Statistical Analysis Plan	
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A Phase I, Randomized, Open-label, Single-dose, 2-way Crossover Study to Compare the Pharmacokinetics of Budesonide Delivered by PT027 to Pulmicort Respules® in Children with Asthma Aged 4 to 8 Years (BLANC)

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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
ANOVA	Analysis of variance
AUC0-inf	Area under the plasma concentration-time curve from time zero to infinity
AUC0-t	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
BDA	Budesonide/albuterol sulfate
BDA MDI (PT027)	Budesonide/albuterol sulfate metered-dose inhaler
BMI	Body mass index
Clast	Drug concentration at last observed (quantifiable) concentration
Cmax	Maximum observed plasma concentration
CRF	Case report form
CSP	Clinical study protocol
eCRF	Electronic case report form
IMP	Investigational medicinal product
λz	Terminal elimination rate constant
LAR	Legally authorized representative
MDI	Metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental analysis
PK	Pharmacokinetic(s)
PT	Preferred term
SAE	Serious adverse event
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
$t_{½\lambda z}$	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
tlast	Time of last quantifiable plasma concentration
tmax	Time to reach maximum observed plasma concentration
TC	Telephone call

AMENDMENT HISTORY

Date	Brief description of change
	N/A

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

Primary Objective:	Primary endpoint:
To determine and compare the systemic exposure of budesonide after single-dose administrations of BDA MDI and Pulmicort Respules.	AUC0-t and Cmax

1.1.2 Secondary objective

Secondary Objective:	Secondary endpoint:
To determine and compare other PK parameters for budesonide delivered by BDA MDI and Pulmicort Respules	tmax, tlast, t½λz, λz, Clast, and AUC0-inf (if feasible)

1.1.3 Safety objective

Safety objective:	Safety endpoints:
To assess the safety and tolerability of BDA MDI and Pulmicort Respules	AEs/SAEs

AE: adverse event; AUC0-inf: area under the plasma concentration-time curve from time zero to infinity; AUC0-t: area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; BDA MDI: budesonide/albuterol sulfate metered-dose inhaler; Clast: drug concentration at last observed (quantifiable) timepoint; Cmax: maximum observed plasma concentration; PK: pharmacokinetic; SAE: serious adverse event. tlast: time of last quantifiable plasma concentration; tmax: time to reach maximum observed plasma concentration; t½λz: half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve.

1.1.4 Exploratory objective

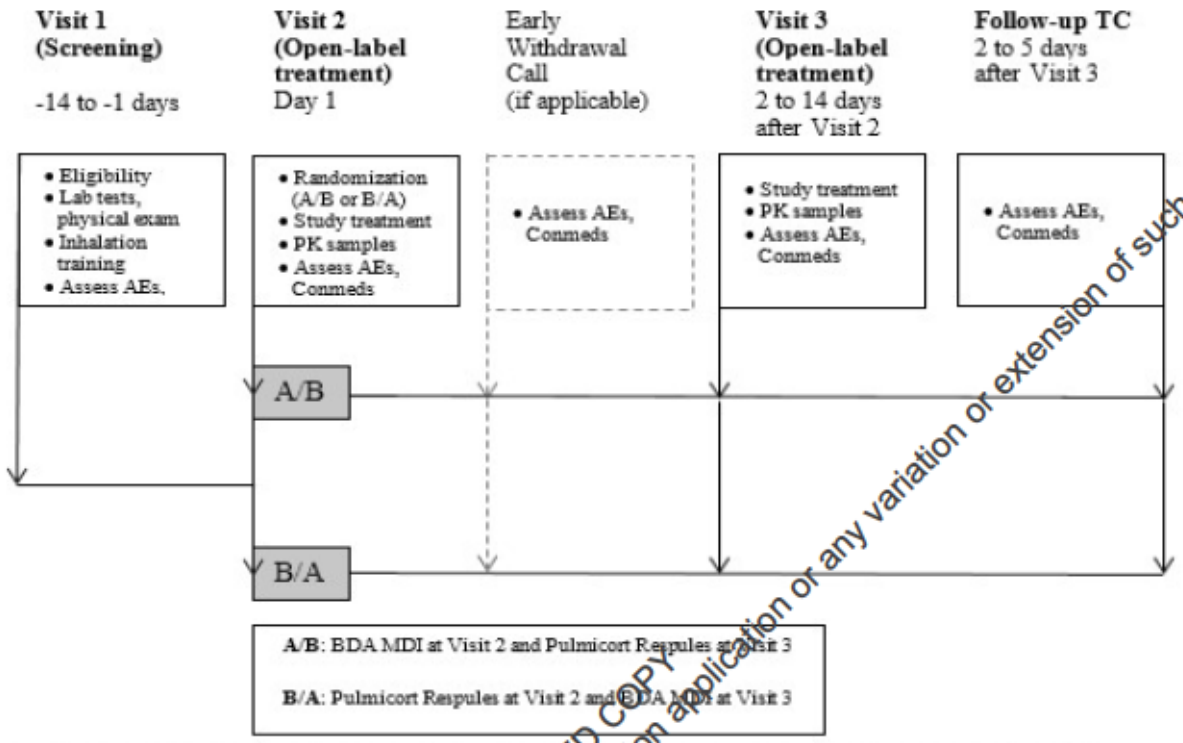
Exploratory objectives are not planned for this study.

1.2 Study design

This is a randomized, multicenter, open-label, single-dose, 2-way crossover study to compare the systemic exposure of budesonide delivered by the combination inhaler (BDA MDI 160/180 ug) with Pulmicort Respules 1 mg. The study consists of a screening visit (Visit 1) and 2 treatment visits (Visit 2 and Visit 3). Randomization takes place at Visit 2. A follow-up (or early withdrawal, if applicable) telephone call (TC) will occur 2 to 5 days after the last dose.

See Figure 1 for a graphical presentation of the study design and Table 1 for a list of study assessments, as per protocol.

Figure 1: Study schema



AE: adverse event; BDA MDI: budesonide/albuterol sulfate metered-dose inhaler; Conmeds: concomitant medication; TC: telephone call

Table 1: Study assessments and procedures

	Screening Period	Open-label Treatment Period		Follow-up or early withdrawal
Visit	1	2	3	4 - TC
Day	Starting from Day -14	1	2 to 14 days after V2	2 to 5 days after V3
Informed consent/assent	X			
Eligibility criteria	X			
Re-check eligibility criteria		X		
Randomization		X		
Routine clinical procedures				
Medical/surgical history	X			
Demography	X			
Physical examination	X			
Height, weight, and BMI	X			
Routine safety measurements				
Laboratory assessments (including local laboratory clinical chemistry, hematology, and urinalysis) [a]	X			
AEs and concomitant medications	X	X	X	X
Seated vital signs (blood pressure and heart rate) [b]	X	X	X	
Placebo MDI training [c]				
Nebulization training	X			
Randomized IMP		X	X	
Blood sampling for PK - Timepoints		A total of 10 samples will be taken per treatment visit at pre-dose and at 10, 20, 40, 60, 120, 240, 360, 480, and 720 min after dosing.		

AE: adverse event; BMI: body mass index; IMP: investigational medicinal product; MDI: metered-dose inhaler; min: minute; PK: pharmacokinetic; TC: telephone call; V: Visit.
a Laboratory assessments (clinical chemistry, hematology and urinalysis) will be performed according to Clinical Study Protocol (CSP), Section 6.3.1.
b Vital signs will be assessed at the beginning (pre-dose) and the end (post-last PK sample) of each study visit.
c Training for placebo MDI will occur at Visit 1 and the placebo MDI will go home with the child for additional training prior to randomization.

1.3 Number of subjects

The target population will be male and female children with asthma, 4 to 8 years of age. Approximately 28 children will need to be screened, assuming an estimated screen failure rate of 50% prior to randomization in order for 14 children to be randomized and 10 to complete. At least 4 children should be randomized in the age range of 4-5 years. Children who do not complete both treatments (BDA MDI and Pulmicort Respules) may be replaced.

1.3.1 Randomization

At Visit 2, eligible subjects are randomized (1:1) to receive 1 of 2 treatment sequences (BDA MDI 160/180 / Pulmicort Respules or Pulmicort Respules / BDA MDI 160/180). Randomization is stratified by study center, so that all subjects can be recruited of a single study center if needed.

1.3.2 Sample Size Calculation

No prospective calculations of statistical power have been made. As the study is descriptive with no formal hypothesis tests, complete data (evaluable data from both BDA MDI and Pulmicort Respules) from 10 children is considered sufficient to provide estimates of the PK parameters in this population without exposing more children than necessary to the IMP. Results will be interpreted in the perspective of the explorative nature of the study.

2. ANALYSIS SETS AND PROTOCOL DEVIATIONS

2.1 Definition of analysis sets

2.1.1 Pharmacokinetic (PK) analysis set

The PK analysis set will consist of all randomized children for whom at least 1 of the primary PK parameters (AUC0-t and Cmax) can be calculated and who have no important protocol deviations impacting the interpretation of the PK data.

Children who do not provide evaluable data for both treatments (BDA MDI and Pulmicort Respules) will be excluded from the analysis of variance (ANOVA).

Any excluded cases will be documented together with the reason for exclusion.

Profiles belonging to the PK analysis set will be summarized and analyzed according to the treatment that was administered at the specific visit. Any treatment errors will be documented as protocol deviations. All PK summaries will be based on the PK analysis set.

2.1.2 Safety analysis set

The safety analysis set is defined as all children receiving any amount of randomized treatment.

Occurrences of safety events (ie, AEs and use of concomitant medication) will be summarized under the actual treatment corresponding to the treatment period of which the event occurred. All safety summaries will be based on the safety analysis set.

2.1.3 All subjects enrolled analysis set

The all subjects enrolled analysis set will be defined as all children who provide informed assent and whose parent(s) or legally authorized representative(s) (LAR) have provided informed consent. This analysis set will be used for descriptive summaries of dispositions.

2.1.4 All subjects randomized analysis set

The all subjects randomized analysis set will be defined as all children who have been randomized to a treatment sequence. This analysis set will be used for listings and descriptive summaries of demographic variables.

Subjects will be listed and summarized according to their randomized treatment sequence.

2.2 Protocol deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Major protocol deviations 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. Important protocol deviations (IPDs) are a subset of major PDs deemed to impact the pharmacokinetics or the safety profile of the study. Minor PDs are the protocol deviations which are neither major nor important.

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 electronic case report form (eCRF). Any children who do not fulfil all the eligibility criteria, but they are subsequently randomized in error and children who are erroneously randomized will be identified as IPDs. Other IPDs may be identified by the sponsor prior to the primary database lock.

A per protocol analysis excluding subjects with IPDs is not planned.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General Definitions

3.1.1 Screening period

Screening assessments are collected at Visit 1 (see Table 1). Any re-screening assessments that may occur (see 3.5.3) will be collected at Re-Screening visit.

3.1.2 Crossover periods

Subjects will be randomized to a particular sequence and will receive the first treatment in their sequence at Visit 2 and second treatment at Visit 3. Period 1 corresponds to the results collected at Visit 2 and Period 2 corresponds to results collected at Visit 3. The below table represents planned treatment group assignment based on randomized sequence and crossover period.

Randomized Treatment Sequence	Planned treatment group	
	Period 1 (Visit 2)	Period 2 (Visit 3)
BDA MDI 160/180; Pulmicort Respules	BDA MDI 160/180	Pulmicort Respules
Pulmicort Respules; BDA MDI 160/180	Pulmicort Respules	BDA MDI 160/180

Pulmicort Respules is administered as a single dose of 1 mg.

3.1.3 Derivation of PK parameters

Plasma samples will be analyzed using non-compartmental analysis (NCA) to determine the PK parameters (AUC0-t, Clast, Cmax, tmax, tlast, λz, t½λz, and AUC0-inf [if feasible]) of budesonide in plasma.

A separate PK analysis plan, authored by the PK specialists, will contain the derivation specifications of the PK parameters to be delivered to [redacted]

The derived PK parameters received from the PK specialists will be mapped to SDTM.PP, which will subsequently be mapped to ADAM.ADPP. The latter analysis dataset will be used for programming data listings and descriptive summaries of the PK parameters.

3.1.4 Relative time from first dose of randomized treatment

Plasma concentrations of budesonide will be measured in blood samples taken at planned timepoints (see Table 1). The actual timepoints with reference to the time of first dose of randomized treatment will be calculated separately for each visit (Visit 2 and Visit 3) as:

[Relative time from first dose (minutes)] = [actual time of blood sample (hh:mm)] – [time of first dose (hh:mm)].

Times of blood samples and time of first dose at the scheduled visits will be recorded on the eCRF at site.

3.1.5 Visit windowing

Due to the design of this trial, there will be no visit windowing applied. Any unscheduled visits which may occur will not be used in analyses, however all data will be listed where appropriate.

Delayed visits due to COVID-19 should be considered in the analyses if it is necessary to safeguard the health of the subject and study center staff or enables an on-site subject visit.

If a return to lockdown is announced or the study center is on lockdown and cannot process a visit, if possible, visits should be rescheduled to earlier/later as required to safeguard subjects and study center staff.

3.1.6 Imputation rules

The following imputation rules will be applied to the raw data in order to enable the PK and Safety analyses.

3.1.6.1 Missing date/time imputations

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

1. 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 Pulmicort Respules then set to dose date of Pulmicort Respules; else set to 01/mm/yyyy
   - End date of medication/ event (after partial date handling has been applied).
2. 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 Pulmicort Respules dose date set to dose date of Pulmicort Respules; Else set to start of the year [01/01/yyyy].
   - End date of medication/ event (after partial date handling has been applied).
3. If completely missing, then impute as the minimum of:

- Date of first dose of BDA MDI, unless missing then date of first dose of Pulmicort Respules.
- End date of medication/ event (after partial date handling has been applied).

The end of study participation is defined as the date of the follow-up TC.

Additionally, AEs will have the start and end time collected. The following imputation rule will be applied to missing or partially missing times.

Partial end time

1. If missing minute [hh:--] then impute as hh:59.
2. If completely missing, then impute as 23:59.

Partial start time

1. If missing minute [hh:--], then:
   - If start date and hour are the same as the dose date and hour of the randomized treatment, then set to the time of dosing.
   - Else set to hh:00.
2. If completely missing, then:
   - If start date is the same as the dose date of the randomized treatment, then set to the time of dosing.
   - Else set to 00:00.

Collection of the start and end time is not planned for concomitant medications. 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.

3.1.6.2 Imputation of plasma concentrations

Plasma concentrations below the lower limit of quantification (LLoQ) that are reported as "<LLoQ" or "≤LLoQ" in the database will be handled as follows;

If they occur after the first quantifiable concentration within each visit-specific concentration profile, then they will be set as missing for the calculation of the descriptive summary statistics. Else if they occur prior to a quantifiable value, or no quantifiable value is provided within a visit-specific concentration profile, then they will be set to 0 for the calculation of the descriptive summary statistics. The original value will be listed.

3.2 Primary endpoints

The following PK parameters are of key interest for evaluating the systemic exposure of budesonide after single-dose administrations of BDA MDI and Pulmicort Respules.

- AUC0-t: Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
- Cmax: Maximum observed plasma concentration

3.3 Secondary endpoints

In addition to the above, the following parameters will be calculated to further assess the pharmacokinetics of BDA MDI compared to Pulmicort Respules:

- tmax: time to reach maximum observed plasma concentration
- tlast: time of last quantifiable plasma concentration
- t½λz: half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve[1]
- λz: terminal elimination rate constant
- Clast: drug concentration at the last observed (quantifiable) timepoint
- AUC0-inf: area under the plasma concentration-time curve from time zero to infinity[1]

[1] Feasibility of endpoint provision will be determined by the PK specialist vendor.

3.4 Safety variables

3.4.1 Vital signs

The following vital signs measurements will be collected at screening Visit 1 and before dose and after the last blood sample is taken at Visit 2 and Visit 3 as per Table 1.

- 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.

3.4.2 Adverse events (including Serious Adverse Events)

3.4.2.1 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.

A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) on or after the first dose of randomized IMP at Visit 2. Any AEs occurring in the washout between successive treatment periods will also be regarded as treatment-emergent and assigned to the treatment administered in the period prior to the washout.

3.4.2.2 Definition 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

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

3.4.2.3 Collection of AEs and SAEs

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

The following variables will be collected on the eCRF for each AE:

- AE term (verbatim)

- Date/time when the AE started and stopped
  - DD/MMM/YYYY
  - HH:MM
- Maximum severity
  - Mild
  - Moderate
  - Severe
- Seriousness
  - Yes or no
- Investigator causality rating against the randomized treatment
  - Yes or no
- Action taken with regard to the randomized treatment
  - Dose not changed
  - Dose increased
  - Dose reduced
  - Drug interrupted
  - Drug permanently discontinued
  - Not applicable
- Outcome
  - Recovered/resolved
  - Recovering/resolving
  - Recovered/resolved with sequelae
  - Not recovered/not resolved
  - Fatal

3.4.2.4 Adverse events data handling

Adverse events will be reported as starting during screening if the AE start date/time is prior to the first dose of randomized treatment taken at Visit 2.

Adverse events will be considered as treatment emergent if the onset date/time is on or after the first dose of randomized treatment at Visit 2. Any AEs occurring in the washout between successive treatment periods will also be regarded as treatment emergent and assigned to the actual treatment administered in the period prior to the washout.

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

Please refer to Section 3.1.6 for the imputation rules to programmatically determine the classification of AEs when there is partial start and/or stop dates recorded.

3.4.3 Laboratory Safety Variables

Samples for determination of clinical chemistry, hematology, and urinalysis will be taken at Visit 1 and at unscheduled visits, if required, as indicated in Table 2.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator.

The clinical chemistry, hematology, and urinalysis assessments will be performed using a local laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at each study center.

Table 2: Laboratory Safety Variables

Hematology/Hemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Basophils (%)	Albumin
Basophils Abs	Alanine aminotransferase
Eosinophils (%)	Alkaline phosphatase
Eosinophils Abs	Aspartate aminotransferase
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 transferase
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*	
Urine blood	
Leukocyte esterase	
Urine protein	
Urine glucose	
Nitrite	

Abs: absolute
*If leukocyte esterase is detected, the site should send the sample for culture. If abnormal levels of blood or protein are detected, the sample should be sent for microscopic examination.

3.5 Other variables

3.5.1 Prior and Concomitant medications

The collection and recording of all concomitant medication, including all pre-enrollment asthma therapies, are performed at each of the scheduled visits as detailed in Table 1.

All medications taken within 3 months before Visit 1 will be recorded as prior medications. Any medication taken on or after Visit 1 and through the follow-up TC will be recorded as concomitant therapy. All medications (prior and concomitant) will be recorded on the eCRF throughout the study.

Disallowed medications will be identified by a physician 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.

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 3.1.6.1 will be considered.

3.5.2 Withdrawal from study

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

- Subject decision
- Adverse event
- Severe non-compliance to protocol
- Condition under investigation worsened
- Subject lost to follow-up
- Investigator decision
- Study terminated by sponsor
- Death
- Consent withdrawal
- Other

Randomized subjects who withdraw prior to Visit 3 are asked to complete an early withdrawal TC (see Table 1).

Subjects who withdraw prior to randomization, or are lost to follow-up following Visit 3 (i.e. the safety follow-up call) will have their end of study status collected in the eCRF under the following fields:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Screen failure
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by subject
- Withdrawal by parent/guardian
- Non-compliance with study drug
- Other (specify)

3.5.3 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 may be re-screened once if

temporary reasons for the original screen failure (eg, respiratory infections, asthma exacerbations, episodes of unstable asthma) have resolved.

If a subject is in screening and cannot complete the randomization visit within 14 days due to local COVID-19 lockdown restrictions, the screening period may be extended to a maximum of 6 weeks. In the event of an extension to the screening period >14 days due to COVID-19, the following safety measurements should be repeated in advance of randomization: safety laboratory assessments, vital signs, concomitant medications, and medical/surgical history.

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 erroneously will be marked as major PDs, considered as IPDs and will be analyzed in accordance with the PK and Safety analysis set definitions (Section 2.1).

4. ANALYSIS METHODS

4.1 Statistical Considerations

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

The study is descriptive. There are no predefined statistical hypotheses and/or decision rules.

4.1.1 Treatment groups

Descriptive summaries and analyses of endpoints listed below will be grouped by treatment. As subjects will receive both BDA MDI 160/180 and Pulmicort Respules, they 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.

Unless stated otherwise, listings will be grouped by randomized treatment sequence and visit.

4.2 Analysis methods

All subjects who are part of the PK analysis set will be analyzed according to the actual treatment they received. Any subjects who are erroneously randomized will be identified as major PDs, considered as IPDs and listed in the CSR.

Unless otherwise stated, descriptive summaries of continuous endpoints will include: The number of subjects included 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.

4.2.1 Subject Disposition

Subject disposition will be summarized for all subjects who have been enrolled and have provided informed consent/assent. 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, included in PK analysis set, included in Safety analysis set, 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). For categories that are post-randomization, summaries will be further split by randomized treatment sequence and overall.

All randomized subjects who were discontinued prematurely will be listed by randomized treatment sequence including date of, and reason for study discontinuation.

A separate listing will display the planned treatment sequence and the actual treatment received for all randomized subjects.

Additionally, subjects in the safety analysis set who were excluded from the PK analysis set will be listed and will include the actual treatment sequence and reason for exclusion.

Moreover, data excluded from the PK analysis set will be listed separately for all subjects in the PK analysis set, including actual treatment and reason for exclusion.

4.2.2 Demographic and Baseline Characteristics

The following demographics and subject characteristics will be collected at Visit 1 and Re-Screening visit, if applicable:

- Age (years)
- Sex: Male, Female
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

These variables will be summarized by randomized treatment sequence and overall for all randomized subjects. This summary will be re-produced for subjects in the PK analysis set.

Additionally, the variables above, along with randomized treatment sequence and country, will be listed for all randomized subjects.

4.2.2.1 Medical history

A standard medical, disease, and surgical history will be recorded on the eCRF at Visit 1. The results of the physical examination at Visit 1 and at unscheduled visits, if applicable, will be documented in medical history for each subject. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

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 screening Visit 1.

Medical, disease and surgical history data will be listed by subject including randomized treatment sequence, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), MedDRA Preferred Term, start date and stop date (or ongoing if applicable) and category (past, current).

Partial dates for the above calculations will be handled as per section 3.1.6.

4.2.2.2 Asthma history

Asthma history will be listed separately by subject and will include randomized treatment sequence, date of asthma diagnosis, asthma diagnosed by clinician for at least 3 months prior to Visit 1 (Yes, No), any life threatening asthma episodes prior to Visit 1 (Yes, No), upper respiratory infection involving antibiotic treatment which was not resolved within the 14 days prior to Visit 1 (Yes, No) and associated conditions / triggers / allergies.

4.2.3 Treatment Exposure

Treatment exposure and dosing information will be collected on the eCRF and will be listed for all subjects in the safety analysis set, including dosing date/time, treatment, total dose, overdose (Yes, No).

4.2.4 Protocol deviations

All randomized subjects with protocol deviations will be listed by randomized treatment sequence, date, visit (if applicable) and reported deviation term and will be sorted by major and minor, with an indication on whether or not the deviation was considered important (Yes, No).

A separate listing including only the COVID-19 related PDs will be produced.

4.2.5 Pharmacokinetics (PK)

The complete PK analysis, derivation and presentation of the associated PK parameters will be described in the PK analysis plan and will be performed by the PK specialists.

The PK listings and summaries described below will be reconciled and compared with the findings from the PK report.

Plasma concentration and PK parameter summaries will be based on the PK analysis set. Individual plasma concentration and pharmacokinetic parameter listings will be based on the safety analysis set.

4.2.5.1 Analysis of the plasma concentrations

A listing of the actual PK blood sample collection times, and all reportable budesonide concentrations will be provided for all children in the safety analysis set. Plasma concentrations outside of the quantification range will be presented as NQ (Not Quantifiable). Concentration data will be presented to 3 significant figures as received from the bioanalytical laboratory.

Plasma concentrations of budesonide will be summarized by treatment and nominal timepoints using the following descriptive statistics:

- n: Number of evaluable observations in the analysis
- n-: Number of observations below the lower limit of quantification (LLOQ)
- Mean: Arithmetic mean calculated using untransformed data
- SD: Standard Deviation calculated using untransformed data
- gMean: Geometric mean, calculated as exp[m], where m = mean(log-transformed data)
- gCV%: Geometric Coefficient of Variation, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on the log scale
- Median: Median calculated using untransformed data
- Min: Minimum value of the untransformed data
- Max: Maximum value of the untransformed data

NQ observations at any timepoint will be handled as per the rules defined in Section 3.1.6.2. Any NQ observations imputed as 0 will be excluded from the calculation of the geometric mean and the geometric coefficient of variation.

As per the PK analysis plan, at least 66% of observations within the quantification range are required at each timepoint for the descriptive statistics to be calculated. Otherwise the statistics will be set as NC (Not Calculable) and only the minimum and maximum will be presented.

Descriptive statistics will be presented to 4 significant figures (sf's) with the exception of the minimum and maximum which will be presented to 3 sf's and gCV to 1 decimal place.

4.2.5.2 Analysis of the primary PK endpoints

The primary endpoints; AUC0-t and Cmax (Section 3.2) for budesonide will be compared separately between treatments with an ANOVA model using the natural logarithm of AUC0-t and Cmax as the response and treatment, treatment sequence, period, and subject within sequence as fixed effects. Please see example SAS® code below:

```
proc mixed data=maxfall method=REML;
        by paramcd;
        class trtan trtseqan aperiod usubjid(trtseqan);
        model log aval = trtan trtseqan aperiod usubjid(trtseqan);
        LSmeans trtan / CL alpha=0.05; * Treatment LSmean estimates with 95% CI;
        LSmeans trtan / diff CL alpha=0.1; * LSmean differences with 90% CI;
run;
```

Least squares mean estimates from the models will be back-transformed to provide the geometric means together with 2-sided 95% confidence intervals for each treatment group. Also, geometric mean ratios between test (BDA MDI) and reference (Pulmicort Respules) treatments, along with the associated 90% confidence limits will be calculated from the models. Moreover, the intra-subject coefficient variation (CV%) will be calculated as $100 \times \sqrt{[\exp(MSE) - 1]}$, where MSE is the mean squared error from the model.

The primary treatment comparison of BDA MDI versus Pulmicort Respules for the relative exposure of budesonide will be conducted on the PK analysis set. Only subjects with evaluable PK measures from both treatment arms will be included in the ANOVA.

Additionally, the primary PK endpoints will be summarized descriptively as per (4.2.5.3, PK parameters).

As this study is primarily descriptive in nature, there are no predefined statistical hypotheses and no predetermined tests or decision rules for the aforementioned analyses.

4.2.5.3 PK parameters

A listing of the derived PK parameters will be provided for all children in the safety analysis set, including treatment and visit, where: Cmax will be presented to the same number of significant figures (sf's) as received from the bioanalytical laboratory; AUC0-t and AUC0-inf will be presented to 3 sf's; λz will be presented to 4 sf's; tmax, tlast and t½λz will be presented in hours with 2 decimal places.

Additionally, the PK parameters (See 3.2 and 3.3) will be summarized by treatment using the following descriptive statistics:

- n: Number of subjects in treatment group
- Mean: Arithmetic mean calculated using untransformed data
- SD: Standard Deviation calculated using untransformed data
- gMean: Geometric mean, calculated as exp[m], where m= mean(log-transformed data)
- gCV%: Geometric Coefficient of Variation, calculated as 100 √ [exp(s^2)-1], where s is the standard deviation of the data on a log scale
- Median: Median calculated using untransformed data
- Min: Minimum value of the untransformed data
- Max: Maximum value of the untransformed data

Descriptive statistics for subjects in the PK analysis set will be presented to 4 significant figures (sf's) with the exception of the minimum and maximum which will be presented to 3 sf's and the gCV% to 1 decimal point. Only median, minimum and maximum will be reported for tmax and tlast.

As per the PK analysis plan, at least 66% of observations per PK parameter are required for the descriptive statistics to be calculated. Otherwise the statistics will be set as NC (Not Calculable) and only the minimum and maximum will be presented.

4.2.6 Analysis of safety variables

The analysis of the safety variables will be based on the safety analysis set and will be reported using the actual treatment associated with the observed data. All data collected prior to study withdrawal will be included in the analyses. Safety data collected during screening will be listed separately.

4.2.6.1 Adverse events

All AEs will be coded using the most recent version of MedDRA dictionary at the time of database lock.

AEs during screening will be listed by actual treatment sequence, MedDRA term, reported term, study day of start of AE, duration of AE, maximum intensity, seriousness and outcome.

Treatment emergent AEs (TEAEs) will be listed by actual treatment received, MedDRA term, reported term, study day of start of AE, duration of AE, maximum intensity, seriousness, action taken with IMP, causality and outcome.

Additionally, a key subject information listing of all SAEs during the entire study will be created, including, actual treatment received (if applicable), corresponding visit, reported term, preferred term, time from start of treatment to onset of AE (days), time from start of treatment to becoming serious (days), outcome, action taken with IMP and causality. Time references are period specific.

Furthermore, subjects with TEAEs, serious TEAEs, TEAEs that led to death, and TEAEs that led to study withdrawal will be separately listed and summarized by SOC and PT.

A high-level descriptive summary will also be produced for subjects with any TEAE in any of the following categories:

- Any TEAE
- Any TEAE with outcome of death
- Any treatment related TEAE
- Any serious TEAE
- Any TEAE leading to withdrawal from study

4.2.6.2 Vital signs

Vital signs variables (Section 3.4.1) will be listed by subject, including actual treatment sequence, visit (repeat/unscheduled assessments inclusive), and date/time of the assessments and clinical significance (Yes, No).

Vital signs variables will be descriptively summarized by actual treatment group and timepoint (pre-dose and post-last PK assessment).

4.2.6.3 Laboratory assessments

The clinical chemistry, hematology, and urinalysis assessments will be listed by actual treatment sequence and visit including repeat/unscheduled measurements. The listings will include the following information: test name, date/time of measurement, result, result units, clinical significance (Yes, No) as determined by the Investigator, and an indicator variable relative to the normal ranges (Low, Normal, High).

4.2.6.4 Prior and Concomitant medication

The number and percentage of subjects who take allowed concomitant medications, and those who take prohibited concomitant medications during the study, will be presented separately by standardized medication name, within generic class (WHO Drug dictionary text) for each actual treatment sequence. Similarly, a summary of prior medications will be produced.

Prior and concomitant medication will be listed separately by subject and will include the following information: actual treatment sequence, reported name, coded preferred term, the route of administration, dose (unit), frequency, start and stop date, indication, ongoing status (Yes, No) and therapy reason. Any identified prohibited medication will be clearly indicated in the listings.

Descriptive summaries and listings of prior and concomitant medication will be based on the safety analysis set.

4.2.7 COVID-19 impacts

Blanc 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 study.

4.2.7.1 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 early-withdrawal TC. 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 all subjects randomized analysis set.

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

COVID-19 tests for subjects or caregiver/ parent may be conducted proactively prior to inclusion or site visits at any point throughout the study in accordance with local and national

guidance. This will be documented as an unscheduled procedure with a positive result recorded as an AE.

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.

4.2.7.3 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 PK 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 COVID-19 related PDs
4. Number of subjects with COVID-19 related AEs
5. 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 2-5.

5. CHANGES OF ANALYSIS FROM PROTOCOL

N/A

BLANC Statistical Analysis Plan V1.0

Final Audit Report [redacted]

Created:	[redacted]
By:	
Status:	
Transaction ID:	

"BLANC Statistical Analysis Plan V1.0" History

[redacted]