*		*X*			*X*
Administer study drug [f]			*X*										
Exercise challenge [g]					*X*								
HR monitoring [h]					*X* ----------								*X*
Concomitant medication monitoring	*X* ----------												*X*
AE monitoring	*X* ----------												*X*

Abbreviations: *AE=adverse event; BP=blood pressure; ECG=electrocardiogram; ECT=exercise challenge test; HR=heart rate; PFT=pulmonary function test.*

Notes:

[a] *Vital signs should be recorded with the subject in the seated position and after 10 minutes of rest.*

[b] *Seated vital signs at the 60-minutes post-exercise challenge time point should be recorded 5-10 minutes AFTER the last PFT (ie, 65 minutes [±5 minutes]).*

[c] *12-lead ECG recording at pre-dose time point should be conducted after 10 minutes of rest.*

[d] *At Visits 2 through 4, if the FEV_1 criteria are not met in the first spirometry measurement (ie, 5 minutes pre-dose), 1 optional pre-dose spirometry measurement can be repeated after 30 minutes of the initial attempt. If first pre-dose FEV_1 fulfill all criteria, then the subject can proceed to dosing.*

[e] *Every attempt should be made to perform the first pre-exercise spirometry measurement prior to 11:00 AM consistently across Visits 1 through 4 visit (ie, ±1 hour of the timing of the initial spirometry performed at Visit 1).*

[f] *At Visit 2, subjects will receive placebo; while at Visit 3 and Visit 4 they will receive IP (BDA MDI or placebo MDI) depending on their randomization assignment.*

[g] *After Visit 1, every attempt should be made to have the subsequent ECTs done ±2 hours of the timing of the maximal exercise test done at Visit 1.*

[h] *Heart rate will be monitored continuously during the ECT and intermittently after ECT until 60 minutes after completion of the exercise challenge (ie, intermittently during PFTs).*

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1.3 Number of subjects

The target population will be outpatient subjects 12 to 70 years of age with asthma and exercise-induced bronchoconstriction (EIB).

1.3.1 Randomization and stratification

At Visit 3, eligible subjects are randomized (1:1) to receive 1 of 2 treatment sequences (BDA MDI 160/180 / Placebo MDI or Placebo MDI / BDA MDI 160/180). Randomization is centralized and stratified by age (adults: 18 years to 70 years; adolescents: 12 years to 17 years) and background ICS therapy (ICS or non-ICS).

Two subgroups of approximately equal size are included in the study, one subgroup of subjects currently treated with short/rapid-acting β2-adrenoreceptor agonist (SABA) prn alone, and a second subgroup on low-to-medium-dose inhaled corticosteroid (ICS) maintenance therapy (according to Global Initiative for Asthma [GINA] guidelines) and SABA prn.

1.3.2 Sample Size Calculation

Prior studies of a similar design have randomized subjects who experience exercise-induced symptoms without other generalized asthma symptoms. Other studies have permitted enrollment of those subjects experiencing exercise symptoms who may or may not be subjects with asthma (Bonini et al 2013). This study will only randomize subjects with asthma who are receiving background therapy for asthma (SABA prn alone; low-to-medium dose ICS plus SABA prn). Sub-analyses will be conducted on the primary endpoint for each of these subgroups of equal size.

Power calculations are based on the properties of the primary endpoint, the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge. A sample size of 30 subjects in each subgroup will provide a 92% probability to detect a difference of -9% between BDA MDI versus placebo MDI, within each of the 2 subgroups of interest (SABA prn alone; low-to-medium dose ICS plus SABA prn), assuming 2-sided, 5% level tests and a within-subject standard deviation of 10%. Randomization of 60 subjects in total will provide >99% overall probability to detect a difference of -9% between BDA MDI versus placebo MDI assuming a 2-sided, 5% level test and an estimated within-subject standard deviation of 10%. Since all subjects randomized in the study will be receiving background therapy for asthma, a more conservative estimate of variability and treatment effect has been assumed compared to studies of similar design (Ostrom et al 2015).

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2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All subjects enrolled

The all enrolled subject population includes patients who have provided signed informed consent for the study. The enrolled population will be used to present overall descriptive summaries of subject disposition.

2.1.2 All subjects randomized

The all subjects randomized population includes all subjects who have been randomized in the trial, irrespective of having at least 1 primary efficacy assessment (see 2.1.3). This population will be used to describe subject allocation and exclusion from the full and safety analysis sets, and stratification factors at randomization. Descriptive summaries based on the randomized population will be grouped by randomized treatment sequence.

2.1.3 Full analysis set

The full analysis set (FAS) is defined as all subjects who are randomized to treatment and have the following available measurements at either Visit 3 or Visit 4:

- Pre-dose baseline FEV_1
- Post-dose, pre-exercise baseline FEV_1

Please see section 4.1.5 for the definitions of baseline FEV_1. Subjects will be analyzed according to the treatment they were assigned as per the randomization scheme regardless of the actual IP received.

Additionally, data suspected to be fraudulent will be reviewed on a case-by-case basis and may lead to exclusion from the FAS. Such exclusions will be fully documented and all data will be readily available in the SDTM and ADaM datasets.

All efficacy analyses will be conducted on the FAS.

2.1.4 Safety analysis set

The safety analysis set is defined as all subjects receiving any amount of the IP. Subjects will be classified on the basis of treatment they actually received within each treatment period regardless of the treatment they were randomized to. Occurrences of safety events will be

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summarized under the actual treatment corresponding to the treatment period of which the event occurred. Further details on treatment assignment for occurrence safety data is described in Section 5.2.6.

All safety summaries will be based on the safety analysis set. Additionally, data suspected to be fraudulent will be reviewed on a case-by-case basis and may lead to exclusion from the safety analysis set. Such exclusions will be fully documented and all data will be readily available in the SDTM and ADaM datasets.

2.2 Protocol deviations

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All protocol deviations classified as important will be listed along with the full deviation term and coded term as provided in the SDTM data. The important deviations will be summarized in terms of the number and percentage of subjects meeting the pre-defined protocol deviation coded. IPDs will be identified by the sponsor prior to the primary database lock and unblinding of the study results.

A per protocol analysis excluding subjects with important protocol deviations is not planned. However, any subjects or site activity identified or suspected to be fraudulent (e.g. subjects who are enrolled on this clinical study more than once or another interventional clinical study, subjects re-enrolling onto the study or fabricated data) will be excluded from the analysis populations defined in section 2.1. Such instances will be reviewed on a case-by-case basis and fully documented by the Sponsor prior to unblinding.

All subjects who failed any inclusion/exclusion criteria will be listed along with details of the failed criteria. This information will also be summarized in terms of the number and percentage of subjects failing any of the inclusion/exclusion criteria and will be based on the FAS.

Any miss-stratified subjects will be identified as important protocol deviations. All subjects who are randomized and are part of the FAS will be analyzed according to the strata they were allocated to in IVRS/IWRS, as opposed to their actual strata.

3. Demography and Subject Characteristics Variables

3.1 Demographics

The following demographic characteristics are collected at Visit 1.

- Ethnicity*

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- Race*
- Sex

* Race and/or ethnicity will be collected depending on local regulations.

Additionally, age is collected at randomization. The age group strata will be derived based on the age at randomization and will be categorized as

- Adolescents: ≥ 12 to 17 years
- Adults: ≥ 18 years

Subjects must meet the eligibility criteria, assessed during screening, to be randomized to treatment. The list of inclusion and exclusion criteria are provided in the protocol. Eligibility criteria not met are collected on the eCRF.

Vital signs collected at Visit 1 includes height (cm), weight (kg) and a derivation of body mass index (BMI) (kg/m^2), as collected in the eCRF.

3.2 Medical, asthma and smoking history

Medical (including surgical), asthma and smoking history are recorded on the eCRF at Visit 1. General medical history will be categorized into past and current medical history. Current medical history will be defined as a condition that is either classified as on-going, or ending after the first dose of randomized treatment.

Additionally, the time since diagnosis of asthma (years) will be calculated as

(Date of first dose of randomized treatment (Visit 3) - Date of diagnosis of asthma)/365.25.

Partial dates for the above calculations will be handled as per section 4.1.9.

3.3 Concomitant medications

All concomitant medication will be recorded on the eCRF throughout the study. Disallowed medications will be identified by a physician or Avillion medical director (or designee) on review of the data which will be completed prior to database lock. All identified medications which are disallowed will be considered for flagging as an IPD during the protocol deviation reviews, prior to database lock and unblinding.

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3.4 Spirometry at study entry

Lung function measurements of FEV_1 (L), FVC (L), FEV_1/FVC (%) are recorded at screening Visit 1 and Visit 2. Please refer to Table 3 and Table 4 for a schedule of assessments for spirometry at screening. Visits 1 and Visit 2 spirometry assessments can be rescheduled if the subject has taken SABA within 6 hours prior to the visit, or has developed an upper respiratory tract infection.

If any of the spirometry criteria are not met at Visit 1, subjects can be retested within 2 to 10 days of the initial visit. Only 1 retest will be permitted for reasons related to technical issues (ie, acceptability) and/or pre-exercise FEV_1 ≥70% predicted, prior to randomization.

3.5 Treatment exposure

Treatment exposure and dosing information is collected on the eCRF. The time of IP administration occurring at the scheduled visits will be collected in the [redacted] device.

4. PRIMARY AND SECONDARY VARIABLES

4.1 General Definitions

4.1.1 Screening period

Screening assessments are collected at Visit 1 and Visit 2 (see Table 2). One retest is allowed for a lack of FEV_1 drop (ie, negative EIB outcome) at V1, these retests are defined as Visit 1a in the raw data.

Lung function data collected at Visit 1a should be used to represent the Visit 1 value for subjects in descriptive summaries at screening.

4.1.2 Crossover periods

Patients will be randomized to a particular sequence and will receive the first treatment in their sequence at Visit 3 and second treatment at Visit 4. Period 1 corresponds to the results collected at Visit 3 and Period 2 corresponds to results collected at Visit 4. Patient data will be grouped by the treatment they received in each period in the study outputs. The below table represents planned treatment group assignment based on randomized sequence and crossover period.

Randomized Treatment Sequence	**Planned treatment group**	
	Period 1 (Visit 3)	**Period 2 (Visit 4)**
BDA MDI 160/180 / Placebo MDI	BDA MDI 160/180	Placebo MDI

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Placebo MDI / BDA MDI 160/180	Placebo MDI	BDA MDI 160/180/

4.1.3 Relative time from exercise challenge test

Many of the efficacy endpoints require the time relative to the ECT, within the specific visit (visit 2, 3 and 4) and will be calculated as:

[Relative time from ECT (minutes)] = [Start time of assessment (HH:mm)] – [Stop time of ECT (HH:mm)]

Times of spirometry assessments are collected in the [redacted] device at site. The start and stop times of the exercise challenge test are collected in the eCRF.

4.1.4 Relative time from first dose of randomized treatment

In order to calculate the baseline FEV_1 endpoints (4.1.5), the time relative to first dose of randomized treatment, within the specific visit (visit 3 and 4) will be calculated as:

[Relative time from first dose (minutes)] = [time of assessment (HH:mm)] – [time of first dose (HH:mm)].

The relative time from first dose of placebo will be calculated at Visit 2 and will use the same derivation provided above.

Times of spirometry assessments and times of dosing at the scheduled visits will be collected in the [redacted] device at site.

4.1.5 Definition of baseline

4.1.5.1 Period specific post-dose pre-exercise baseline

Post-dose pre-exercise baseline is defined as the FEV_1 result taken post-dose of randomized treatment and prior to the exercise challenge test conducted at Visit 3 and Visit 4 (approximately occurring 30 minutes post dose of IP, Table 4). The post-dose pre-exercise baseline is period specific and therefore will be calculated at each Visit 3 and Visit 4.

The post-dose pre-exercise baseline will be used to calculate the primary, secondary and exploratory efficacy endpoint of changes from baseline.

Only lung function measurements of acceptable, or borderline acceptable quality will be considered for the assignment of baseline. If all post-dose pre-exercise spirometry efforts available are of an unacceptable quality, then the baseline will be missing.

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4.1.5.2 Period specific pre-dose baseline

The period specific pre-dose baseline is defined as the spirometry measurement taken prior to dosing of randomized treatment, which should occur at 5 minutes pre-dose of IP (Table 4). The period specific pre-dose baseline will be calculated separately at Visit 3 and Visit 4.

The period specific pre-dose baseline will be included as a covariate in parametric analyses of the primary, secondary and exploratory endpoints.

Only lung function measurements of acceptable, or borderline acceptable quality should be considered for the assignment of baseline. If all pre-dose spirometry efforts available are of an unacceptable quality, then the baseline will be missing.

The period specific pre-dose baseline will additionally be used to calculate changes from baseline in safety endpoints of vital sign parameters and ECG parameters.

4.1.5.3 Average pre-dose baseline

The average pre-dose baseline will be calculated as the average of the non-missing period specific pre-dose baseline result for each subject. The average pre-dose baseline will be included as a covariate in parametric analyses of the primary, secondary and exploratory endpoints.

4.1.6 Absolute and percent change from baseline

Absolute change from baseline outcome variables is computed as

Absolute change from baseline = (post-baseline value – baseline value).

Percent change from baseline is computed as

*Percentage change from baseline = [(post-baseline value – baseline value) / baseline value] * 100%.*

If either the post-baseline value or the baseline value is missing, then the absolute/percent change from baseline value will also be set to missing. Unacceptable quality spirometry measurements will not be used in the calculation of absolute/percentage change from baseline.

4.1.7 Percentage fall from post-dose pre-exercise baseline FEV_1

Percentage fall from post-dose pre-exercise baseline FEV_1 will be used to calculate primary, secondary and exploratory lung function endpoints and is defined as

[Percentage fall from post-dose pre-exercise baseline] = [(post-dose pre-exercise baseline value – post-exercise value) / post-dose pre-exercise baseline value] × 100%.

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The percentage fall from post-dose pre-exercise FEV_1 will be calculated at each post-exercise timepoint at Visits 2, 3 and 4.

If either the post-baseline value or the baseline value is missing, then the percentage fall from baseline value will also be set to missing. Unacceptable quality spirometry measurements will not be used in the calculation of percentage fall from baseline.

4.1.8 Visit windowing

Due to the design of this trial, there will be no visit windowing applied other than the identification of baseline as per definitions given in section 4.1.5. Any unscheduled visits which may occur will not be used in analyses, however all data will be listed where appropriate.

4.1.9 Imputation rules

When determining whether concomitant medication or adverse event emergence is pre- or post-randomized treatment, the following imputation methods will be applied.

Partial end date

1. If missing day [--/mm/yyyy] then impute as minimum{the end of the month, end of study participation}.
2. If missing month [--/--/yyyy] then impute as minimum{[31/12/yyyy], end of study participation}
3. If completely missing, then set to end of study participation.

Partial start date

4. If missing day [--/mm/yyyy] then impute as the minimum of:
    - If mm/yyyy is the same as the dose date of BDA MDI then set to dose date of BDA MDI; else if mm/yyyy is the same as the dose date of post-randomization Placebo MDI then set to dose date of Placebo MDI; else set to 01/mm/yyyy
    - End date of medication/ event (after partial date handling has been applied).
5. If missing month [--/--/yyyy] then impute as the minimum of:
    - If yyyy same year as BDA MDI then set to date of BDA MDI dose; else if yyyy same year as post-randomization Placebo MDI dose date set to dose date of Placebo MDI; Else set to start of the year [01/01/yyyy].
    - End date of medication/ event (after partial date handling has been applied).
6. If completely missing, then impute as the minimum of:
    - Date of first dose of BDA MDI, unless missing then date of first dose of randomized Placebo MDI.
    - End date of medication/ event (after partial date handling has been applied).

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This imputation method is defined to enable the classification of adverse events and concomitant medications as pre- or post-treatment for reporting in summary tables. The above imputation process will additionally assign the occurrence to the BDA MDI treatment group, unless it can be unequivocally determined otherwise, based on the partial information collected. The raw, original dates will be presented in any listings produced.

The primary endpoint of maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will have missing values imputed as part of a sensitivity analysis. Please refer to Section 5.2.9 for further details on this imputation method.

4.1.10 Serial spirometry data

Serial spirometry data collected by the [redacted] device will be conducted at timepoints as specified in Table 3 and Table 4. At any scheduled timepoint, several spirometry efforts will be carried out by the patient for up to a maximum of 8 efforts. Of these 8 efforts, a best effort is identified by the [redacted] device. The SDTM datasets will contain all efforts produced at each scheduled timepoint, with an indicator variable showing which effort was determined the best by [redacted].

Generally, for all endpoint analyses of lung function data, the best effort will be used for analysis. The exception to this rule is the time to recovery exploratyory endpoint (See section 4.4.2) which will use the all efforts data to more precisely identify the time in which a patient returns to 15% of their baseline result.

4.2 Primary Efficacy Measure

4.2.1 Maximum fall from post-dose, pre-exercise baseline in FEV_1

The maximum percentage fall during the 60-minute assessment period, prior to the use of rescue medication, will be calculated at Visit 3 and Visit 4. Only acceptable and borderline acceptable quality FEV_1 measurements will be considered.

4.3 Secondary Efficacy Measures

4.3.1 Derivation of responder status in post exercise FEV_1 (10% threshold)

A binary response variable will be assigned to identify subjects with a maximum percentage fall in FEV_1 post-exercise of <10% separately at Visit 3 and Visit 4:

- Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge <10%
- Not Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge ≥10%

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The maximum percentage fall will be defined as per the primary endpoint in Section 4.2.1. If a subject has a missing maximum percentage fall from post-dose, pre-exercise baseline in FEV1 up to 60 minutes post-exercise challenge, then they will be classified as a non-responder.

4.4 Exploratory Efficacy Measures

4.4.1 Derivation of responder status in post exercise FEV1 (20% threshold)

The secondary endpoint on responder status as detailed in section 4.3.1 will be repeated based on a 20% threshold:

- Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge <20%
- Not Protected: Maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 up to 60 minutes post-exercise challenge ≥20%

If a subject has a missing maximum percentage fall from post-dose, pre-exercise baseline in FEV1 up to 60 minutes post-exercise challenge, then they will be classified as a non-responder.

4.4.2 Time to recovery in post-exercise FEV_1

Time to recovery at each of Visits 3 (period 1) and 4 (period 2) will be derived as the time (minutes) from the end time of the exercise challenge test to the time in which the FEV_1 result returns to within 10% of the value recorded at the post-dose, pre-exercise baseline.

For time to recovery endpoints, the actual time will be used and will consider all efforts produced that are of an acceptable, or borderline acceptable quality. This will allow greater precision in identifying the time to recovery compared to using the best efforts for each nominal timepoint. Please see Section 4.1.10 for a summary of best effort and all effort spirometry data.

If a subject has not observed a fall greater than 10% of the post-dose pre-exercise baseline in their post-exercise challenge test by 60 minutes, they will be left censored at 0 minutes. Subjects with an observed fall and have required rescue medication during the post-ECT assessments will be censored at the time of receiving rescue medication. Subjects who do not recover to within 10% of the post-dose, pre-exercise baseline will be censored at their last assessment taken at the visit.

Once the event time has been derived for each subject and period, period preferences will be assigned as follows:

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Time to event	Period preference
$t_1 < t_2$	Period 1
$t_1 > t_2$	Period 2
$t_1 = t_2$ [a]	No preference

t_i = time to event in period i. If a subject is censored at a particular period, t_i represents the time to censoring.

[a] If event times have required censoring and it cannot be determined which period is of preference, then *no period preference* will be assigned for that subject. A working example is as follows: If a subject required rescue medication at 10 minutes post-ECT in period 1, and at 20 minutes in period 2, then we have censored event times of [>10 minutes, >20 minutes] for t_1 and t_2, respectively. Since $t_1 - t_2$ spans a range of possible outcomes that includes a difference of 0 minutes (−10 minutes, + ∞ minutes), this subject is classified as having no period preference for their time to recovery.

4.4.3 Derivation of FEV_1 $AUC_{0\text{-}30min}$

FEV_1 $AUC_{0\text{-}30min}$ will be derived for the changes from the post-dose, pre-exercise baseline using the trapezoidal rule and will be normalized by dividing by the actual time (in minutes) from the exercise challenge test to the last included measurement, scheduled at 30 minutes post-exercise challenge at each of Visits 3 and 4. Only FEV_1 results prior to the use of rescue medication will be considered when calculating FEV_1 $AUC_{0\text{-}30min}$.

$$AUC_{0-30\ minutes} = \frac{1}{t_N - t_0} \times \sum_{i=1}^{N} \frac{(y_{i-1} + y_i) \times (t_i - t_{i-1})}{2}$$

For FEV_1 change from baseline results y_i recorded t_i minutes after the exercise challenge test (actual clock time) at $i = 0, 1, 2, \ldots, N$ actual timepoints. If all post-exercise timepoints are available, then $N = 4$, t_0 corresponds to the end time of the exercise challenge test and $y_0 = 0$. Only FEV_1 results of 'acceptable' or 'borderline acceptable' (investigator assigned) quality will be used in the derivation of FEV_1 $AUC_{0-30\ minutes}$. If a FEV_1 result is missing or recorded in the database, but assigned an 'unacceptable' quality grade at the scheduled assessment, then the assessment will be excluded from the calculation of FEV_1 $AUC_{0\text{-}30\ minutes}$. To calculate FEV_1 $AUC_{0\text{-}30\ minutes}$, there must be at least 1 non-missing post-dose FEV_1 within 0 to 30 minutes post-dose. Missing FEV_1 post-dose measures will not be imputed.

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4.5 Safety variables

4.5.1 Vital signs

The following vital signs measurements are conducted throughout the study and as per Table 3 and Table 4.

- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

Any clinically significant changes in vital signs are recorded as an AE if applicable.

Changes from baseline to each post-ECT timepoint in vital sign parameters will be calculated based on the period-specific baseline result (4.1.5.2) for each visit 3 and visit 4.

4.5.2 Adverse events (including Serious Adverse Events)

4.5.2.1 Definition of adverse event

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom (e.g., nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including the screening period, even if no randomized treatment has been administered.

4.5.2.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e., after the signing of the informed consent/assent through to the safety follow-up TC), that fulfills 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

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All SAEs will be identified by the investigator and entered in the eCRF. The 'Serious?' field will be set to 'Y'.

4.5.2.3 Collection of AEs and SAEs

AEs and SAEs will be collected from time of signature of informed consent/assent, through the safety follow-up period.

The following variables will be collected for each AE:

- AE term (verbatim)
- The date when the AE started and stopped
  - YYYY/MMM/DD
- Maximum intensity
  - Mild
  - Moderate
  - Severe
- Serious
  - Yes or no
- Investigator causality rating against the randomized treatment
  - Yes or no
- Action taken regarding randomized treatment
  - Dose not changed
  - Drug interrupted
  - Drug permanently discontinued
  - Not applicable
- Outcome
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal

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4.5.2.4 Adverse events data handling

Adverse events will be reported as starting during screening if the AE start date is prior to the first dose of randomized treatment taken at Visit 3.

Adverse events will be considered as treatment emergent if the onset date is on or after the first dose of randomized treatment at visit 3.

If an AE has a missing onset date, then, unless the stop date of the AE indicates otherwise, this will be considered as treatment emergent. Similarly, if an AE has a partial onset date, then unless the partial onset date or the stop date indicates otherwise, this will be considered as treatment emergent. AEs will be represented under the randomized treatment group the AE was preceded by, if it cannot be unequivocally determined based on partial date collection, the AE will be summarized under the BDA MDI treatment group.

Please refer to Section 4.1.9 for the imputation rules to programmatically determine the classification of AEs when there is partial start and/or stop dates recorded.

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4.5.3 Laboratory Safety Variables

The following laboratory variables described in Table 5 Laboratory Safety Variables will be collected at screening and at unscheduled visits, if required:

Table 5 Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	***Clinical Chemistry (serum or plasma)***
Basophils (%)	*Albumin*
Basophils Abs	*Alanine transaminase*
Eosinophils (%)	*Alkaline phosphatase*
Eosinophils Abs	*Aspartate transaminase*
Hemoglobin	*Bilirubin, total*
Hematocrit	*Calcium, total*
Mean Corpuscular Hemoglobin	*Chloride*
Mean Corpuscular Hemoglobin Concentration	*Cholesterol, total*
Mean Corpuscular Volume	*Creatinine*
Monocytes (%)	*Creatine kinase*
Monocytes Abs	*Gamma-glutamyl transpeptidase*
Neutrophils (%)	*Glucose (random)*
Neutrophils Abs	*Magnesium*
Red blood cells (erythrocytes)	*Phosphate*
White blood cells (leukocytes)	*Potassium*
Platelet count	*Protein, total*
Lymphocytes Abs	*Sodium*
Lymphocytes (%)	*Triglycerides*
Urine	*Urea*
Urine β-hCG pregnancy (at Visit 3) [a]	*Serum β-hCG pregnancy (Visit 1, 4 and PDV)* [a]
Urine hemoglobin	
Urine erythrocytes	
Urine protein	
Urine albumin	
Urine glucose	

Abbreviations: Abs=absolute; β-hCG=β-human chorionic gonadotropin; PDV=premature discontinuation visit

[a] β-hCG pregnancy testing for women of childbearing potential only

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4.5.4 12-lead electrocardiogram

A resting 12-lead ECG is performed at Visit 1 (Table 2). The 12-lead ECG is obtained using a centralized laboratory after the subject has been resting semi-supine for at least 10 minutes. For all ECGs, details of rhythm, PR, RR, QRS, and QT intervals, as well as an overall evaluation are recorded.

Additionally, ECG results are collected pre-dose and post-exercise challenge at Visit 2 Visit 3 and Visit 4. The maximal heart rate is recorded during the exercise challenge test and entered on the eCRF.

Changes from baseline in mean heart rate (beats/min), pulse rate interval (msec), QRS duration (msec), QT interval (msec), QTcB interval (msec), QTcF interval (msec) and RR interval (msec) will be calculated at Visit 3 and Visit 4, using the period-specific pre-dose baseline.

4.6 Other variables

4.6.1 Concomitant medications

The collection and recording of all concomitant medication, including all pre-enrollment asthma therapies, are performed at the visits detailed in Table 2.

If a concomitant medication is recorded with partial start date and/or end date of administration, a conservative approach will be considered such that unless it can be unequivocally determined that the medication started and ended prior to the first dose of randomized study drug, based on available information from the partial date(s), the medication will be classified as concomitant. To facilitate this decision-making process programmatically, the imputation process defined in section 4.1.9 will be considered.

4.6.2 Withdrawal from study

Reasons for premature withdrawal from the study for randomized subjects are collected on the eCRF and include the following fields:

- Patient Decision
- Adverse Event
- Severe non-compliance to protocol
- Condition under investigation worsened
- Lack of Therapeutic Response
- Development of study specific discontinuation criteria
  - A severe exacerbation event
  - Pregnancy

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- Subject lost to follow-up
- Other

Randomized subjects who withdraw prior to Visit 4 are asked to complete a PDV (see Table 2).

Patients who withdraw prior to randomization, or are lost to follow-up following Visit 4 (i.e. the safety follow-up call) will have their end of study status collected in the eCRF under the following fields:

- Adverse Event
- Completed
- Death
- Lost to Follow-Up
- Protocol Deviation
- Screen Failure
- Withdrawal by Subject
- Withdrawal by Parent/Guardian
- Other (specify)

4.6.3 Screen Failures

Screen failures are subjects who do not fulfill the eligibility criteria for the study, and therefore must not be randomized. These subjects should be recorded as a 'Screen Failure' on the disposition eCRF page. Subjects who are screen failures will not be rescreened.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the medical monitor immediately, and a discussion should occur between the medical monitor and the investigator regarding whether to continue or withdraw the subject in the study. The medical monitor must ensure all decisions are appropriately documented. All subjects randomized in error will be analyzed in accordance with the FAS and Safety analysis set definitions (Section 2).

4.6.4 Maximum fall from post-dose, pre-exercise baseline in FEV_1 at Visit 2

Maximum percentage fall will be derived at scheduled Visit 2 for all subjects as per the derivation given in Section 4.2.1. The post-dose pre-exercise baseline is defined as the 30 minute post-dose measurement taken prior to exercise at Visit 2.

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5. ANALYSIS METHODS

5.1 Statistical Considerations

All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations are identified.

Analyses described within this Statistical Analysis Plan will be performed by [redacted].

5.1.1 Estimands

Two estimands are of interest in this study:

The primary estimand of interest is the Efficacy Estimand, defined as the effect of the randomized treatments in all subjects and in the absence of intercurrent events which may impact the interpretation of the treatment effect. This estimand could be considered a while-on-treatment strategy or a hypothetical strategy as defined in the draft ICH E9 Addendum. Per protocol, subjects will have serial spirometry procedures stopped prematurely if the post-exercise FEV_1 result drops below 40% and requires rescue therapy (SABA). Rescue therapy in this scenario is not an intercurrent event since reaching the maximum fall has triggered administration of rescue. However, rescue medication use that is prior to the first spirometry reading being taken or if there are no spirometry data that meet ATS/ERS acceptability criteria prior to the use of rescue medication will constitute an intercurrent event. This estimand targets the treatment difference in a scenario where the intercurrent event does not occur, such that outcomes for subjects without the intercurrent event are as observed, and outcomes for subjects with the intercurrent event are treated as though they had completed the observation period. A while on treatment strategy will be used such that missing maximum percentage fall data will be assumed missing at random (MAR) and handled by the direct likelihood methods of the mixed effects model.

Missing data not preceded by an intercurrent event, such as subjects who withdraw from study will be assumed to be MAR under the efficacy estimand.

The efficacy estimand will be applied to the primary analyses and exploratory analyses of: Maximum percentage fall from post-dose pre-exercise FEV_1, up to 60 minutes following the ECT; Time to recovery in post-exercise FEV_1 and post-exercise FEV_1 $AUC_{0\text{-}30\ mins}$.

The second estimand of interest is the attributable estimand, defined as the effect of treatment in subjects attributable to the randomized treatment. Patients who administer rescue therapy prior to any post-exercise challenge spirometry measures, or have no spirometry data that meet ATS/ERS acceptability criteria prior to the use of rescue medication will be considered a negative outcome. In these cases, subjects' maximum percentage fall from post-dose pre-exercise FEV_1 will be imputed using a reference based approach as detailed in section 5.2.9.

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The analysis of the primary endpoint under the attributable estimand will be considered a supportive analysis to assess robustness of conclusions made under the efficacy estimand.

Additionally, the secondary and exploratory responder analyses as specified in sections 5.2.5.1 and 5.2.7.1 will be conducted under the attributable estimand. Patients with missing post-exercise challenge FEV_1 measurements will be imputed as non-responders.

5.1.2 Type I error control

Two subgroups of approximately equal size will be included in the study, 1 subgroup of subjects on SABA prn only and the other subgroup on low-dose ICS maintenance therapy according to GINA guidelines. All primary, secondary and exploratory analyses will be repeated on each of these subgroups of interest. For the primary analyses in each subgroup, a sequential testing strategy will be adopted, controlled at $\alpha = 5\%$ for each comparison. The subgroup comparisons will be conducted in the following sequence:

1. Overall population (SABA prn only OR low-to-medium dose ICS plus SABA prn background therapy)
2. Subjects taking SABA prn only for background therapy
3. Subjects taking low-to-medium dose ICS plus SABA prn for background therapy

If a comparison is significant (alpha=0.05, 2-sided), testing will proceed to the next comparison. Comparisons will stop if a non-statistically significant result occurs. All comparisons are of superiority of BDA MDI 1609/180 versus Placebo MDI. Please refer to section 5.2.4 for further detail on the primary analysis.

5.1.3 Treatment groups

Descriptive summaries and analyses of endpoints listed below will be grouped by treatment. As subjects will receive both BDA 160/180 MDI and Placebo MDI. Subjects will be represented by the treatment they receive at each visit. Therefore, post-randomization analyses of endpoints will not be broken down by visits, since visits will be mutually exclusive per subject and their dosed treatment combinations.

5.2 Analysis methods

All tests will be 2-sided and conducted at 5% level of significance unless otherwise stated.

When appropriate, statistical analysis models will be adjusted to include the stratification factor of background ICS which will be used to describe the populations of clinical interest for the study. All subjects who are randomized and are part of the FAS will be analyzed according to the strata they were allocated to in IVRS/IWRS. Any subjects who are miss-stratified will be identified as important protocol deviations and listed in the CSR.

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In addition to the analyses described below, all variables will be summarized descriptively where appropriate.

Unless otherwise stated, descriptive summaries of continuous endpoints will include: The number of evaluable subjects in the analysis (n); Mean; Standard Deviation; Median; Minimum; Maximum. Summaries of categorical endpoints will include the absolute counts and percentage, with the denominator used in the percentage calculation clearly defined in the footnote of the table. Unless stated otherwise, the denominator will be the number of subjects in the analysis set used for the descriptive summary.

5.2.1 Subject Disposition

Subject disposition will be summarized for all subjects who have been enrolled and have provided informed consent. The number of subjects who were enrolled, screened and screen failed will be summarized. The number and percentage of subjects will be presented by the following categories; randomized, not randomized (and reasons), randomized who received study treatment, randomized who did not receive study treatment (and reasons), completed, and discontinued the study (and reasons). If the reason for premature discontinuation is "Development of study specific discontinuation criteria" the specify field, which contains standard text, will be reported as a sub-field in the summary table. For categories that are post-randomization, summaries will be further split by treatment sequence.

A separate table will present the number and percentage of subjects randomized to each treatment sequence, by country and center. This table will be based on the FAS.

A descriptive summary of the number subjects allocated to the safety analysis set and FAS will be presented by treatment sequence. This summary will use the all randomized subjects population.

5.2.2 Demographic and Baseline Characteristics

The summary of demographic and baseline characteristics will be performed on the FAS and will be summarized by treatment sequence (including total across sequence groups).

Demographic characteristics of age (years), sex, race and ethnic group will be summarized descriptively.

Subject height (cm), weight (kg) and BMI (kg/m^2) will be summarized by treatment sequence (including total across sequence groups).

Maximal heart rate at screening Visit 1 and Visit 2 will be summarized by treatment sequence (including total across sequence groups). At Visits 3 and 4, the maximal heart rate will be summarized descriptively by treatment group.

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Lung function endpoints of pre-ECT FEV_1 (L), FVC (L) and FEV_1/FVC (%) will be summarized at Visit 1 and Visit 2 descriptively, within treatment sequence and across treatment sequences. Additionally, maximum percentage fall in post-dose pre-exercise challenge will be presented for Visit 2 by treatment sequence and overall. All lung function data collected at screening will be listed.

Medical (past and current) and surgical histories will be summarized by MedDRA preferred term within MedDRA system organ class. The MedDRA version used for coding will be provided in the corresponding programmed output footnotes.

Smoking status will be summarized categorically as the number of subjects who have never smoked, are current smokers or are former. Nicotine pack years, e-cigarette pack years and total (nicotine + e-cigarette) pack years will be summarized as continuous endpoints.

Asthma history variables collected on the eCRF will be summarized descriptively. Time since diagnosis of asthma will be summarized as a continuous scale and present the median, minimum and maximum result by treatment sequence.

5.2.3 Treatment Exposure

Treatment exposure will be listed for all subjects.

5.2.4 Analysis of the primary endpoint

The maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will be analyzed with a mixed effect model including categorical fixed effects for treatment, treatment period and treatment sequence. Continuous covariates include period-specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1 in order to eliminate cross-level bias whilst using pre-treatment baselines (Kenward and Roger, 2009). A random subject within treatment sequence effect will be specified. Estimated treatment differences in maximum percentage fall from post-dose pre-exercise FEV1 up to 60 minutes post-ECT will be presented from the model, along with associated 95% confidence intervals (CIs) and 2-sided p-values.

The corresponding hypotheses for the primary analysis are as follows:

H_{01}: Difference between treatments = 0,

H_{A1}: Difference between treatments ≠ 0.

The primary treatment comparison of BDA MDI 160/180 versus placebo MDI for the maximum percentage fall from post-dose, pre-exercise baseline in FEV_1 observed up to 60 minutes post-exercise challenge will be conducted on the FAS and include all data up to study withdrawal as per the Efficacy Estimand. Missing results for maximum percentage fall in

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FEV_1 are unlikely (i.e., rescue medication will most likely occur after to the collection of the 5 minutes measure) and will be assumed to be missing at random. Based on previous studies it is highly unlikely that a subject will require rescue medication prior to their first post-ECT measurement (Ostrom et al 2015).

The primary analysis will be repeated on the subgroups of clinical interest (SABA prn alone; low-to-medium dose ICS plus SABA prn). To control the overall type-I error controlled at 5%, a hierarchical testing strategy will be adopted. The treatment comparisons of BDA MDI 160/180 versus placebo MDI will be conducted on the subject sub-populations of the FAS in the sequence given below:

1. Overall population (SABA prn only OR low-to-medium dose ICS plus SABA prn background therapy)
2. Subjects taking SABA prn only for background therapy
3. Subjects taking low-to-medium dose ICS plus SABA prn for background therapy

If a comparison is significant (alpha=0.05, 2-sided), testing will proceed to the next comparison. Comparisons will stop if a non-statistically significant result occurs. All comparisons are of superiority. Least squares mean estimates, 95% confidence intervals and associated p-values of the treatment difference will be calculated for the subgroups of clinical interest by additionally adjusting for background therapy and background therapy*treatment group interaction in the mixed model.

All subjects who are randomized and are part of the FAS will be analyzed according to the ICS stratum they were allocated to in IVRS/IWRS in this primary analysis. A sensitivity analysis will be conducted based on subjects' actual strata to assess the impact of miss-stratification on the model results.

A forest plot will be created showing the difference in least squares mean estimates and associated 95% confidence intervals for the Overall, ICS and non-ICS subgroups.

5.2.5 Analysis of the secondary efficacy variables

In addition to the analyses described below, all variables will be summarized descriptively where appropriate. All descriptive and inferential analyses will be described in accordance with the attributable estimand. The analyses will be repeated in the key subgroups of clinical interest (SABA prn alone; low-to-medium dose ICS plus SABA prn). No type-I error control is applied to the secondary efficacy analyses.

5.2.5.1 Responder analysis in post-exercise FEV_1

The odds of being protected against EIB (i.e., having a maximum percentage fall in FEV_1 post-exercise challenge of <10%) will be analyzed using a generalized linear mixed model with logit link function to compare the treatments. The model will be adjusted with fixed

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effects for treatment, treatment period and treatment sequence, period specific pre-dose baseline FEV_1 and average pre-dose baseline FEV_1 as continuous covariates, and a random subject within treatment sequence effect. The odds ratio and 95% CI will be reported for pairwise treatment comparisons.

This analysis will be repeated for subgroups of clinical interest by additionally adjusting for background therapy (non-ICS, ICS) and background therapy*treatment group interaction.

5.2.6 Analysis of safety variables

The safety analyses will include all data collected prior to study withdrawal and will use the safety analysis set. Safety data collected during screening will be listed separately.

5.2.6.1 Adverse events

Adverse events will be summarized by treatment group, system organ class and preferred term assigned to the event by the Medical Dictionary for Regulatory Activities, using the most recent version available at the time of database lock. The following summaries will be included:

- Number of subjects with any AE in any category during randomized treatment period.
- Incidence of adverse events in the randomized treatment period by SOC and PT.
- Number of subjects with AE with outcome of death by SOC and PT.
- Serious adverse events during the randomized treatment period by SOC and PT.

All adverse events data collected, including adverse events occurring during screening will be listed for each subject in the safety analysis set.

A separate listing will be produced detailing any other significant adverse events as identified by the scientific review prior to database lock and unblinding of the trial.

5.2.6.2 Vital signs

Absolute values and changes from baseline in vital signs variables (Section 4.5.1) will be descriptively summarized by timepoint within treatment group. Vital signs will be listed for all subjects in the safety analysis set.

5.2.6.3 Clinical chemistry and hematology

All laboratory data collected during the screening period and at unscheduled visits will be listed for subjects in the safety analysis set.

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5.2.6.4 Electrocardiogram

ECG parameters will be summarized as absolute values and changes from baseline by treatment group. All ECG data will be listed.

5.2.6.5 Concomitant medication

The number and percentage of subjects who take allowed concomitant medications, and those who take disallowed concomitant medications during the study, will be presented by standardized medication name, within generic class (WHO Drug dictionary text) for each treatment group.

Listings will be grouped by prior medication, medication occurring during the randomized treatment period.

5.2.7 Analysis of exploratory variables

In addition to the analyses described below, all variables will be summarized descriptively where appropriate. All descriptive and inferential analyses will be described in accordance with the Efficacy Estimand, unless states otherwise in the endpoint specific subsections (below). The analyses will be repeated in the key subgroups of clinical interest (SABA prn alone; low-to-medium dose ICS plus SABA prn). No type-I error control is applied to the exploratory efficacy analyses.

5.2.7.1 Responder analysis in post-exercise FEV_1 (20% threshold)

The odds of having a maximum percentage fall in FEV_1 post-exercise challenge of <20% will be separately analyzed using a generalized linear mixed model to compare treatments as specified in Section 5.2.5.1. Any subjects who required rescue medication prior to the 5 minute lung function assessment will be considered a non-responder, in accordance with the attributable estimand for responder analyses. This analysis will be repeated for subgroups of clinical interest by additionally adjusting for background therapy (non-ICS, ICS) and background therapy*treatment group interaction.

Additionally, a scatter plot of maximum percentage fall from post-dose pre-exercise FEV_1 will be graphically represented with reference regions annotated to show the unprotected (>20% fall), partially protected (10%-20% fall) and protected (<10% fall) subjects, grouped by treatment.

5.2.7.2 Time to recovery

The median time to recovery will be reported descriptively by treatment. P-values will be calculated using Prescott's period-adjusted sign test, based on categorizing subjects into period preferences (Senn 1993). Analyses will be stratified by background therapy categories of: All subjects, non-ICS and ICS.

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5.2.7.3 Fall in post-exercise FEV_1 at individual time points

The percentage fall in FEV_1 post-exercise challenge will be summarized descriptively by treatment group and planned time point within 60 minutes of the serial spirometry assessments conducted post-exercise challenge. An analysis of percentage fall in FEV_1 post-exercise challenge will be conducted using methods as per the primary analysis, with an additional adjustment for planned time point in the repeated measures model. The covariance within subject-periods will be unstructured over the time points. Only FEV_1 results prior to administration of rescue therapy (within the study visit) will be included in the analyses, as per the Efficacy Estimand. This analysis will be repeated for subgroups of clinical interest by additionally adjusting for background therapy (non-ICS, ICS), background therapy*treatment group and background therapy*treatment group*planned timepoint interactions.

The mean percentage fall from post-dose pre-exercise FEV1 will be plotted at each nominal (planned) post-exercise timepoint for each treatment group. Error bars will be provided showing the mean ± standard error.

5.2.7.4 Post-exercise FEV_1 $AUC_{0\text{-}30min}$

The post-exercise FEV_1 $AUC_{0\text{-}30\ min}$ will be analyzed with a similar mixed effects model as described in Section 5.2.4 for the maximum percentage fall in FEV_1 without exercise pre-treatment. Only the FEV_1 $AUC_{0\text{-}30\ min}$ measurements prior to administration of rescue SABA therapy will be included in the analyses. This analysis will be repeated for subgroups of clinical interest by additionally adjusting for background therapy (non-ICS, ICS) and background therapy*treatment group interaction.

5.2.8 Subgroup analysis

The assessment of treatment effect will also be investigated for primary and secondary endpoints in the other clinically important subgroups described in Table 6.

Table 6 Subgroup Analysis

Group	***Subgroup***
Sex	Male
	Female
Age group (years)	Adolescents: ≥ 12 - < 18
	Adults: ≥ 18 - < 65
	Elderly: >= 65
BMI (kg/m^2)	Median value cut-off [1]
Baseline FEV_1	Median value cut-off [1]

[1] Subgroup will be categorized into two groups defined by the median value observed at baseline.

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For all subgroup analyses, if there are less than 10 subjects/events available within a subgroup and at least 5 subjects with data available per treatment group under comparison, or the model does not converge, then only descriptive (summary) statistics will be presented. Subgroup analyses will be further broken down into the overall population, and ICS and non-ICS key populations of interest. Subjects with insufficient data to be allocated to a subgroup category will be excluded from the subgroup analyses.

Generalized additive models (GAM) will be fit to explore any potential non-linear association between the crossover differences in the primary endpoint versus age, BMI and baseline FEV_1 as continuous measures. The GAM will use the gaussian link and plots will be presented showing the smoothing splines and associated 95% confidence limits.

Forest plots will be produced showing the least squares mean difference and associated 95% confidence intervals within each subgroup for the primary endpoint of maximum percentage fall from post-dose, pre-exercise baseline in FEV_1.

5.2.9 Supportive analysis

5.2.9.1 Attributable estimand

Analysis under the attributable estimand will be conducted in the FAS and will act as a supportive analysis to the primary endpoint (section 5.2.4). Data that are missing will be imputed using reference-based imputation. Subjects with a missing maximum percentage fall in the 60-minute assessment period, for any visit, will be imputed using the least squares mean estimate of the maximum percentage fall in the Placebo MDI treatment group from a mixed model as specified in 5.2.4, using the observed data. The dataset of complete data, following imputation, will be re-analyzed as per section 5.2.4 and estimated treatment differences, associated 95% confidence intervals (CIs) and p-values will be provided.

5.2.10 COVID-19 impacts

Tyree is an on-going trial throughout the coronavirus disease 2019 (COVID-19) outbreak. Due to the design and short study duration, it is not expected that trial data or the analyses will be greatly impacted by the pandemic. Although, it is important to be able to identify any potential intercurrent events due to COVID-19 and to be able to quantify their impact on the efficacy and safety profile of the study.

5.2.10.1 Missed Visits due to COVID-19

Due to the design of Tyree, a missed visit is not expected to occur. If a subject misses a Screening visit (Visit 1/1a, Visit 2/2a) then the subject has not provided suitable eligibility criteria to enroll and will not be randomized. If a subject misses Visit 3 and it is not rescheduled, then they will not have been randomized to the study and will be screen failed. If they miss Visit 4 and it is not rescheduled, then the subject will be considered as a premature withdrawal from the study and will be documented as such in the eCRF.

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5.2.10.2 Premature discontinuation due to COVID-19

If a subject cannot continue with procedures and scheduled assessments due to COVID-19 post-randomization, they will be withdrawn from the trial and will be asked to complete the PDV. A separate listing of subjects who prematurely withdraw due to COVID-19 will be provided. The listing will detail the reason for withdrawal and relationship to COVID-19. The listing of premature withdrawals due to COVID-19 will be based on the full analysis set.

It is not expected that premature withdrawals will be related to randomized treatment. Therefore, the missing data subsequent to withdrawal will be considered as missing at random, in accordance with the efficacy estimand.

5.2.10.3 Assessments not done due to COVID-19

Spirometry assessments

Any subject that has not performed serial spirometry assessments at a post-randomization visit will be listed. The listing will provide the subject ID, the scheduled visit name and the corresponding reason for the missed assessment, detailing how COVID-19 impacted the missed assessment. The listing of missed spirometry data will be presented in the full analysis set.

Any missed spirometry data due to COVID-19 is not anticipated to be related to randomized treatment and as such, missed spirometry assessments will be considered missing at random, in accordance with the efficacy estimand.

Scheduled safety assessments

Any scheduled safety data, including clinical laboratory, pregnancy tests, ECG and vital signs that are missing due to COVID-19 will be listed for each subject. The listing will detail the safety procedure missed and its relationship to COVID-19. The listing of missed safety assessments will be presented in the safety analysis set.

5.2.10.4 Adverse events and serious adverse events due to COVID-19

All subjects with a suspected or confirmed diagnosis of COVID-19 will be listed. The listing will present any AEs with either a suspected or confirmed relationship to COVID-19. The relationship between an AE and COVID-19 will be determined by the investigator and appropriately captured in the eCRF. The listings will provide an indication of whether the AE was serious or non-serious.

Listings of adverse events linked to COVID-19 will be based on the safety analysis set.

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5.2.10.5 Overall descriptive summary

A high-level descriptive summary will be provided and grouped by randomized sequence and total number of subjects (across sequences). The following frequencies and percentages of subjects in the full analysis set will be presented:

1. Number of subjects affected by COVID-19 [a]
2. Number of premature withdrawals due to COVID-19
3. Number of subjects with spirometry not done due to COVID-19
4. Number of subjects with clinical laboratory not done due to COVID-19
5. Number of subjects with pregnancy tests not done due to COVID-19
6. Number of subjects with ECG not done due to COVID-19
7. Number of subjects with vital signs not done due to COVID-19
8. Number of subjects with COVID-19 related AEs
9. Number of subjects with COVID-19 related SAEs

[a] Defined as the number of subjects who meet at least one of the listed criteria in points 2-9.

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6. CHANGES OF ANALYSIS FROM PROTOCOL

6.1.1 COVID-19 impacts

As the TYREE protocol was finalized prior to the COVID-19 outbreak, the planned descriptive summaries as detailed in section 5.2.10 of this statistical analysis plan are not described within the protocol.

It is not expected that trial data or the analyses will be greatly impacted by the pandemic and therefore no changes to the planned primary, secondary or exploratory analyses will be performed. Although, it is important to be able to identify any prospective intercurrent events which may occur due to COVID-19 and be able to quantify their impact on the efficacy and safety profile of the study. As a result, patient-level listings detailing trial aspects that have been impacted due to COVID-19 will be provided, along with a high-level summary of these impacts, if any. Please refer to section 5.2.10 for further details.

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7. REFERENCES

1. Ostrom NK, Taveras H, Iverson H, Pearlman DS. Novel albuterol multidose dry powder inhaler in patients with exercise-induced bronchoconstriction: a single-dose, double-blind, randomized, 2-way crossover study. *Respir Med*. 2015;109(11):1410-1415.

2. Senn S, *Cross-over Trials in Clinical Research.* Wiley, Chichester.1993.

3. Kenward M, Roger J. The use of baseline covariates in crossover studies. *Biostatistics.* 2009;11(1):1-17.

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