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TITLE PAGE

Protocol Title:	A randomized, double-blind, parallel group, multi-center study to evaluate the long-term safety of salbutamol rescue medication when administered via metered dose inhalers containing the propellant HFA-152a or reference HFA-134a.
Study Number:	220735
Compound Number:	AH3365 (Salbutamol)

Sponsor Name: GlaxoSmithKline Research & Development Limited

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VERSION HISTORY

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	19 April 2024	2.0 (07 December 2023)	Not Applicable	Original version
SAP Amendment 1	28 Aug 2025	Protocol Amendment 1 (24 April 2024) Protocol Amendment 2 (28 November 2024)	• The study will be conducted CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] Subgroup analysis to assess the incidence of AEs and SAEs for age category will not be performed as study population is based on adult participants only.	• Updated SAP for age to address regulatory agency feedback.
			• Move exploratory endpoint to secondary efficacy endpoints.	• Updated SAP to address regulatory agency feedback.
			• Geographical location has been updated.	• As per team's suggestion, geographical location should be presented by combining the countries as per its location.
			• Summary and derivation for overall compliance of ACQ-6 score	• Compliance of eCOA is mandatory as per GSK

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			(eCOA) has been added. • No interim analysis will be perfomed • CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI • Subgroup analysis is added. • For each category of subgroup, incidence of AEs and SAEs will be presented if there is ≥5% participants across treatment groups except baseline reversibility and baseline maintenance class of therapy. Baseline reversibility and baseline maintenance class	eCOA guideline. • Updated interim analysis section as per EMA regulatory agency feedback • To support the 3:1 randomization allocation • Submission requirement. • To present the appropriate incidence of AEs and SAEs for subgroup. To analyze the incidence of AEs and SAEs for reversible and non-reversible category and each maintenance class of therapy according to

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			of therapy subgroup are added.	classify at baseline.
			• Add summary tables for AE of interest to propellant.	• Summary tables added as per EMA regulatory agency feedback.
			• KM curve will be created for study treatment discontinuation from the study.	• To examine the pattern of study treatment discontinuation from the study for test (HFA-152a MDI) or reference (HFA-134a MDI) treatment groups.
			• For all sensitivity and supplementary analysis for AEs and SAEs, 95%CI will be computed using exact score statistics.	• To examine the occurrence of small numbers of AEs or SAEs in one or both the treatment groups.
			• Summary of asthma maintenance therapy at study entry and shift table during treatment period are added.	• To analyze the asthma maintenance therapy.
			• Criteria for classification and	• To identify the potential

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			analysis of safety signals is added.	adverse drug reactions.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 220735. Details of the optional interim analysis, as well as the final analysis, are provided.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of 3 months treatment with a formulation of salbutamol administered via MDI containing propellant test HFA-152a or reference HFA-134a in participants ≥18 years of age with asthma	• Incidence of AEs
Secondary	
Safety	
• To assess the safety and tolerability of salbutamol test (HFA-152a MDI) or reference (HFA-134a MDI) in participants ≥18 years of age with asthma.	• Incidence of SAEs • Minimum serum potassium • Absolute values for serum potassium at each assessed visit • Change from baseline for serum potassium at each assessed visit • Absolute values for clinical laboratory assessments at each assessed visit • Change from baseline for clinical laboratory assessments at each assessed visit. • Absolute values for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit • Change from baseline for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit. • Absolute values for 12 Lead ECGs in QTc and heart rate at each assessed visit • Change from baseline for 12 Lead ECGs in QTc and heart rate at each assessed visit.
Efficacy	
• To assess ACQ-6 score and FEV1 in salbutamol test (HFA-152a MDI) or reference (HFA-134a MDI) in participants ≥18 years of age with asthma.	• Change from baseline for ACQ-6 score at each assessed visit. • Change from baseline for FEV1 at each assessed visit

Primary estimand:

The primary clinical question of interest is to assess the incidence of adverse events (AEs) in asthma participants (≥18 years of age) up to 3 months on- treatment period for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups after administration at a minimum of 2x100 µg once daily and as needed for symptoms, not to exceed 800 µg daily.

The primary estimand is described by the following attributes:

- The population should include male and female participants aged ≥18 years with asthma.
- The primary endpoint is incidence of AEs throughout the 3 months treatment period.
- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent event (ICE) and estimand strategy are as follows:
  - Study treatment discontinuation due to any reason (While on-treatment strategy). Interest lies in group of participants from first dose to end dose of test (HFA-152a MDI) or reference (HFA-134a MDI) treatment groups including 7 days follow up period.
- The population level summary to be estimated is:
  - Counts and percentages for incidence of AEs in the on-treatment (3 months) period for test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- Rationale for primary estimand:
  - The primary clinical question of interest is whether taking investigational product adversely affects patients in targeted population while they are taking the product. Therefore, the AEs will be captured for on-treatment (3 months) from first dose to last dose in treatments with additional 7 days (inclusive) follow up period.

Estimands for supporting secondary safety and efficacy objectives:

The secondary safety and efficacy clinical question of interest is to assess the safety and tolerability profile of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in asthma participants (≥18 years of age)

The estimands for supporting secondary safety and efficacy objectives are same as primary estimand except for the attributes of the endpoints and population-level summary measures as detailed below:

The estimand attributes for the secondary safety and efficacy objectives are as follow:

- The population is male and female participants aged ≥18 years with asthma.
- The secondary endpoints are:
- Safety endpoints-
  - Incidence of SAEs
  - Minimum serum potassium
  - Absolute values for serum potassium at each assessed visit.

- Change from baseline for serum potassium at each assessed visit.
- Absolute values for clinical laboratory assessments at each assessed visit.
- Change from baseline for clinical laboratory assessments at each assessed visit.
- Absolute values for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Change from baseline for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Absolute values for 12 lead electrocardiograms (ECGs) in QTc and heart rate at each assessed visit.
- Change from baseline for 12 Lead ECGs in QTc and heart rate at each assessed visit.
- Efficacy endpoints-
- Change from baseline for ACQ-6 score at each assessed visit.
- Change from baseline for pre-bronchodilator FEV1 at each assessed visit.

- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent event (ICE) strategy for secondary objectives follows the primary estimand strategy (while on treatment).
- The population level summary to be estimated are:
- Safety endpoints-
  - Counts and percentages for incidence of SAEs in on treatment (3 months) period for test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
  - Mean difference in minimum serum potassium between test (HFA-152a MDI vs reference (HFA-134a MDI) treatment groups and its associated 95% CI in on-treatment period.
  - Mean of absolute values for clinical laboratory assessments including serum potassium, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), and 12 lead ECG parameters (QTc and heart rate) in on-treatment period.
  - Mean of change from baseline values for clinical laboratory assessments including serum potassium, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), and 12 lead ECG parameters (QTc and heart rate) in on-treatment period.
- Efficacy endpoints-
  - Mean of change from baseline values for ACQ-6 at each assessment on-treatment period
  - Mean of change from baseline values for pre-bronchodilator FEV1 at each assessment on-treatment period.

- Rationale for estimands supporting secondary safety objectives:
  - The clinical question of interest for secondary objectives is whether taking investigational product can adversely affects patients in targeted population while they are taking the product. Therefore, the secondary endpoints will be captured for on-treatment period from first dose to last dose in treatments with additional 7 days (inclusive) follow up period.

Supplementary estimands for supporting safety objectives:

Supplementary estimands will address additional safety clinical questions of interest by evaluating the safety and tolerability profile of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in asthma participants (≥18 years of age) for overall follow-up period (including any post-treatment follow-up).

The estimand attributes for the supplementary estimands are as follows:

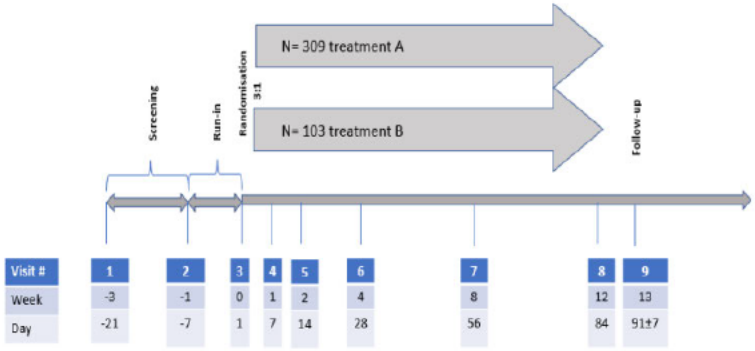
- The population is male and female participants aged ≥18 years with asthma.
- The endpoints are AEs, SAEs, serum potassium, clinical laboratory assessment, vital signs, and ECGs data are specifically defined in primary estimand and estimands for supporting secondary safety objective.
- The treatment condition is salbutamol minimum of 2x100 µg once daily and as needed for symptoms not to exceed 800 µg daily for the test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.
- The intercurrent event (ICE) strategy for the supplementary analyses are as follows:
  - Study treatment discontinuation due to any reason (treatment policy strategy). Interest lies in the group of participants irrespective of whether they discontinued study treatment.
- The population level summary to be estimated are defined in primary estimand and estimands for supporting secondary safety objective.
- Rationale for supplementary estimands:
  - Treatment policy approach will facilitate analysis efforts to whereby analysing participant safety data provided from regularly scheduled assessments even after they discontinue the investigational product, thereby providing a transparent and complete analysis of all safety events recorded during follow-up.

1.2. Study Design

Overview of Study Design and Key Features	
Design Features	The Study design schematic is shown in Figure 1

Figure 1 Study Design overview

Figure 1 Study design overview



Treatment A: HFA-152a (Experimental group)
Treatment B: HFA-134a (Reference group)

- Phase III multicenter, randomized, double-blind, parallel group study.
- Participants meeting all the inclusion criteria and none of the exclusion criteria during the screening visit (Visit 1) will enter the study open-label run-in period where they will be asked to switch from their current rescue inhaler to the salbutamol HFA-134a MDI.
- During run-in period, subjects will be instructed to self-administer this reliever inhaler at a dosage of 2x100 µg actuations once daily ± as required for symptom relief (up to maximum 800 µg daily). Subjects will continue their daily maintenance therapy throughout the run-in period.
- Baseline safety evaluations and baseline measures of asthma status will also be performed at screening.
- At the end of the run-in period, the start of Week 0 (Visit 3) subjects meeting randomization criteria will stop using the salbutamol HFA-134a MDI and will be randomly assigned to continue receiving the salbutamol HFA-134a MDI or new test salbutamol HFA-152a MDI.

	• Subjects will be instructed to self-administer their assigned reliever inhalers 2x100 µg once daily ± as required for symptoms (up to maximum 800 µg daily). Subjects will continue their regular daily maintenance therapy throughout the study. • Approximately 412 participants will be randomly assigned with 3:1 ratio in the study, 309 participants in salbutamol test (HFA-152a MDI) treatment group to achieve 300 participants and 103 participants in salbutamol reference (HFA-134a MDI) treatment group to achieve 100 participants for the primary analysis. • Subjects will attend 5 on-treatment visits at Visits 3,4,6,7, and 8 (Weeks 0, 1, 4, 8, and 12 respectively). Visit 5 at Week 2 will be a virtual/telephonic visit. A follow-up visit will be performed 1 week after completion of the 12-week treatment period.
Study treatment	• The Experimental treatment group - Salbutamol MDI inhaler containing HFA-152a propellant. • The Reference treatment group - Salbutamol MDI inhaler containing HFA-134a propellant
Study treatment Assignment	• Minimum 2x100 µg actuations once daily + as needed up to maximum 800 µg for both experimental and reference treatment group
Interim Analysis	• No interim analysis will be perfomed.

2. STATISTICAL HYPOTHESES

The nature of the study is purely descriptive therefore, no formal hypothesis testing will be performed for the primary and secondary endpoints.

2.1. Multiplicity Adjustment

No multiplicity adjustment will be performed for the primary and secondary endpoints.

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Intent to Treat (ITT)	• All participants who were randomly assigned to study treatment in the study. • The screened, enrolled, and randomized populations (ITT) must be nested, i.e., the enrolled population must be a subset of the screened population, the randomized population (ITT) must be a subset of the enrolled population. • Note: Participants who were incorrectly randomized should not be part of ITT population.	• Study Population
Safety	• All randomized participants who take at least 1 puff/actuation of study treatment. Participants will be analyzed according to treatment they actually received.	• Estimands primary and secondary safety objectives

4. STATISTICAL ANALYSES

4.1. General Considerations

The purpose of statistical analysis is to estimate the incidence of adverse events (AEs) and serious adverse events (SAEs) in asthma participants having age ≥18 years for the salbutamol test group (propellant HFA-152a MDI) and reference group (HFA-134a MDI).

Statistical analysis will be presented as per estimands for primary and secondary objectives. ICEs and strategies for primary and secondary estimands are defined in Section 1.1.

Secondary efficacy endpoints will be analysed using the ITT analysis set. Participants will be analyzed according to treatment they were randomized too.

Safety endpoints will be analysed using safety analysis set. Participants will be analyzed according to treatment they actually received.

Two-sided 95% confidence intervals will be reported unless otherwise stated.

4.1.1. General Methodology

Participants who prematurely withdraw from study will not be replaced.

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of participants. No imputation of study data will be applied, unless specified otherwise. Percentages will be presented as per GSK statistical display principles.

4.1.2. Baseline Definition

For all endpoints baseline value will be defined as per Table 1

Table 1 Baseline definition

Parameter	Study Assessments Considered as Baseline			Baseline To be used in Analysis/Summaries
	Screening/-D21	Run-in/ -D7	Day 1 (pre-dose)	
Safety				
12 lead ECG [1]	x		x	Day 1 (mean of the pre-dose) [2]
Vital Signs	x		x	Day 1(pre-dose)
Hematology	x		x	Day 1(pre-dose)
Clinical chemistry	x		x	Day 1(pre-dose)
Urinalysis	x		x	Day 1(pre-dose)
Efficacy				
FEV1	x		x	Day 1(pre-dose)
Asthma Control Questionnaire (ACQ-6)	x		x	Day 1(pre-dose)
Asthma Exacerbation Assessments	x	x	x	Day 1(pre-dose)

[1] Taken in triplicate.
[2] Mean of the triplicate 12-lead ECG measurement from the Day 1 assessment (pre-dose).

If day 1 (pre-dose) assessment is missing for any endpoint, then latest data prior to day 1 (pre-dose) will be considered as baseline.

Screening visit assessment of FEV1 reversibility will be considered as baseline.

If either baseline or post-baseline data is missing, then change from baseline will be set to missing at that visit.

Maintenance therapy has been taken by participants on or before screening and run-phase will be considered as baseline.

4.2. Primary Endpoint Analysis

Primary estimands (refer Section 1.1) for primary endpoint will be applied for the primary analysis. Primary endpoint analysis will be based on safety analysis set.

4.2.1. Definition of primary endpoint

The primary safety endpoint is to estimate the incidence of adverse events (AEs) in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for "on-treatment" period. On-treatment period is defined as adverse events (AEs) occurring between treatment start date and treatment end date plus 7 follow-up days (inclusive).

All reported on-treatment AEs will be coded using the standard GSK dictionary, (MedDRA version ≥ 26.1) and grouped by body system and preferred terms.

4.2.2. Main analytical approach

The incidence of adverse events (AEs) will be summarized by counts and percentages in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for on-treatment period.

Point estimate of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one AE will be computed along with its Wald 95% CI for on-treatment period.

Wald confidence interval for the risk difference is computed as -

$$\hat{d} \pm \left(z_{\alpha/2} \times \text{se}(\hat{d}) \right)$$

Where $\hat{d} = \hat{p_1} - \hat{p_2}$

$\hat{p_1}$ = percentage of participants with at least one AE for salbutamol test treatment group (HFA-152a MDI).

$\hat{p_2}$ = percentage of participants with at least one AE for salbutamol reference treatment group (HFA-134a MDI).

$Z\alpha_{/2}$ is the 100(1- $\alpha/2)^{th}$ percentile of the standard normal distribution and standard error (SE) is copulated from the sample proportion as

$$\text{se}(\hat{d}) = \sqrt{\hat{p}_1(1-\hat{p}_1)/n_{1\cdot} + \hat{p}_2(1-\hat{p}_2)/n_{2\cdot}}$$

n_1 = Total number of participants in salbutamol test treatment group (HFA-152a MDI).

n_2 = Total number of participants in salbutamol reference treatment group (HFA-134a MDI).

4.2.3. Sensitivity analysis

Sensitivity analysis will be performed for risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups. Point estimate of risk difference and its 95% CI using exact score statistic [Agresti, 2001] will be presented for on-treatment period to examine the occurrence of small numbers of AEs in one or both the treatment groups.

4.2.4. Supplementary estimands

To analyse AEs for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in overall follow-up (on- and post-treatment) period and within post-treatment follow-up period, a supplementary estimand by using treatment policy strategy for the ICE of study treatment discontinuation due to any reason will be performed. The supplementary estimand will be estimated using the safety analysis set. AE data will be summarized by counts and percentages for both treatment groups.

Point estimate of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one AE will be computed along with its Wald 95% CI for overall treatment period.

4.2.4.1. Sensitivity analysis of supplementary estimands

Sensitivity analysis of supplementary estimands will be performed for risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment. Point estimate of risk difference and its 95% CI using exact score statistic [Agresti, 2001] will be presented for overall period to examine the occurrence of small numbers of AEs in one or both the treatment groups.

4.3. Secondary Endpoint(s) Analyses

Secondary safety and efficacy endpoints will be reported using the secondary estimand and the supplementary estimand (refer Section 1.1). Safety analysis set will be used to report safety endpoints.

4.3.1. Secondary endpoint(s)

The secondary safety endpoints are -

- Incidence of serious adverse events (SAEs)
- Minimum serum potassium
- Absolute values for serum potassium at each assessed visit.
- Change from baseline for serum potassium at each assessed visit.
- Absolute values for clinical laboratory assessments at each assessed visit.
- Change from baseline for clinical laboratory assessments at each assessed visit.

- Absolute values for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Change from baseline for vital signs parameters (systolic blood pressure, diastolic blood pressure, pulse rate) at each assessed visit.
- Absolute values for 12 lead ECGs in QTc and heart rate at each assessed visit.
- Change from baseline for 12 Lead ECGs in QTc and heart rate at each assessed visit.

The secondary efficacy endpoints are -

- Change from baseline for ACQ-6 score at each assessed visit.
- Change from baseline for FEV1 at each assessed visit

4.3.1.1. Definition of secondary endpoints

Incidence of serious adverse events (SAEs) for on-treatment period: -

Incidence of SAEs will be presented in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for "on-treatment" period. On-treatment period is defined as serious adverse events (SAEs) that occur between treatment start date and treatment end date plus 7 follow-up days (inclusive).

Definition for change from baseline: -

Change from baseline will be calculated by subtracting the baseline values from the individual post-randomization for ACQ-6 score, FEV1, serum potassium, clinical laboratory, vital signs and 12-lead ECGs.

4.3.1.2. Main analytical approach

The incidence of SAEs will be summarized by counts and percentages in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for "on-treatment" period.

Point estimate of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one serious adverse event (SAE) will be computed along with its 95% CI using exact score statistic (Agresti and Min 2001) for on-treatment period.

Descriptive statistics will be presented for minimum serum potassium, absolute and change from baseline value for serum potassium, clinical laboratory, vital signs, and 12-Lead ECGs. Refer Section 4.5.3 for further details.

Minimum of serum potassium will be analyzed using a general linear model with treatment, average daily dose, age, and baseline serum potassium as covariates (fixed effect) including interaction effect for treatment by average daily dose. Point estimate of mean difference in serum potassium between salbutamol test (HFA-152a MDI vs reference (HFA-134a MDI) treatment group and its associated 95% CI will be produced.

All common AEs (≥3% incidence) (Preferred Term)

Poisson regression (count data model) analysis will be performed for assessing the impact of different average daily doses between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment group considering treatment, baseline ACQ, baseline pre-bronchodilator trough FEV1, age, reversibility and average daily dose (refer Section 4.5.1 for further details) as covariates and duration of exposure as offset variable for all common AEs (≥3% incidence).

The point estimate of risk ratio (RR) and its associated two-sided 95% CI for each common AE (≥3% incidence) for salbutamol test (HFA-152a MDI) vs reference (HFA-134a MDI) treatment group will be computed. Risk ratio will be ratio of cumulative incidence of each common AE (≥3% incidence) for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment group.

Asthma Control Questionnaire (ACQ) Assessment: -

The ACQ-6 [Juniper, 1999] questionnaire consists of the 6 symptoms of asthma questions scored on a 7-point scale from 0 = no impairment/limitation to 6 = maximum impairment/limitation. The questions are equally weighted, and the ACQ-6 score will be the mean of the 6 questions. If a subject does not complete more than 1 of the 6 questions at a visit, then their ACQ-6 score will be set to missing at that visit. No imputation method will be used for the missing ACQ-6 score.

Participants will complete the ACQ at specified study visits. The 6 questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath, wheeze, and rescue medication use) enquire about the frequency and/or severity of symptoms over the previous week.

Descriptive statistics (n, mean, standard deviation (std), median, minimum, and maximum) for absolute and change from baseline ACQ score at Visit 8 (Week 12) will be computed and presented by study treatment groups using ITT analysis set.

Mixed effect linear model analysis will be used to analyse the change from baseline in ACQ-6 score at Visit 8 (Week 12) including baseline ACQ-6 score, treatment, age, sex reversibility and maintenance therapy at baseline as fixed effect covariates for the calculation of point estimates and 95% confidence intervals of salbutamol test (HFA-152a MDI) and salbutamol reference (HFA-134a MDI) treatment groups.

Forced Expiratory Volume in 1 second (FEV1) Assessment: -

Analysis of absolute and change from baseline in clinic pre-bronchodilator FEV1 at Visit 8 (Week 12) will be summarized in descriptive nature (n, mean, standard deviation (std.), median, minimum, and maximum) and presented by study treatment groups using ITT analysis set.

Mixed effect linear model analysis will be used to analyse the change from baseline in pre- bronchodilator FEV1 at Visit 8 (Week 12) including baseline pre-bronchodilator FEV1, treatment, age, sex reversibility and maintenance therapy at baseline as fixed effect covariates for the calculation of point estimates and 95% confidence intervals of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.

Participants who are withdrawn from the study are included at week 12 summary and statistical analysis of ACQ-6 score and FEV1 if and only if they will be completed ≥50% (≥42 days) duration of study treatment.

4.3.1.3. Sensitivity analyses

No sensitivity analysis will be performed for the secondary endpoints.

4.3.1.4. Supplementary estimand for secondary endpoint analyses

A supplementary estimand for secondary safety endpoints using treatment policy strategy for the ICE of study treatment discontinuation due to any reason (refer Section 1.1 supplementary estimands for supporting safety objectives) will be considered to evaluate SAEs, serum potassium, clinical laboratory assessment, vital signs, and ECGs data for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups in overall follow-up (on- and post-treatment) period and post- treatment follow-up period. The supplementary estimand will be estimated using the safety analysis set.

SAEs data will be summarized by counts and percentages. Point estimate of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one serious adverse event (SAE) will be computed along with its 95% CI using exact score statistic [Agresti, 2001] for overall treatment period.

Descriptive statistics of absolute values and change from baseline at each assessed visit will be presented for serum potassium, clinical laboratory assessment, vital signs, and ECGs data in salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups.

4.3.2. Supportive secondary endpoints

No supportive analysis will be performed for the secondary endpoints.

4.4. Exploratory Endpoints Analyses

No exploratory analysis will be performed for the secondary endpoints.

4.5. Safety Analyses

Safety analyses will be performed using safety analysis set and displayed by study treatment groups.

4.5.1. Extent of Exposure

The total exposure on study treatment (salbutamol test HFA-152a MDI or salbutamol reference HFA-134a MDI) is calculated as the date of last dose of study treatment minus first dose plus one of study treatment groups. Subjects who entered in study treatment phase but did not report any treatment dates will be categorized as having zero days of exposure.

Average daily dose is derived as -

Total dose of study treatment / Total exposure (days) on study treatment

Average daily puff is defined as -

Total number of puffs of study treatment / Total exposure (days) on study treatment

Study treatment exposure will be summarized for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) using safety analysis set. Time on study treatment (days), the average number of puffs, average daily dose and cumulative actual total dose and puff will be presented in treatment exposure summary. Dose administration and exposure data for all participants will be generated in the listing.

4.5.2. Adverse Events

The applicable definitions of AE and SAE are in the study protocol Sections 8.4 and 10.3.

An AE is considered study treatment emergent (on-treatment) if the AE onset date is on or after study treatment start date and on or before study treatment stop date plus 7 days (inclusive) follow-up or worsens (change in AE severity from lower severity to higher severity category) relative to the pre-study treatment state. Refer Section 4.2.1 for MedDRA dictionary version.

Overview of AEs: Summary of overview of AEs will be presented using the total number of adverse events reported and the number of participants who experienced at least one AE, AE by maximum severity intensity, drug-related AE, SAE, drug-related SAE, non-fatal SAE, drug-related non-fatal SAE, SAE leading to death, AE leading to discontinuation of study treatment and AE leading to withdrawal from study.

AEs and SAEs by SOC and PT: Summary (counts and percentages) of AEs and SAEs will be produced by system organ classes (SOCs), preferred terms (PTs). Summary for SAEs will be summarized by SOCs and PTs with number of subjects and occurrences. Summary of exposure adjusted incidence rate for AEs by SOCs and PTs will be displayed. The exposure-adjusted AE summaries will include rates for any AE by SOC and PT will be derived as follows:

Rate per 1000 patient years = 1000*Number of Adverse Events / ([Total Duration of Exposure in Days]/365.25)

Total Duration of exposure will be calculated as - Date of last dose +1 – date of first dose.

Common AEs: Summary of (counts and percentages) common (≥3% incidence) (before rounding) AEs by preferred terms (PTs) will be produced. Summary for common (≥3%) non-SAEs will be produced by SOCs and PTs with number of subjects and occurrences.

AEs and SAEs related to study treatment: Relationship to study treatment, as indicated by the investigator, is classified as “not related” or “related”. AEs with a missing relationship to study treatment will be recorded as “related” to study treatment. If a participant reports the same AE more than once within an SOCs/PTs, the AE with the worst-case relationship to study treatment will be used in the corresponding relationship summaries.

Summary tables for drug-related AEs and SAEs will be generated by SOCs, PTs and maximum severity. Summary for drug-related AEs and SAEs (fatal and non-fatal) will also be produced by PTs. Summary of non-serious drug-related adverse events by overall frequency will also be created.

AEs by severity: Adverse event severity is categorized as mild, moderate, severe. Adverse events starting after the first dose of study treatment with a missing severity will be classified as severe. If a participant reports an AE more than once within an SOCs/PTs, the AE with the worst-case (maximum) severity will be used in the corresponding severity summaries. Summary tables for severity of AEs and SAEs will be provided by SOCs, PTs, and maximum severity. Summary table for AEs and SAEs leading to permanent discontinuation of study treatment or withdrawal from study by SOCs and PTs and maximum severity will be generated.

Adverse events analyses including the analysis of AEs and SAEs will be based on GSK Core Data Standards.

Separate listings will be produced for all AEs for safety analysis set. Summary of death will be summarized and participants profile for death will also be listed using enrolled participants.

In summary tables, SOCs will be sorted in descending order of the total incidence then alphabetically, PTs will be sorted in descending order of the total incidence then alphabetically within the SOC.

For completely missing or partial missing AE start date or end date, imputation rules will be applied following Appendix 3 Section 6.3.6.

Details of the planned displays for AEs and SAEs are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.2.1. Adverse Events Potentially Associated with Local Tolerance of Propellant

On-treatment adverse events that are potentially associated with local tolerance are listed below:

- Bronchospasm
- Cough
- Dysgeusia
- Dysphonia
- Respiratory irritation
- Taste disorder
- Throat irritation

Summary of (counts and percentages) AEs that are potentially associated with local tolerance will be displayed by PTs for salbutamol test (HFA-152a) and reference (HFA-134a) propellent. A summary table for AEs potentially associated with local tolerance related to study treatment will also be presented by PTs for salbutamol test (HFA-152a) and reference (HFA-134a) propellent.

4.5.3. Additional Safety Assessments (if applicable)

4.5.3.1. Laboratory Data

Laboratory evaluations including the analyses of chemistry laboratory tests, hematology laboratory tests and urinalysis will be based on GSK Core Data Standards.

Table 2 Parameters of laboratory tests assessments

Laboratory Tests	Parameters	
Hematology	Platelet count	
	Red blood cell (RBC) count	
	RBC indices	Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes
	WBC count with differential:	Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Hemoglobin	
	Hematocrit	
Clinical chemistry	Blood urea nitrogen (BUN)/Urea Potassium Creatinine* Sodium Calcium Glucose [non-fasting] Creatine phosphokinase (CPK)	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase[1] Total bilirubin Direct bilirubin
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal) Epithelial cells Red Blood cells WBC Casts Crystals Culture (if positive: specify pathogen)	

*To assess the kidney function, use the estimated glomerular filtration rate (eGFR) 2021 calculator (CKD-Epi creatinine equation). eGFR (based on CKD-Epi) will be measured at all time points when creatinine is measured.
[1]If alkaline phosphatase is elevated, consider fractionating

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented study treatment groups for quantitative measurements of continuous laboratory parameters at baseline, absolute and change from baseline value.

Counts and percentages will be produced for qualitative measurements measure laboratory parameters.

Summary of worst-case for clinical laboratory parameters results relative to normal range from baseline to post-baseline will be displayed using categories of “To Low”, “To Normal or No Change” or “To High”.

Summary of shifts in clinical laboratory parameters relative to normal range from baseline to post-baseline will be produced using categories of "High", "Normal" or "Low".

The derivation rule follows:

- Laboratory values will be classified as "Low", "Normal", or "High" based on the provided normal ranges.
- Change from baseline values will be classified relative to normal range as "To Low", "To Normal or No Change", or "To High". Participants who do not change categories or move from out-of-range to normal will be classified as "To Normal or No Change".
- A "worst case post-baseline" change classification relative to normal ranges will be derived for each treatment in which participants will be counted in the "To Low" or "To High" categories if they reported a change from a "Normal" baseline to a value below or above the normal range, respectively, at any on-treatment scheduled, unscheduled, or early withdrawal visits. Participants who did not report a change to a value outside the normal range at any visit will be counted in the "To Normal or No Change" category.
- Participants having both high and low values relative to normal ranges at post-baseline on-treatment visits for safety parameters will be counted in both the high and low categories of the "worst-case post-baseline" row of related summary tables.

Summary of worst case for urinalysis results from baseline to post-baseline using will be created using categories of "No Change/Decreased" or "Any Increase" or "Increase to TRACE". A "worst case post-baseline" change classification relative from baseline will be derived for each treatment in which participants will be counted 'No Change/Decreased', 'Increase to TRACE', 'Increase to 1+ or Increase to 2+', 'Increase to 1+ or to 1 MG/DL', etc. 'Decreased' indicates a "lesser" result including change to a negative result.

Summary of liver monitoring/stopping event will be summarized by counts and percentages. Hepatobiliary laboratory abnormalities for liver event will also be produced. Refer to protocol Section 10.5 Appendix Liver safety for more description of liver events.

Participants listing for all clinical laboratory data will be produced for safety analysis set.

If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '≤' or '≥' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

- Example 1: 2 significant digits = '≤ x' becomes x – 0.01
- Example 2: 1 significant digit = '≥ x' becomes x + 0.1
- Example 3: 0 significant digits = '≤x' becomes x – 1

Details of the planned displays for clinical laboratory evaluations are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.3.2. 12 Lead ECG

The arithmetic mean of the three recorded 12 lead ECGs measurements will be presented in all data summaries at baseline and single recorded twelve-lead ECGs measurements at each assessed visit. ECG measurements will be recorded, including heart rate (HR), PR interval, QRS duration, QT interval, and RR interval. QT intervals will be based on Fridericia's formula and reported as per captured in eCRF:

Descriptive statistics (n, mean, standard deviation (SD), median, minimum value (min), and maximum value (max)) will be presented study treatment groups at baseline, and absolute and change from baseline 12 lead ECGs at each assessed visit.

Summary of maximum QTc(F) values from baseline to post-baseline will be summarized to show the number of subjects with maximum values (msec) in the following categories:

- ≤450 msec
- >450 – ≤480 msec
- >480 – ≤500 msec
- >500 msec

Summary of maximum increase in QTc(F) values from baseline to post-baseline will be summarized to show the number of subjects with maximum values (msec) in the following categories:

- ≤30 msec
- >30 - 60 msec
- >60 msec

Summary (counts and percentages) of 12 lead ECG findings will be summarized by treatment group at baseline and each assessed visit. Abnormal will include sub-categories of Clinically significant and non-clinically significant according to eCRF classification. When multiple ECGs were performed at the same planned timepoint, the worst-case post-baseline finding will be summarized, except at baseline mean of triplicate baseline assessments will be taken. Clinically significant change from baseline will also be presented for following categories:

- no change/insignificant change from baseline
- significant favourable change from baseline
- significant unfavourable change from baseline

Shift table of Fridericia's QTc from baseline to post-baseline value will also be created.

Participants listings will be provided for all 12 lead ECGs findings for participants with an abnormal ECG for Safety analysis set.

Details of the planned displays for ECG parameters are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.5.3.3. Vital Signs

The analyses of vital signs parameters will be based on GSK Core Data Standards.

The following vital signs measurements will be measured in a supine position after 5 minutes rest at baseline and each assessed visit.

- Temperature
- Systolic and Diastolic blood pressure
- Pulse rate

Descriptive statistics (n, mean, standard deviation [SD], median, minimum value [min], and maximum value [max]) will be presented at baseline, absolute and change from baseline of vital signs parameters by study treatment groups at each assessed visit.

Summary (counts and percentages) of worst-case vital signs results relative to normal range from baseline to post-baseline will be displayed using categories of "To Low", "To Normal or No Change" or "To High". Normal range for vital signs parameters are as follows –

Parameters	Unit	Normal Range
Temperature	degrees Celsius	32.5 - 40.0
Systolic Blood Pressure	mmHg	50.0 - 200.0
Diastolic Blood Pressure	mmHg	40-150
Pulse Rate	beats/min	40 - 180

The derivation rule of shifts in vital signs parameters relative to normal range from baseline to post-baseline will be produced similar to Section 4.5.3.1.

Participants listing for all vital signs data will be produced for Safety analysis set.

Details of the planned displays for vital signs parameters are provided in Output programming specifications (OPS) and will be based on GSK Data Standards and statistical principles.

4.6. Other Analyses

4.6.1. Subgroup analyses

Subgroup analyses will be performed to assess the incidence of AEs and SAEs in on-treatment, post-treatment, and overall period for salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for following subgroup -

Subgroup	Categories
Sex	Male, Female
Race	American Indian or Alaska Native, Asian (Central/South Asian Heritage, Chinese Heritage, Korean Heritage, Japanese Heritage, South East Asian Heritage), Black or African American, Native Hawaiian or Other Pacific Islander, White (Arabic/North African Heritage, White/Caucasian/European Heritage)
Geographical Location	North America (USA and Canada), Europe (Spain, Italy, France, Poland, United Kingdom (UK) and Greece), Central & South America (Panama and Argentina), Southeast Asia (Thailand and Philippines), Australia (Australia)
Baseline Reversibility	Reversible, Non-reversible
Baseline Maintenance Class of Therapy	SABA ICS+SABA ICS/LABA+SABA ICS/LABA/LAMA+SABA

Counts and percentages of incidence of AEs and SAEs will be produced as per above categories of subgroups by SOCs and PTs. If any subgroup category of subgroups excluding baseline reversibility and baseline maintenance class of therapy has less than 5% of participants across the treatment groups, analyses for the incidence of AEs and SAEs will not be conducted for that subgroup. All data of AEs and SAEs will be summarised for baseline reversibility and baseline maintenance class of therapy subgroups.

4.6.2. Asthma Exacerbations

Summary statistics for asthma exacerbations during the study will be summarized using ITT analysis set.

4.6.3. Maintenance Class of Therapy

Summary statistics for maintenance class of therapy at baseline will be presented using ITT analysis set for example ICS/LABA + SABA, ICS/LABA/LAMA + SABA etc. Shift table of maintenance class of therapy from baseline to post-baseline value will also be created in safety analysis set for on-treatment period.

4.6.4. Classification and Analysis of Safety Signals

Counts and percentages of on-treatment AEs by SOC and PT, as along with risk differences (RD) with 90% CIs for each SOC and PT, for the comparison between the test (salbutamol HFA-152a MDI) and reference (salbutamol HFA-134a MDI) treatment groups. Exact score statistic method [Agresti, 2001] will be used to construct 90% CI.

A quantitative screening of 220735 study intervention emergent AEs for identification of potential adverse reactions (i.e., "short list" events) will be performed using quantitative measures [Crowe, 2013]. After the "short list" has been identified using the quantitative thresholds, each event will undergo a qualitative assessment to determine if there is enough evidence to support a causal association.

The following quantitative criteria to "short list" an AE the PT level will be based on absolute incidence in participants, point estimate of unadjusted RD (vs. salbutamol HFA-134a MDI) and the corresponding 90% CI. Any PT meeting any of the following criteria will be added to the "short-list":

Criteria	**RD (salbutamol HFA-152a MDI vs. salbutamol HFA-134a MDI**	**90% CI for RD**
AE	At least 3%	Lower CI >0

Summary of adverse events according to time at first occurrence of adverse events will be generated by SOC, PT and treatment groups in on-treatment period to investigate the temporal association.

4.6.5. Other variables and/or parameters

Not applicable

4.6.6. Analyses to Support Regional Submission

Not applicable

4.7. Interim Analyses

No interim analysis will be performed.

4.8. Changes to Protocol Defined Analyses

Additional analyses have been added for the following –

- Sensitivity analysis for primary endpoint (refer Section 4.2.3)
- Sensitivity analysis for supplementary estimands of primary endpoint (refer Section 4.2.4.1)
- Point estimate of risk difference along with its 95% CI between test and reference treatment groups for the participants with at least one SAE in main and supplementary estimand analysis (refer Section 4.3.1.2 and 4.3.1.4)
- Subgroup analyses (refer Section 4.6.1)

The 95%CI for all sensitivity analyses of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one AE will be calculated by exact score statistics [Agresti, 2001].

The 95%CI for main and supplementary analyses of risk difference between salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups for participants with at least one SAE will be calculated by exact score statistics [Agresti, 2001].

5. SAMPLE SIZE DETERMINATION

The sample size of primary interest in the salbutamol test (HFA-152a MDI) treatment group was determined based on the calculation of the probability of observing an adverse event (AE).Table 3 and Table 4 provide the probabilities of observing various numbers of Adverse Events (AEs) based on a series of theoretical risks of an event occurring assuming 300 participants in salbutamol test (HFA-152a MDI) treatment group and 100 participants in salbutamol reference (HFA-134a MDI) treatment group during a study of 3 months duration.

For an example, for a theoretical risk of an AE of 1/100 for sample size of 300 in salbutamol test (HFA-152a MDI) treatment group, we would have a greater than 95.09% chance of observing at least one participant having the AE, and for a theoretical risk of an AE of 3/100 for sample size of 100 in reference (HFA-134a MDI) treatment group, we would have a greater than 95.24% chance of observing at least one participant having the AE.

Table 3 Probabilities of observing a given number of participants experiencing an adverse event or more (k) for given theoretical risks in a study for a sample size of 300 participants in salbutamol test (HFA-152a MDI).

	Theoretical Risk of an Event*				
K	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**
1	95%	100%	100%	100%	100%
2	80%	98%	100%	100%	100%
3	58%	94%	99%	100%	100%
4	35%	85%	98%	100%	100%
5	18%	72%	95%	99%	100%
6	8%	56%	89%	98%	100%
7	3%	39%	80%	96%	99%
8	1%	26%	68%	92%	98%
9	<1%	15%	55%	85%	97%
10	<1%	8%	41%	76%	94%

*Theoretical risk of an event occurring in a given participants in a study of 3 months duration.

Table 4 Probabilities of observing a given number of participants experiencing an adverse event or more (k) for given theoretical risks in a study for a sample size of 100 participants in reference (HFA-134a MDI)

	Theoretical Risk of an Event*				
K	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**
1	63%	87%	95%	98%	99%
2	26%	60%	81%	91%	96%
3	8%	32%	58%	77%	88%
4	2%	14%	35%	57%	74%
5	<1%	5%	18%	37%	56%
6	<1%	2%	8%	21%	38%
7	<1%	<1%	3%	11%	23%
8	<1%	<1%	1%	5%	13%
9	<1%	<1%	<1%	2%	6%
10	<1%	<1%	<1%	<1%	3%

*Theoretical risk of an event occurring in a given participants in a study of 3 months duration.

For a given or assumed sample size of 400, the description of precision estimates, risk difference and 95% CIs (calculated by Wald method) has been presented using different scenarios in Appendix 4 Section 6.4.

Approximately 412 participants will be randomly assigned with 3:1 ratio in the study, 309 participants in salbutamol test (HFA-152a MDI) treatment group to achieve 300 participants and 103 participants in salbutamol reference (HFA-134a MDI) treatment group to achieve 100 participants for the primary analysis. A smaller reference group for HFA-134a has been proposed because the primary estimand is a descriptive characterization of AE incidence in each group, and both salbutamol and the propellant HFA-134a have been on the market for several decades. Salbutamol has a well-established safety profile, supported clinical trial data and over 50 years of on-the-market data. Clinical trials have previously observed common AEs with greater occurrence than placebo such as throat irritation, upper respiratory inflammation, viral respiratory infections, cough, and musculoskeletal pain in Ventolin HFA arm occurring at 5-10% frequency. [FDA, 2021]

In addition, HFA-134a is considered biologically inert. This is supported by several studies which show that HFA-134a is not metabolized or retained in the body, but is exhaled out rapidly after exposure [Gunnare, 2007; Pike, 1995; Shin, 2015]. Given this evidence and the extensive history of salbutamol usage, a sample size of 100 participants in the salbutamol HFA-134a treatment arm is considered appropriate for the evaluation of adverse events.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

The study population analyses will be based on the ITT analysis set, unless otherwise specified. A summary of the number of participants in each of the participant level analysis set will be provided.

Study population analyses will be included in analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, study treatment compliance based on GSK Core Data Standards.

6.1.1. Participant Disposition

Participant disposition will be tabulated by study treatment groups for all participants combined with the counts and percentages of participants who complete the study, prematurely withdraw, and the reason for study withdrawal in ITT analysis set. Participant listing of the reasons for study withdrawal will be provided for ITT analysis set.

Summary of treatment status and reasons for discontinuation of study treatment will be produced for study treatment, with the number of participants who completed double-blinded study treatment, or prematurely discontinued treatment, and the primary reasons for treatment discontinuation tabulated for the ITT analysis set.

Summary of screen failure (did not meet inclusion/exclusion criteria, adverse event, study terminated by sponsor, physician decision, withdrawal by participants, death or other) and its reason will be provided for screened participants.

Summary of run-in failure including randomization criteria (did not meet inclusion/exclusion criteria, adverse event, study terminated by sponsor, physician decision, withdrawal by participants, death or other) and its reason will be provided for enrolled participants.

Summary of number of subjects by country and site will be produced using ITT analysis set and enrolled participants.

Listing of planned and actual treatments will also be generated for ITT analysis set.

Table will be generated for summarizing the number of participants in each analysis set for all participants who provided informed consent. A separate table will also be constructed that summarizes the reasons for exclusion from safety analysis set using ITT analysis set. Listing of participants excluded from any analysis set will also be produced for enrolled participants.

A Kaplan-Meier curve will be generated for time to study treatment discontinuation from study using Safety analysis set. Time to study treatment discontinuation from study is measured from the date of first dose date of study treatment to the date of discontinuation from the study treatment. Participants who complete the study treatment according to protocol are censored at the date of end of study treatment visit. For subjects who discontinue from study treatment, the date of study treatment discontinuation will be used for the calculation of time to study treatment discontinuation from the study.

6.1.2. Demographic and Baseline Characteristics

Demographic characteristics such as age, sex, race, ethnicity, childbearing potential, height, weight, and body mass index (BMI) will be summarized and tabulated by study treatment groups and overall using participants in ITT analysis set and enrolled participants. Listing for demographic characteristics will be produced for ITT analysis set.

Descriptive statistics will be presented for age, age group 1 (≥18 - ≤64 years, ≥ 65 years) height, weight, and BMI. Counts and percentages will be presented by sex, race, ethnicity, and childbearing potential.

Baseline disease characteristics will be summarized using in ITT analysis set for baseline ACQ-6 score, participants history of asthma, duration of asthma and history of exacerbations in the previous 6 and 12 months from the screening visit.

Spirometry at Visit 1 and Visit 3: Descriptive statistics for pre-bronchodilator FEV1, FVC, FEV1/FVC and % predicted FEV1 will be presented using ITT analysis set. Change in pre-bronchodilator from visit 1 to pre-dose FEV1 at visit 3 will also be summarized descriptively.

Participants reversibility will be assessed at screening (Visit 1). To determine reversibility, the subject will follow bronchodilator procedures as per the protocol.

Reversible is defined as an increase in FEV1 of ≥12% and ≥200mL following administration of bronchodilator (albuterol/salbutamol) at screening (Visit 1).

Percent reversibility is calculated as -

(Post-bronchodilator FEV1 – Pre-bronchodilator FEV1) x 100 / Pre-bronchodilator FEV1

Non-reversible is defined as a post-albuterol/salbutamol increase in FEV_1 of <200mL or ≥200mL increase that is <12% from pre-albuterol/salbutamol FEV_1.

Summary statistics for reversibility will be produced at baseline (screening) using ITT analysis set.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized using ITT analysis set by study treatment groups and overall. Listing of important protocol deviation will also be generated for ITT analysis set.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations (where possible without knowing the study treatment details) are captured and categorized in the protocol deviations dataset.
- This dataset will be the basis for summaries of important protocol deviations.
- Data will be reviewed prior to unblinding and freezing the database to ensure all deviations leading to analysis population exclusions are captured and categorized in the protocol deviations ADaM dataset (note these exclusions are not captured in the SDTM dataset).

6.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO Drug dictionary version on or after Global B3 Sept 2023.

The counts and percentages of participants reporting each concomitant medication will be presented by study treatment groups for ITT analysis set. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-treatment, on-treatment, and post- treatment separately. Pre/on-treatment/post-treatment respiratory medications (Respiratory medication class) will be summarized separately.

A medication will be summarized in every period (pre/on/post) in which it was taken, so a medication that was started in the screening or run-in and stopped during active treatment will appear in both the pre-treatment and the on-treatment tables.

Summary of asthma maintenance therapy at study entry will be presented for following class of asthma maintenance therapy -

- SABA
- ICS + SABA
- ICS/LABA + SABA
- ICS/LABA/LAMA +SABA

Shift table of asthma maintenance therapy from baseline to post-baseline (during on-treatment period) will also be created.

Participants listing for concomitant medication will also be generated for ITT analysis set.

6.1.5. Medical History and Current Medical Conditions

Counts and percentages for medical history and current medical conditions will be presented for each body system of participants by study treatment groups using ITT analysis set.

6.1.6. Cardiovascular Risk Factors and Smoking History

Count and percentages will be presented by study treatment groups for family history (Cardiovascular history and risk factors) for ITT analysis set.

Smoking history (smoking status of non-smoker or former smoker, cigarettes/day, years smoked, pack years for former smokers and Nicotine oral/Topical use) will also be summarized using ITT analysis set. Smoking pack years will be calculated as: -

Smoking pack years = (Number of cigarettes smoked per day/20) x number of years smoked.

6.1.7. Study Treatment Compliance

A summary of overall compliance for minimum daily dose (2x100 µg) of salbutamol test (HFA-152a MDI) and reference (HFA-134a MDI) treatment groups based on the exposure data will be produced. Overall compliance will be summarized using descriptive statistics as well as the categories <80%, 80%-100%.

Study treatment Compliance (%) for minimum daily dose = [Total cumulative actual minimum daily dose (2x100 µg) / Total cumulative scheduled minimum daily dose (2x100 µg)] *100.

6.2. Appendix 2 ACQ-6 Score (eCOA) Compliance

6.2.1. Study Level compliance

Overall compliance will include all received ACQ-6 score data points over all expected ACQ-6 score data points. Overall ACQ-6 score compliance (across all ACQ-6 score and all participants) for the study is calculated as:

[Total number of complete ACQ-6 scores across all participants / Total expected number of complete ACQ-6 scores across all participants] *100

E$xpected\ number\ of\ complete$ ACQ-6 score =

$$\sum_{i=1}^{n}\sum_{j=1}^{c} \text{data points expected for ACOQ–6j (participant i)}$$

where c represents the total number of ACQ-6 scores collected and n represents the total number of participants.

Subject's overall compliance will be calculated as:

[Total number of complete ACQ-6 scores by participant / Total expected number of complete ACQ-6 scores across by participant] *100

Overall compliance and Subject's overall compliance with 0 - <50%, 50% - ≤75%, > 75% -≤100% categories will be summarized by study treatment using ITT analysis set –

If a subject withdraws during the course of the study, and the number of visits (for visit-based collection) up until the study withdrawal date should be considered.

6.3. Appendix 3 Data Derivations Rule

6.3.1. Criteria for Potential Clinical Importance

Not applicable

6.3.2. Study Period

Assessments and events will be classified according to the time of occurrence relative to the study treatment period.

Pre-Treatment: For the presentation of serious adverse events (SAEs), concomitant medications, and other assessments in pre-treatment is defined as -

Date of assessment < Study treatment start date.

On-Treatment: For the presentation of adverse events (AEs), serious adverse events (SAEs), concomitant medications, 12-lead ECG, vital signs, and other assessments, on-treatment is defined as -

Study treatment start date ≤ Date of assessment ≤ Study treatment stop date or early withdrawal + 7 days

Worsening in AE (change in AE severity from lower severity to higher severity category) relative to the pre-study treatment state will also be considered as on-treatment AE.

If time of assessment or study treatment is not collected (missed), the following assessment on the first dose date will be assumed to be taken prior to the first dose and therefore considered pre-treatment.

Post-Treatment: For the presentation of adverse events (AEs), serious adverse events (SAEs), concomitant medications, 12-lead ECG, vital signs, and other assessments in post-treatment is defined as -

Date of assessment > Study treatment stop date or early withdrawal + 7 days.

Please refer Section 6.3.6 for handling of missing and partial dates of assessments.

6.3.3. Study Day and Reference Dates

The safety reference date is the study treatment start date and will be used to calculate study day for safety measures.

The efficacy reference date is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics, as well as efficacy durations.

The study day is calculated as below:

- Assessment Date = Missing → Study Day = Missing
- Assessment Date < Reference Date → Study Day = Assessment Date – Ref Date
- Assessment Data ≥ Reference Date → Study Day = Assessment Date – Ref Date + 1

6.3.4. Assessment Window

Analysis timepoint windows will be defined for by- timepoint summary and analysis purposes for safety and efficacy data. For adverse events (AEs) and concomitant medications, study data will not be reported by visit as this assessment are collected through the study.

If there are multiple assessments (including scheduled and unscheduled) within the same window, a scheduled visit will be prioritized over un-scheduled visits for the analysis. If multiple record of an assessment (including scheduled or unscheduled) for exist within the same analysis timepoint window, then the record occurring closest to the target day will be utilized in all analyses. If multiple record (including scheduled or unscheduled) of

an assessment is equally close to the target day, then the later record will be utilized. Where two or more ECG findings slot to the same visit interval, the most 'abnormal' results will be used, i.e., according to the following hierarchy: Abnormal-Clinically Significant > Abnormal – not clinically significant > Normal.

For data summaries by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a target visit based on visit window defined in Table 5 and Table 6.

Table 5 Analysis visit window for Safety endpoints (Unscheduled and Early Withdrawal visit)

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window[a]		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety	ECG, Clinical laboratory, and Vital signs	Day -21	Before first dose of study treatment (Day 1)		Baseline
		Day 1	Day 1		Visit 3 (Week 0)
		Day 7	Day 2	Day 18	Visit 4 (Week 1)
		Day 28	Day 19	Day 42	Visit 6 (Week 4)
		Day 56	Day 43	Day 70	Visit 7 (Week 8)
		Day 84	Day 71	Day 88	Visit 8 (Week 12)
		Day 91	Day 89	≥ Day 91	Visit 9 (Week 13)

[a] Relative to the starting point of an analysis phase, e.g., it will be relative to randomization date or on-treatment analysis phase and the first dose of double-blind study drug for the treatment-emergent analysis phase.

Table 6 Analysis visit window for Efficacy endpoints

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window[a]		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Efficacy	FEV 1 and ACQ-6 score	Day -21	Day -21	Before first dose of study treatment	Baseline
		Day 1	Day 1		Visit 3 (Week 0)
		Day 84	Day 42	Day 91	*EOT (Visit 8 (Week 12).

[a] Relative to the starting point of an analysis phase, e.g., it will be relative to randomization date or on-treatment analysis phase. * End of Treatment including early withdrawal visit

For data summaries by visit, scheduled visits with nominal visit description as well as the worst-case post baseline will be displayed. Unscheduled will be included in the derivation of worst-case post baseline assessment. All unscheduled visits will be displayed in the listing.

6.3.5. Multiple measurements at One Analysis Time Point

When triplicate 12-lead ECG assessments are taken, the mean of the 3 measurements will be calculated first and summary statistics will be based on the calculated mean. This will apply only for baseline. A single assessment of 12-lead ECG will be performed for post-baseline visits.

If multiple assessments are taken from the same type of lab/ECG/vital parameters, the worst case will be used.

6.3.6. Handling of Partial Dates

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>General</td><td>

Partial dates will be displayed as captured in participant listing displays.
However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data to study phases or for specific analysis purposes as outlined below.
Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

</td></tr>
<tr><td>Adverse Events</td><td>

Partial dates for AE recorded in the CRF will be imputed using the following conventions:

<table>
<tr><td>Missing start day</td><td>If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
Else if study treatment start date is not missing:
• If month and year of start date = month and year of study treatment start date, then
– If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.
– Else set start date = study treatment start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
Else if study treatment start date is not missing:
• If year of start date = year of study treatment start date, then
– If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.
– Else set start date = study treatment start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing end day and month</td><td>No Imputation will be applied in case of AE with missing end day and month</td></tr>
<tr><td>Completely missing start/end date</td><td>• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
• Adverse events with entirely missing or unknown start dates will be assumed to be on-treatment and treatment emergent for reporting.</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/Medical History</td><td>
• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
Else if study treatment start date is not missing:
• If month and year of start date = month and year of study treatment start date, then
– If stop date contains a full date and stop date is earlier than study treatment start date, then set start date= 1st of month.
– Else set start date = study treatment start date.
Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
Else if study treatment start date is not missing:
• If year of start date = year of study treatment start date, then
– If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = January 1.
– Else set start date = study. treatment start date.
Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year).</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>• Completely missing start or end dates will remain missing, with no imputation applied.</td></tr>
</table>
</td></tr>
<tr><td>Age</td><td>Age is derived using the date of first dose. When first dose date is missing, the ICF date is used. Only year of birth is collected so Day and Month of birth are imputed as 30 June.
Formula for deriving age is the integer component of:
• (First Dose Date – 30 Jun of collected birth year +1)/365.25</td></tr>
</table>

6.3.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study treatment completion is defined as if the participant has taken all doses of the study treatment. Participants who discontinue study treatment will not be considered withdrawn from the study and should attend Follow-up Visits as applicable.
	• Participants study completion (i.e., as specified in the protocol) is defined as if the participant has completed all study visits including the Follow-up Visit

6.3.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Efficacy	• As defined in the exploratory endpoint variables, participants with missing measurements will be treated as missing for corresponding visits (unless otherwise specified for sensitivity analyses).
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

6.3.6.3. Reporting Process

Software
• The currently supported versions of SAS software will be used through DOMINO (METEOR) workspace.
Analysis Datasets
• Analysis datasets will be created according to CDISC standards (SDTM IG Version ≥3.3 & ADaM IG Version ≥1.1)
Analysis Results Metadata (ARM)
• Analysis Results Metadata (ARM) will be created for primary and key secondary endpoint analysis. Please see programming notes for which displays require ARM.
Generation of RTF Files
• RTF files will be generated for all reporting efforts described in the Statistical Analysis Plan.

6.3.6.4. Reporting Standards

General
The current GSK Statistical Display Standards in the GSK Standards Library (IDSL) will be applied for reporting, unless otherwise stated (Library Location for GSK Statistical Display Standards: GSK Data & Analysis Standards Library – Data Standard - By Component
Planned and Actual Time
• Reporting for tables, figures, and formal statistical analyses: • The impact of any major deviation from the planned assessment times and/or scheduled timepoint on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Unscheduled or unplanned readings will be presented within the participant's listings.
Unscheduled Visits
• Unscheduled visits and Early withdrawal visits may be included in summary tables and/or figures as described in Section 6.3.4. Analysis timepoints and analyses such as "all post baseline", "worst case post baseline", and "max post baseline" etc. All unscheduled visits and Early Withdrawal visits will be included in listings.

6.3.7. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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SAS

6.4. Appendix 4 Sensitivity table of sample size based on risk difference between Salbutamol Test (HFA-152a MDI) and Reference treatment (HFA-134a MDI) for participants with at least one AEs, Precision criteria (HW) and 95%CIs

N1	N2	P1 (%)	P2 (%)	[P1-P2] (%)	Half-width (HW) (%)	Lower Limit of 95% CI	Upper Limit of 95% CI
300	100	35	32	3	10.62	- 7.6	13.6
300	100	37	32	5	10.65	- 5.7	15.7
300	100	39	32	7	10.68	- 3.7	17.7
300	100	42	32	10	10.72	- 0.7	20.7
300	100	69	66	3	10.66	-7.7	13.7
300	100	71	66	5	10.61	-5.6	15.6
300	100	73	66	7	10.56	-3.6	17.6
300	100	76	66	10	10.47	-0.5	20.5

N1 = Number of participants in HFA -152a MDI treatment; N2 = Number of participants in HFA-134a MDI treatment; P1 = Percentage of participants for at least one AEs in HFA-152a MDI treatment; P2 = Percentage of participants for at least one AEs in HFA-134a MDI treatment group.

Note: A total sample size of 400 (as described in Section 5), and percentage of participants for at least one AEs in salbutamol reference (HFA-134a MDI) treatment group (P2) 32%, the half width of the 95% CI for observed risk difference (P1-P2) 10 % between salbutamol test (HFA-152a MDI) and reference groups (HFA-134a MDI) is estimated to be within 10.72% of point estimate for risk difference. For an example, if the observed risk difference (P1-P2) 10% and P2 = 32%, the upper limit of the 95% CI for observed risk difference will be 20.7 the lower limit will be -0.7.

6.5. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACQ	Asthma Control Questionnaire
AE(s)	Adverse event(s)
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical code
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form

Abbreviation	Definition
CSR	Clinical study report
ECG	Electrocardiogram
eCRF	Electronic case report form
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
EMA	European Medical Agency
FEV1	Forced expiratory volume in 1 second
FSFV	First subject first visit
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HFA	Hydrofluoroalkane
HFA-134a	1,1,1,2-tetrafluoroethane
HFA-152a	1,1-difluoroethane
HR	Heart rate
HRT	Hormonal replacement therapy
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonization
ICS	Inhaled Corticosteroid
IRB	Institutional review board
ITT	Intention to treat population
LABA	Long-acting bronchodilator
LAMA	Long-acting muscarinic antagonist
LLT	Lowest Level Term
LSLV	Last Subject Last Visit
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
PT	Preferred Term
PFT	Pulmonary function testing

Abbreviation	Definition
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RR	Respiratory rate
SABAs	Short-Acting β2-Adrenoreceptor Agonists
SAE(s)	Serious adverse event(s)
SAP	Statistical Analysis Plan
SE	Standard Error
SoA	Schedule of activities
SOC	System Organ Class
SRT	Safety Review Team
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VS	Vital Signs
WBC	White Blood Cells

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