Statistical Analysis Plan

Study ID: 214263

Study Official Title: A Phase III, 12 Week, Randomized, Double-blind, 4 Arm Parallel Group Bridging Study, Comparing the Efficacy, Safety and Tolerability of the Fixed Dose Combination FF/UMEC/VI Once-daily Via a Dry Powder Inhaler With Dual Combination of FF/VI, Administered in Chinese Participants With Inadequately Controlled Asthma

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TITLE PAGE

Protocol Title:	A Phase III, 12 week, randomized, double-blind, 4 arm parallel group bridging study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI once-daily via a dry powder inhaler with dual combination of FF/VI, administered in Chinese participants with inadequately controlled asthma.
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Version History

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	14 July 2021	Final Amendment 01 28 April 2021	Not Applicable	Original version
SAP Amendment 1	07 Aug 2024	Final Amendment 02 18 July 2022	1. Add the randomized population; 2. Add the 3rd estimand to assess the impact of COVID-19 infection; 3. Clarify the AESI and MACE definition; 4. Define the rule of multiple measurements of ACQ assessment selection. 5. Clarify that the 7th item response of ACQ-7 will be derived based on the percent-predicted FEV1 value. 6. Add eCOA compliance definition; 7. Administrative updates to add clarification and/or remove discrepancies.	Updates related to protocol amendment and 2nd dry-run.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the CSR for Study 214263. Details of the final analyses are provided. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

1.1. Objectives, Estimands and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of FF/UMEC/VI 100/62.5/25 µg on lung function compared with FF/VI 100/25 µg after 12 weeks of treatment	• Change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 12
Secondary	
• To evaluate the efficacy of FF/UMEC/VI 200/62.5/25 µg on lung function compared with FF/VI 200/25 µg after 12 weeks of treatment	• Change from baseline in trough FEV_1 at Week 12
Other secondary	
• To evaluate the effects of FF/UMEC/VI compared with FF/VI on asthma control after 12 weeks of treatment	• Change from baseline in ACQ-7 total score at Week 12
Exploratory objectives	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
Safety	
• To evaluate the safety of FF/UMEC/VI (100/62.5/25 and 200/62.5/25 µg) compared with FF/VI (100/25 and 200/25 µg) throughout the 12-week treatment period.	• Incidence and type of adverse events • Incidence of exacerbations • Change from baseline in ECG parameters • Incidence of worst vital sign results relative to normal range • Incidence of worst clinical hematological and chemistry results relative to normal range

Primary estimand

The primary clinical question of interest is: What is the effect of adding UMEC to FF/VI in a single inhaler when compared with FF/VI on change from baseline in trough FEV_1 after 12 weeks of treatment in Chinese participants with inadequately controlled asthma?

This question will be addressed regardless of study treatment discontinuation unrelated to a pandemic or due to pandemic infection and in the absence of study treatment discontinuation due to the indirect impact of a pandemic (e.g. participant or site related impact such as participant unable to collect/obtain study treatment due to restrictions in place, pharmacist not available to conduct the study and maintain the blind).

For this primary clinical question of interest, participant's trough FEV_1 measurements at Week 12 will be used regardless of whether they discontinued study treatment due to pandemic infection (e.g. participant got COVID-19) or for reasons not related to the pandemic. There could be cases of the pandemic at the time of the conduct of this China bridging study and beyond. Given that the disease area of interest is a respiratory disease it is important to estimate the treatment effect regardless of the participant being diagnosed with pandemic infection as this is likely to be the situation that FF/UMEC/VI (if approved and prescribed for asthma) would be taken in. It is unknown currently whether indirect consequences of the pandemic (such as the participant unable to collect/obtain study treatment due to local restrictions/lockdowns) will be an issue at the time of the study, but if participants are unable to collect medication or attend the study site due to concerns around the pandemic (or other operational issues) this is unlikely to be the situation in the future; therefore, we want to estimate the treatment effect in the absence of this.

The primary estimand is described by the following attributes:

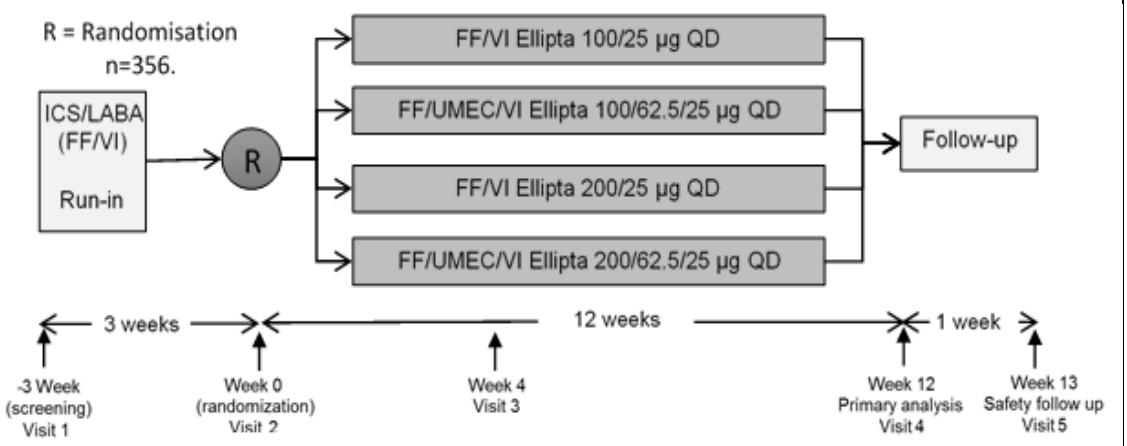
- Population: participants with inadequately controlled asthma.
- Treatment condition: FF/UMEC/VI (100/62.5/25 μg) or FF/VI (100/25 μg) given once daily in the morning (primary treatment comparison is FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25). In addition, rescue albuterol/salbutamol will be provided and is permitted during the study.
- Variable: change from baseline in trough FEV_1 at week 12.
- Summary measure: Mean change from baseline. Comparison: difference in mean change from baseline
- Intercurrent events:
    - Study treatment discontinuation – if related to an indirect impact of a pandemic it will be handled with a hypothetical strategy (i.e. had the intercurrent event not occurred. In this situation, data collected after study treatment discontinuation will not be included in the statistical analysis and will be treated as missing data). Otherwise it will be handled with a treatment policy strategy and data collected after study treatment discontinuation will be included in the analysis. This will be the primary intercurrent event strategy.

An additional estimand supporting the primary objective is defined similar to the primary estimand except a different intercurrent event strategy will be followed, where study treatment discontinuation due to an indirect impact of the pandemic will be handled with a treatment policy rather than a hypothetical strategy (i.e. all data collected after study treatment discontinuation will be included in the analysis).

A 3rd estimand to assess the impact of COVID-19 infection is also defined in which the incurrent event of COVID-19 infection is handled with the hypothetical strategy and the treatment discontinuation is handled with the treatment policy strategy.

The estimand for the secondary objective assessing FEV_1 is the same as the primary estimand except the treatment conditions are FF/UMEC/VI (200/62.5/25 μg) or FF/VI (200/25 μg) given once daily in the morning.

1.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	This is a 12-week, Phase III, randomized, double-blind, active controlled, 4-arm parallel group, bridging study using Bayesian Dynamic Borrowing (BDB) in Chinese asthma participants evaluating: • FF/UMEC/VI (100/62.5/25 µg) versus FF/VI (100/25 µg) and, • FF/UMEC/VI (200/62.5/25 µg) versus FF/ VI (200/25 µg) All given once daily in the morning. Participants who meet all the eligibility criteria at screening (Visit 1), will enter the run-in period for 3 weeks in order to continue to assess the participant's eligibility for the study. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF/VI (100/25 µg via the ELLIPTA dry powder inhaler [DPI]) once a day, taken in the morning, during the 3-week run-in period. Rescue medication (albuterol/salbutamol) will be provided to use on an as-needed basis throughout the study. At the conclusion of the 3-week run-in period (Visit 2), all participants who meet the additional predefined criteria will be randomised 1:1:1:1 to receive either FF/UMEC/VI (100/62.5/25; 200/62.5/25 µg) or FF/VI (100/25; 200/25 µg) via the ELLIPTA DPI once daily in the morning for the duration of the 12-week treatment period (stratified by pre-study ICS treatment strength [medium, high]).

Overview of Study Design and Key Features	
	In accordance with the protocol-defined visit schedule, participants will have two on-treatment clinic visits conducted on an outpatient basis scheduled at Visits 3 (Week 4) and Visits 4 (Week 12). One week following the end of the study (or after the early withdrawal visit) a follow-up telephone call or clinic visit will be performed for safety assessments. A participant will be considered to have completed the study when he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA, Protocol Section 1.3). The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial**.**
Study intervention	The ELLIPTA device will be used during the run-in period and the treatment period. The ELLIPTA DPI is a moulded plastic two-sided device that can hold two individual blister strips. Each participant will be instructed on the proper use of the ELLIPTA and will inhale once from the ELLIPTA each morning for the duration of the 3-week run-in period and the subsequent treatment period. At Visit 2, the run-in period ELLIPTA device will be collected from all participants. All 356 participants will be randomized to one of the 4 double-blind treatment arms. Participants will self-administer their first dose of double-blind study treatment in the clinic during Visit 2 and will continue to administer double-blind study treatment at approximately the same time each morning for the duration of the treatment period. Participants will take their last dose of study treatment in the clinic during Visit 4/EOS (or at the Early Withdrawal Visit, if applicable) and a safety follow-up will be conducted approximately one week later. Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Visit 1. An albuterol/salbutamol MDI for as needed (prn) use throughout the study will be provided starting at Visit 1; at the Investigator's discretion, more than one MDI may be provided at any time. Albuterol/salbutamol will be sourced from local commercial stock. If not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements.

Overview of Study Design and Key Features	
Study intervention Assignment	All participants who meet the additional predefined criteria will be randomized 1:1:1:1 to receive one of the following interventions: • FF/VI 100/25 µg once daily (QD) • FF/VI 200/25 µg QD • FF/UMEC/VI 100/62.5/25 µg QD • FF/UMEC/VI 200/62.5/25 µg QD Study treatment will be administered via the ELLIPTA DPI in the morning.
Interim Analysis	Not applicable

2. STATISTICAL HYPOTHESES

This is a bridging study designed to evaluate the add-on benefit of UMEC in a single inhaler when compared to FF/VI in Chinese patients with inadequately controlled asthma. The primary objective is to evaluate the effects of FF/UMEC/VI 100/62.5/25 µg on lung function, as measured by change from baseline in trough FEV_1 regardless of study treatment discontinuation unrelated to a pandemic or due to any pandemic infection and in the absence of study treatment discontinuation due to the indirect impact of a pandemic, compared with FF/VI 100/25 µg in Chinese participants with asthma over a 12-week treatment period. The effects of FF/UMEC/VI 200/62.5/25 µg on change from baseline in trough FEV_1 at week 12 compared with FF/VI 200/25 µg will also be assessed (secondary objective). The Chinese patient data collected in this study will be supplemented with data on the treatment difference for the same lung function endpoint from the global PhIIIa study 205715, using a Bayesian Dynamic Borrowing approach to analysis of the study [Schmidli, 2014].

A frequentist hypothesis test will not be performed. Instead, the posterior distributions of the difference for both FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg and FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg in trough FEV_1 at Week 12 will be derived, based on the Bayesian analysis including the global PhIIIa study 205715 information and the data collected on Chinese patients in this study. The hypothesis of interest for each treatment comparison is that this difference is larger than zero, and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the difference is larger than zero is at least 95% (a “positive result”). Please see Protocol Section 10.7.1 (Protocol Appendix 7) for further information on the choice of posterior probability.

2.1. Multiplicity Adjustment

There are multiple doses being compared in this study. A hierarchical testing approach will be used to test each treatment comparison of the change from baseline in trough FEV_1 at week 12. If the test for the primary treatment comparison of FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg meets the definition of a positive result then the study will be deemed a success and then the secondary treatment comparison of FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg will be tested. All other efficacy endpoint will be analysed in a descriptive manner with no formal hypothesis testing and therefore no further multiplicity adjustments will be applied.

3. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Analysis Set	Definition / Criteria	Analyses Evaluated
Enrolled	This population will comprise all participants for whom a record exists on the study database, including pre-screened participants that sign the informed consent document but do not complete any of Visit 1 (screening) procedures (i.e., pre-screening failures), or participants that complete at least one of Visit 1 procedures but do not enter the run-in period (i.e., screening failures). This population will be used for the summary of participant disposition.	• Disposition
All Participants Screened Population	This population contains all participants that complete at least one Visit 1 (Screening) procedure.	• Disposition
Randomized Population	This population contains all participants who were randomized (i.e. received a randomization number).	• Study population
Intent-to-Treat (ITT) Population	This population will comprise all randomized participants, excluding those who were randomized in error. A participant who is recorded as a screen failure or run-in failure but is randomized and does not receive a dose of study treatment, is considered to be randomized in error. Any other participant who receives a randomization number will be considered to have been randomized. This will constitute the primary population for all efficacy analyses. Participants will be analyzed according to the intervention they were randomized to.	• All efficacy analyses • Demographic and baseline characteristic
Safety Population	All randomized participants who take at least 1 dose of study intervention. This will constitute the primary population for all safety analyses. Participants will be analyzed according to the intervention they actually received.	• All Safety analyses

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

In the case of wrong stratification assigned at the time of randomization, the analyses will be performed based on the actual stratum per data collected in eCRF.

All raw and derived variables will be listed and described using summary statistics.

For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category.

For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), median, minimum and maximum.

4.1.2. Baseline Definition

For clinic FEV1, the baseline value is the latest acceptable assessment with non-missing value at the randomization visit (Visit 2).

For ACQ, baseline value for each endpoint is the derived value based on the questionnaire items assessed at the randomization visit (Visit 2).

For safety endpoints, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline except adverse event.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

For participants that did not receive any randomized study treatment, baseline is defined as the value from the protocol schedule baseline visit. Unscheduled visits will not be considered. All baselines will be referred to as ‘Baseline’ in the summary outputs.

4.2. Primary Endpoint(s) Analyses

4.2.1. Definition of Endpoint

The primary efficacy endpoint is the change from baseline in trough FEV_1 at the end of the 12-week treatment period. Only acceptable/borderline acceptable FEV_1 values will be included in the analysis, and values graded as “not acceptable” will be excluded.

4.2.2. Main Analytical Approach

The primary efficacy analysis will evaluate the primary estimand in the Intent-to-Treat population, by first using a mixed-model repeated measures (MMRM) analysis of the observed China study data conducted across all the four treatment arms to get an estimate of the treatment difference for FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 as well as an estimate of the variability. These estimates will then be combined with the global 205715 study using the pre-specified robust mixture prior to obtain the posterior distribution for the China treatment difference. If the posterior probability of the treatment difference >0 is greater than or equal to 95%, the hypothesis for difference of the treatment comparison (FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25) is larger than zero is supported.

The primary analysis is to use a combination of multiple estimand strategies. Intercurrent events considered to have an impact on estimation of the treatment effect are:

- Study treatment discontinuation related to an indirect impact of a pandemic
- Study treatment discontinuation due to reasons other than indirect impact of a pandemic

The impact of the intercurrent event of study treatment discontinuation related to an indirect impact of a pandemic in general is not expected in the clinical practice thus the event will be handled by the hypothetical strategy i.e. had the intercurrent event not occurred. As the event is not relevant to the subject but an administrative reason e.g. the lockdown of an investigational site, it is reasonable to consider a missingness mechanism of Missing at Random (MAR) for the missing primary endpoint values after the event. If the reason of the treatment discontinuation for a participant is reported due to COVID-19 pandemic by the “COVID-19 Pandemic Study Impact” eCRF page, and the participant does not have positive / indeterminate COVID-19 test result or does not have any confirmed/ probable/ suspected case diagnosis if the COVID-19 test is not performed according to the “COVID-19 Coronavirus Infection Assessment” eCRF page, the reason of his/her treatment discontinuation is considered an indirect impact of a pandemic.

For the intercurrent event of study treatment discontinuation due to reasons other than indirect impact of a pandemic, the data collected before and after the event will be included into the primary analysis, that is, the event will be handled using the treatment policy strategy.

Primary endpoint values which should be collected and included in the primary analysis but missing, including intermittent missing values, will be considered MAR. Missing values in the covariates will not be imputed.

Mean FEV_1 over time will be plotted by treatment and treatment completers/withdrawals if data permits.

4.2.2.1. MMRM Modelling

With the MAR missingness assumption, the primary endpoint will be analysed firstly by a MMRM model. The model will include treatment, interaction between treatment group and visit, interaction between baseline trough FEV_1 and visit, eCRF-reported pre-study ICS dosage strength (med, high), sex, baseline trough FEV_1, visit and age at screening as fixed effects. If the model fails to converge due to imbalance in a covariate, this covariate may be removed. The restricted maximum likelihood (REML) approach will be employed to estimate the unstructured variance-covariance matrix of the within-patient repeated measures. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. If the model fails to converge, Kenward-Roger-2 method (DDFM=KENWARDROGER2 option in the Proc MIXED) or the residual method (DDFM=RESIDUAL option in the Proc MIXED) may be employed to estimate the denominator degrees of freedom.

The MMRM analysis will be conducted using the following example SAS code based on the data from all four treatment arms, in which the italic variables need to be replaced to reflect the actual study data structure:

```
proc mixed data=adam_dataset method=reml;
        class subject treatment ICS sex visit;
        model chg_FEV1 = treatment ICS sex age visit baselineFEV1 treatment*visit
                         baselineFEV1*visit  / ddfm=kr s cl;
        repeated visit/subject=subject type=un;
        lsmeans treatment*visit / cl diff om=om_dataset at (baselineFEV1
        age)=(&baselineFEV1 &age);
run;
```

The estimated treatment difference and the corresponding 95% CI will be presented. Due to the fact that the design is not frequentist the p-value for the comparison will not be reported.

The LS-means of FEV_1 and the LS-means of change from baseline of FEV_1 with the corresponding standard error in each visit for each treatment arm will also be reported. In the derivation of these LS-means using Proc MIXED, a dataset *om_dataset* will be constructed to reflect the data structure of no missing observations, i.e. had each subject been reported with the same visits. *&baselineFEV1 &age* are the mean values of the baseline FEV_1 and age of subjects in ITT population respectively.

4.2.2.2. Bayesian Dynamic Borrowing

The primary analysis will be conducted in the Bayesian paradigm using the pre-specified mixture prior distribution, which will be updated with the treatment difference between FF/UMEC/VI 100/62.5/25 and FF/VI 100/25 estimated in the MMRM analysis of the observed China study data.

Let y denote the observed treatment difference FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 in trough FEV_1 at Week 12 in Chinese participants estimated from the MMRM model in section 4.2.2.1, and let σ^2 be the associated squared standard error. We assume y follows a normal distribution:

$$y|\Delta \sim \mathrm{N}(\Delta, \sigma^2)$$

where Δ is the true treatment difference.

The pre-specified prior for Δ is a 2-component robust mixture prior constructed from 205715 study result:

$$p(\Delta) = 0.3 * N(\text{Mean} = 86,\ \text{SD} = 20.1) + 0.7 * N(\text{Mean} = 0,\ \text{SD} = 494.97)$$

For this mixture prior distribution $p(\Delta) = \sum_{j=1}^{2} w_j p_j(\Delta)$, the posterior distribution is also a mixture distribution:

$$p(\Delta|y) = \sum_{j=1}^{2} w'_j p_j(\Delta|y),$$

where

$$w'_j = \frac{w_j L_j(y)}{\sum_{i=1}^{2} w_i L_i(y)}$$

and $L_j(y)$ is the marginal likelihood corresponding to the j-th component in the mixture prior As in this case each component of the mixture prior $p_j(\Delta)$ is a normal distribution with mean μ_j and variance σ_j^2, each posterior $p_j(\Delta|y)$ could be derived by the standard conjugate Bayesian analysis:

Given prior $p_j(\Delta)$, then

$$p_j(\Delta|y) = \mathrm{N}\left(\frac{\mu_j\sigma^2 + y\sigma_j^2}{\sigma_j^2 + \sigma^2}, \frac{1}{1/\sigma_j^2 + 1/\sigma^2}\right)$$

and w'_j could be derived using:

$$L_j(y) = \frac{1}{\sqrt{2\pi(\sigma^2 + \sigma_j^2)}} \exp\left[-\frac{1}{2(\sigma^2 + \sigma_j^2)}(y - \mu_j)^2\right]$$

The specific expression of the posterior distribution will be provided using the posterior weights, means and standard deviations of each component.

The posterior mean, median and 90%, 95% credible intervals of this posterior distribution $p(\Delta|y)$ will be reported, along with the probability that the true difference is greater than zero: $\Pr(\Delta > 0|y)$. If the posterior probability is greater than or equal to 95%, the hypothesis for difference of the treatment comparison (FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25) is larger than zero is supported.

4.2.3. Sensitivity Analyses

4.2.3.1. Sensitivity Analysis 1: Tipping Point Analysis for All the Missing Values in Change form Baseline of FEV_1 at Week 12

A tipping point analysis will be conducted to assess the robustness of MAR missingness assumption in the primary endpoint.

This method will explore the potential effect of missing data on the reliability of the results by using different assumptions regarding the primary endpoint outcome. Missing values in the post-baseline change from baseline in trough FEV_1 at week 12 will be imputed first assuming a MAR mechanism and then adding on a "delta" value prior to analyzing the imputed datasets and combining the results. The deltas range from some degree of worsening to some degree of improvement and are to vary independently for FF/UMEC/VI and FF/VI.

The analysis results will be used to evaluate the plausibility of the assumed difference from MAR for missing outcomes on each treatment arm under which (Tipping Point) the conclusions change, i.e., under which there is no longer evidence of a treatment effect, and clinical judgment will be applied as to the plausibility of the associated assumptions.

Missing Data Imputation

The monotone missing values of the primary endpoint in the FF/UMEC/VI 100/62.5/25 arm will be imputed with different delta adjustment.

- Missing values in the post-baseline change from baseline in trough FEV_1 will firstly be imputed under MAR assumption using the sequential regression method with the covariates of the MMRM model in section 4.2.2.1. In the imputation of the change from baseline in trough FEV_1 at week 12 the observed or imputed change from baseline in trough FEV_1 at week 4 will also be included as a fixed covariate. 1000 complete datasets including both observed and imputed values will be generated.

The example SAS code to be conducted on the data from all four treatment arms follows in which the italic variables need to be replaced to reflect the actual study data structure:

```
PROC MI DATA=adam_dataset SEED=20210603;
        CLASS treatment, ICS, sex;
        VAR treatment ICS sex age baseline_FEV1 chg_FEV1_visit3 chg_FEV1_visit4;

        MONOTONE REG (chg_FEV1_visit3 = treatment ICS sex age baselineFEV1);
        MONOTONE REG (chg_FEV1_visit4 = treatment ICS sex age baselineFEV1
        chg_FEV1_visit3);
RUN;
```

If the missingness pattern does not support the example SAS code (i.e. the data has a non-monotone pattern), these variables will be imputed using separate MI procedures in the same sequence as the example SAS code.

Missingness in the model covariates may be imputed in advance when needed:

```
PROC MI DATA=adam_dataset;
        BY treatment;
        VAR ICSn (i.e. 0/1) sexn (i.e. 0/1) age baseline_FEV1;
        MCMC;
RUN;
```

Delta adjustment is applied to the imputed monotone missing values at week 12 only.

For each complete data, with each applied with one of 9×9 delta adjustment scenarios, 81 delta-adjusted complete data will be generated. Delta-adjusted values are:

$$\text{Delta-adjusted value} = \text{Imputed value} + \text{Delta}$$

The deltas to be investigated are pre-selected multiples of the observed treatment effect from the MMRM model in section 4.2.2.1. If the observed treatment effect from the primary analysis is x, the deltas to be investigated will range from -3x to +x mL for each treatment arms, in increments of 0.5x mL, i.e.

$$-3x, -2.5x, -2x, -1.5x, -x, -0.5x, 0, 0.5x, x$$

The increment or range may be refined based on the analysis results and the location of the tipping point. For the comparison of triple vs. dual, the delta for relevant FF/UMEC/VI and FF/VI arms will be allowed to vary independently, thus will form 9×9 delta adjustment scenarios. The delta adjustment scenario when both deltas are zero is corresponding to the MAR assumption.

Substantive Model

Each delta-adjusted complete data with observed and imputed values will be analyzed by a same MMRM model as the one in the section 4.2.2.1 based on the data from all four treatment groups.

Combination of the Estimates

The estimates for the treatment difference in primary endpoint at week 12 as well as the corresponding standard errors from each complete dataset with the same delta adjustment scenario will be combined using the Rubin's rule.

Bayesian Dynamic Borrowing

The estimates from each delta adjustment scenario will be used in the Bayesian paradigm. In the $y|\Delta \sim N(\Delta, \sigma^2)$, y is estimated as the delta-adjusted MI-based treatment difference, σ^2 is estimated as the squared delta-adjusted MI-based standard error. The posterior mean, median and 90% credible interval of the posterior distribution $p(\Delta|y)$ will be reported for each delta adjustment scenario, along with the probability that the true difference is greater than zero: $\Pr(\Delta > 0|y)$.

4.2.3.2. Sensitivity Analysis 2: Tipping Point Analysis for the Treatment Discontinuation Due to Reasons Other Than Indirect Impact of a Pandemic

As the intercurrent event of treatment discontinuation due to an indirect impact of a pandemic is not relevant to the subject but an administrative event e.g. the lockdown of an investigational site, it is reasonable to consider a missingness mechanism of Missing at Random (MAR) for the missing primary endpoint values after the event.

Missing values after the intercurrent event of treatment discontinuation due to other reasons may have a Missing Not at Random (MNAR) missing mechanism. This will be assessed by applying tipping point analysis analogous to the one specified in section 4.2.3.1 only on the missing values which occurred after the treatment discontinuation due to a reason other than an indirect impact of a pandemic. Other missing values in the change from baseline in FEV_1 and in baseline FEV_1 will be imputed under MAR.

4.2.3.3. Sensitivity Analysis 3: Impact of the Change in the Prior Weight

Another sensitivity analysis will be conducted to assess the impact of the different prior weights of the two normal components in the robust mixture prior for primary endpoint.

The prior weights of the informative global component of the prior will be investigated from 0 to 1 in the increment of 0.05. When the prior weight is 0 or 1, the mixture prior will become a normal distribution thus the Bayesian diagram will be the standard conjugate analysis.

The posterior mean, median and 90% credible interval of the posterior distribution $p(\Delta|y)$ will be reported for each prior weight, along with the probability that the true difference is greater than zero: $\Pr(\Delta > 0|y)$.

4.2.4. Additional Estimands

4.2.4.1. Estimand with Treatment Policy Strategy Only (Estimand 2)

An additional estimand supporting the primary objective is defined similar to the primary estimand except a different intercurrent event strategy will be followed, where study treatment discontinuation due to an indirect impact of the pandemic will be handled with a treatment policy rather than a hypothetical strategy (i.e. all data collected after study treatment discontinuation will be included in the analysis).

The analysis using this estimand is analogous to the primary analysis: the analysis will be conducted first by applying a MMRM then combining the prior information using the Bayesian dynamic borrowing method.

4.2.4.2. Estimand to Assess the Impact of COVID-19 Infection (Estimand 3)

A 3rd estimand is defined to assess the impact of COVID-19 infection.

If the participant got COVID-19 infection on or prior to randomization date, the participant will be excluded from the analysis. If the participant got COVID-19 infection after randomization day, the intercurrent event of COVID-19 infection will be handled with hypothetical strategy, data collected after COVID-19 infection will not be included in the statistical analysis and will be treated as missing data. Meanwhile, the intercurrent event of study treatment discontinuation will be handled with treatment policy strategy.

The analysis using this estimand is analogous to the primary analysis: the analysis will be conducted first by applying a MMRM then combining the prior information using the Bayesian dynamic borrowing method. The missingness will be handled with MAR assumption.

4.3. Secondary Endpoint Analyses

4.3.1. Secondary Endpoint

The secondary endpoint is the change from baseline in trough FEV_1 for the comparison between FF/UMEC/VI (200/62.5/25 μg) or FF/VI (200/25 μg).

The primary estimand analysis, the sensitivity analyses and the supplementary analysis of the secondary endpoint are analogous to the ones of the primary endpoint, except:

- The endpoints in FF/UMEC/VI (200/62.5/25 μg) or FF/VI (200/25 μg FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 are used.
- The mixture prior is

$$\Delta \sim p(\Delta) = 0.3 * N(\text{Mean} = 100,\ \text{SD} = 20.0) + 0.7 * N(\text{Mean} = 0,\ \text{SD} = 494.97)$$

The delta-adjustment in the sensitivity analysis will be conducted conservatively in which a same multiplier (-3, -2.5, -2, -1.5, -1, -0.5, 0, 0.5, or 1) as of the primary endpoint would be used in each delta adjustment scenario.

Based on the hierarchical testing approach, if the test for the primary treatment comparison of FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 did not meet the definition of a positive result then the analysis of the secondary endpoint will be considered supportive only.

4.3.2. Other Secondary Endpoint

The other secondary endpoint is the change from baseline in ACQ-7 total score at Week 12.

The ACQ-7 consists of seven attributes of asthma control. All 7 items of ACQ have response on 0-6 ordinal scale (0=no impairment/limitation, 6=total impairment/ limitation). For each version of ACQ (5, 6, 7), the total score is calculated as the average of all non-missing item responses. Only one of the first five item responses are allowed to be missing in calculating the total score.

The 7th item response of ACQ-7 at specific visit (i.e., visit 2, visit3, visit 4 and EW visit) will be derived based on the value of percent-predicted FEV1 (round down to integer percent first) based on below table:

The percent-predicted FEV1 (%)	The seventh item response score of ACQ
Value > 95	0
90 ≤ Value ≤ 95	1
80 ≤ Value ≤ 89	2
70 ≤ Value ≤ 79	3
60 ≤ Value ≤ 69	4
50 ≤ Value ≤ 59	5
Value < 50	6
Missing	Missing

The endpoint will be analyzed in a descriptive manner with no formal hypothesis testing to be performed. The estimand will be the same as the estimand for the primary analysis except the variable is the change from baseline in ACQ-7 total score at Week 12. The treatment difference for the change from baseline in ACQ-7 total score at Week 12 will be assessed for each of below comparisons separately:

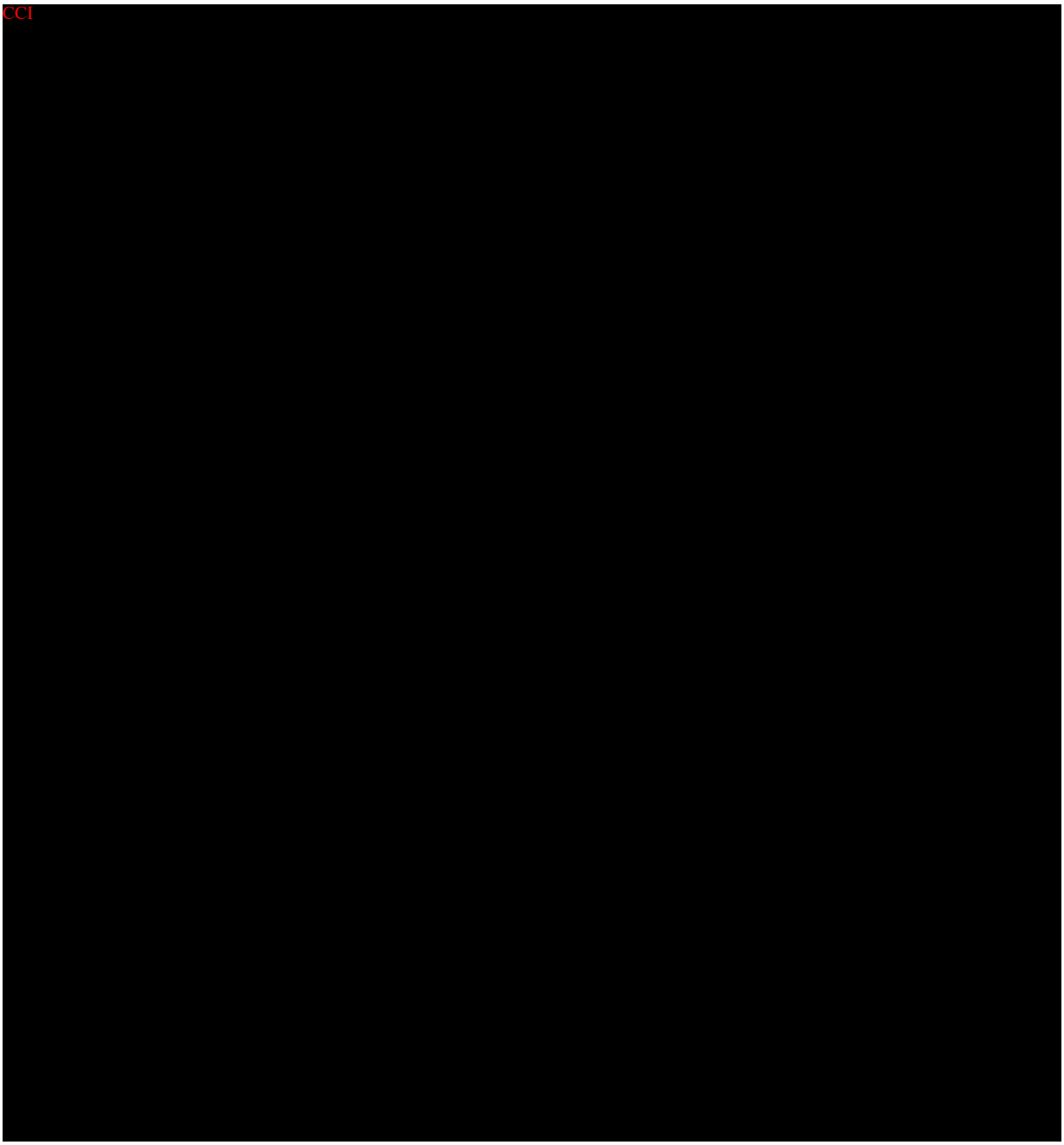
- FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25
- FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25

Each comparison will be conducted using a MMRM to be conducted on the data from all four treatment arms analogous to the one described in section 4.2.2.1, except the text of FEV_1 changed to the text of ACQ-7 total score.

The estimated treatment difference and the corresponding 95% CI will be presented. The LS-means of ACQ-7 total score and the LS-means of the change from baseline of ACQ-7 total score with the corresponding standard error in each visit for each treatment arm will also be reported.

4.4. Exploratory Endpoints Analyses

CCI



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[redacted]

CCI

4.5. Safety Analyses

Safety data will be summarized based on the Safety Population and will be presented by each actual received treatment.

4.5.1. Extent of Exposure

The extent of exposure to FF/VI 100/25 µg via the ELLIPTA DPI during the run-in period, to randomized study treatment and post-treatment data will be summarized. The number of days of post-treatment data will be summarized for all participants with at least one day of post-treatment data.

- Duration of exposure to FF/VI 100/25 during the run-in period is calculated as:
  - Run-in treatment stop date - Run-in treatment start date+1
- Duration of treatment exposure to study treatment is calculated as:
  - treatment stop date – treatment start date +1

- Post-treatment study duration is calculated as:
    - Last Scheduled Clinic Visit (i.e., Visit 4 or Early Withdrawal Visit) date – (randomized treatment stop date +1).
- Treatment Exposure will be summarized as continuous, and using the following categories:
    - ≥1 day, ≥4 weeks, ≥8 weeks, ≥12 weeks, week 12 (-7/+7 days, inclusive)
    - Run-in Period: ≥1 day, ≥1 week, ≥2 weeks, ≥3 weeks
    - Post-treatment duration: >0 to 4 weeks, >4 to 12 weeks, >12 weeks

In case of missing dates, no imputation will be performed. Exposure will be considered missing.

If a dose counter start count is missing, then it will be assumed to be 30 for the ELLIPTA DPI. If any dose counter stop is missing, then it will be assumed to be 0 for the ELLIPTA DPI. Number of doses of study drug taken by each participant from each inhaler = Dose counter start value – Dose counter stop value.

4.5.2. Adverse Events

The CRF texts for adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

An overview summary of on-treatment AEs, including counts and percentages of participants with any AE, AEs leading to permanent discontinuation of study treatment or withdrawal from study, SAEs, drug-related AEs, drug-related SAEs, fatal AEs, and fatal drug-related SAEs will be produced.

AEs during screening/run-in period, on-treatment AEs, post-treatment and post-study AEs will be summarised separately.

AEs during screening/run-in period will be separately summarised by System Organ Class (SOC) and the Preferred Term (PT) in the order of decreasing frequency in the overall population.

On-treatment AEs will be separately summarised by System Organ Class (SOC) and the Preferred Term (PT) in the order of decreasing frequency in the overall population for:

- AEs
- AEs by maximum intensity
- Drug-related AEs
- Drug-related AEs by maximum intensity
- SAEs
- Drug-related SAEs

- AEs leading to permanent discontinuation of study drug or study withdrawal
- Non-SAEs
- Common (3% or more participants in any treatment arm) AEs

Where drug-related AE is defined as an AE for which the investigator classifies the possible relationship to study intervention as "Yes". A worst-case scenario approach will be taken to handle missing relatedness data, i.e. if the relationship to study intervention is missing the AE will be classified as drug-related AE. Overview of on-treatment AEs and summary of on-treatment AEs will be repeated adjusted for exposure (per thousand person-years) to account for variable treatment duration. Event rate per thousand person-years will be calculated as the total number of events across the participants x 1000 divided by the total participant exposure during the time-period of interest.

Post-treatment AEs will be separately summarised by System Organ Class (SOC) and the Preferred Term (PT) in the order of decreasing frequency in the overall population for:

- AEs
- Drug-related AEs
- SAEs
- AEs leading to permanent discontinuation of study drug or study withdrawal

Post-study AEs will be summarised by System Organ Class (SOC) and the Preferred Term (PT) in the order of decreasing frequency in the overall population.

All AEs, AEs leading to discontinuation of study treatment or withdrawal from the study and reasons for considering as a SAE will be listed.

4.5.2.1. Adverse Events of Special Interest (AESI)

Adverse events of special interest have been defined as AEs which have specified areas of interest for one or more of the compounds (FF, VI and/or UMEC) or combination therapies (FF/UMEC/VI and/or FF/VI). These consist of groupings of preferred terms based on the MedDRA dictionary version used in each reporting effort. Subgroups may be defined, based on relevant combination of preferred terms, or on Standardized MedDRA queries (SMQ).

The table below presents the special interest AE groups for FF, UMEC and VI, defined upon the release of up-to-date version of the MedDRA dictionary.

Special Interest AE Group	Special Interest AE Subgroup	SMQ/PTs for Inclusion
Cardiovascular effects	Cardiac arrhythmia	Cardiac arrhythmia (SMQ), excluding congenital and neonatal arrhythmias
	Cardiac failure	Cardiac Failure (SMQ)
	Cardiac ischaemic	Ischaemic Heart Disease (SMQ)
	Stroke	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
	Hypertension	Hypertension (SMQ)
Pneumonia		Infective pneumonia (SMQ)
LRTI excluding infective pneumonia SMQ		Selected PTs
Decreased bone mineral density and associated fractures		Osteoporosis/Osteopenia (SMQ) Selected PTs
Hypersensitivity		Hypersensitivity (SMQ) Angioedema (SMQ) Anaphylactic reaction (SMQ)
Anticholinergic Syndrome		Anticholinergic Syndrome SMQ
Gastrointestinal obstruction		Gastrointestinal obstruction SMQ
Adrenal Suppression		Selected PTs
Antimuscarinic ocular effects / Corticosteroid Associated Eye Disorders	Glaucoma (antimuscarinic / corticosteroid)	Glaucoma (SMQ),
	Cataracts (corticosteroids)	Lens disorder (SMQ)
Effects on Glucose		Hyperglycaemia/new onset diabetes mellitus (SMQ)
Local steroid effects		Selected PTs
Urinary retention		Selected PTs
Effects on potassium		Selected PTs
Tremor		Selected PTs
Asthma/Bronchospasm for Asthma-related intubations and deaths		Asthma/bronchospasm SMQ
Dry mouth / Drying of airway secretions		Selected PTs (narrow and broad focus)

Adverse events of special interest will be summarized by AESI category and Preferred Term. Preferred Terms may contribute to more than one Special Interest Group. AESIs will be counted in each Special Interest Group in which they appear.

4.5.2.2. Major Adverse Cardiac Events (MACE)

Major Adverse Cardiac Events (MACE) will be analyzed using broad and narrow definitions.

The broad MACE includes below, excluding those with fatality outcome:

- Central Nervous System Haemorrhages and Cerebrovascular Conditions (SMQ)
- Myocardial infarction (SMQ)
- Other ischemic heart disease (SMQ)

The narrow MACE includes below, excluding those with fatality outcome:

- PT of "myocardial infarction"
- PT of "acute myocardial infarction"
- Central Nervous System Haemorrhages and Cerebrovascular Conditions (SMQ)

4.5.2.3. COVID-19 Assessment and COVID-19 AEs

Number of participants with suspected, probable or confirmed for COVID-19 infection will be summarized according to the "COVID-19 Coronavirus Infection Diagnosis" and "COVID-19 Coronavirus Infection Assessment" eCRF page.

Number of participants with COVID-19 as reported as an on-treatment AE are summarized. All COVID-19 AEs will be flagged in the AE listings.

4.5.3. Additional Safety Assessments

4.5.3.1. Severe Exacerbation

The frequency and percentage of participants with severe asthma exacerbations, and the relevant outcome will be presented.

4.5.3.2. Laboratory Data

Change from baseline for Chemistry and Hematology will be summarized.

Change from baseline for laboratory values will also be summarized using categories of 'To Low', 'To Normal or No Change', or 'To High'. 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 the 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 relative to baseline' classification of urinalysis (occult blood and urine protein) results will be summarized by the 'Any Increase' category and 'No Change/Decreased' category. 'Any Increase' is defined as a change from baseline to a worse category, at any on-treatment post-baseline assessments including scheduled, unscheduled, or EW visits. 'No Change/Decreased' is defined as only no change or decreased post-baseline relative to baseline results. The result category levels from best to worst are 'Negative (-)', '+-', '+', '++', and '+++'. Participants with missing baseline are assumed to have a result of NEGATIVE for the baseline value.

Liver Monitoring/Stopping Event Reporting will be summarized. The abnormality of urinalysis is based on its potential clinical importance which is defined as an increase in Protein or Occult Blood post-baseline relative to Baseline (Screening).

4.5.3.3. Vital Signs

Change from baseline for vital signs will be summarized.

Change from baseline for vital signs values will also be summarized by visit and worst-case post-baseline using categories of 'To Low', 'To Normal or No Change', or 'To High'. The derivation rule is similar to Laboratory data's (section 4.5.3.2) except the classification is based on the following potential clinical importance:

- Pulse Rate (bpm): Low (<60), Normal (≥60 to ≤100), High (>100);
- Systolic Blood Pressure (mmHg): Low (<90), Normal (≥90 to ≤140), High (>140)

  Diastolic Blood Pressure (mmHg): Low (<60), Normal (≥60 to ≤90), High (>90)

4.5.3.4. ECG

When triplicate/multiple ECG assessments are taken, mean of the measurement will be calculated first and summary statistics will be based on the calculated mean. This will apply to both baseline and post baseline assessments.

A summary of the change from baseline in each ECG parameter by treatment group and visit will be provided.

The worst-case post-baseline ECG findings will be summarized using the categories of:

- 'Abnormal' if any on-treatment assessment is evaluated as 'Abnormal'
- 'Unable to evaluate' if all on-treatment assessments are 'Unable to evaluate'
- 'Normal' if any on-treatment assessment is evaluated as 'Normal' and there are no on-treatment assessments evaluated as 'Abnormal'

The maximum post-baseline QTc(F) values will be summarized using the categories of:

- ≤ 450 msec
- > 450 to ≤ 480 msec
- > 480 to ≤ 500 msec
- > 500 to ≤ 530 msec
- > 530 msec

The maximum increase in post-baseline QTc(F) values relative to baseline will be summarized using the categories of:

- <-60 msec
- ≥ -60 to < -30 msec
- ≥ -30 to < 0 msec
- ≥ 0 to < 30 msec
- ≥ 30 to < 60 msec
- ≥ 60 msec

4.6. Other Analyses

Not applicable.

4.7. Interim Analyses

No interim analysis is planned in this study.

4.8. Changes to Protocol Defined Analyses

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 2 dated 18 Jul 2022.

5. SAMPLE SIZE DETERMINATION

Approximately 890 participants will be screened to achieve 356 randomly assigned to study intervention (89 patients per arm). This sample size denotes the number of participants with trough FEV_1 data at Week 12, regardless of whether they are still on randomized treatment or have discontinued randomized treatment early (for reasons that are NOT an indirect impact of a pandemic). Study treatment discontinuation related to an indirect impact of a pandemic will be handled with a hypothetical strategy. This corresponds to the primary estimand strategy.

The proposed sample size of 89 participants per arm has been determined using a pragmatic approach and reflects ~22% of the global Ph3a study (205715) sample size which would generally satisfy the requirement for a consistency evaluation within a global study. Please see Section protocol 10.7.2 for further information on the selected sample size.

With this sample size, and using Bayesian dynamic borrowing with initial weight of 0.3 on the global 205715 study results (see protocol Section 9.4.2), the probabilities of the study achieving a positive result for each treatment comparison under various assumptions about the true treatment difference in Chinese patients are shown in Table 1 (for further details on the a range of possible observed treatment differences in China see Protocol Statistical Appendix Section 10.7.3). These probabilities assume a between-individual SD of 350mL for the primary endpoint (though probabilities are also shown for alternative SDs to assess the sensitivity to the assumed between participant sampling variation). This value was chosen based on results from the global asthma study 205715 (and the Japanese subset from the study) as well as global and Asian FF/VI asthma studies. It is a higher SD than observed in the global 205715 study (approximately 280-305mL (Japanese subset (225-245mL) based on the reported standard errors at Week 12 and Week 24), but a conservative estimate was chosen to take into account the higher variability that has been seen in other relevant asthma studies (FF/VI global and Asian studies' SD ranged approximately 300-400mL).

The probability of a false positive result for the primary treatment comparison (assuming true treatment difference = 0 mL) is 19% (Table 1). This is higher than the typical type 1 error usually applied in fully powered registration studies but should be considered within the context of the bridging approach. A bridging approach is proposed because of the expected similarity of the treatment difference in Chinese patients and the global population (supported by similarities in the epidemiology, pathophysiology, pharmacology and clinical management of patients and consistency of treatment differences across key demographic factors including ethnicity), and hence there is low probability of the null effect being true.

If the true treatment difference for the primary treatment comparison is 100 ml, the probability of the primary treatment comparison (FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25) meeting the definition of a positive result is 85% (equivalent to the power of the study). If a positive result for the primary treatment comparison in the testing hierarchy is achieved, the secondary treatment comparison (FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25) will be tested and the probability of meeting the definition of a positive result is 83%, assuming the true treatment difference is 100ml.

Table 1 Probability of Success for a range of possible true treatment differences and varying standard deviation

Treatment comparison	Standard Deviation	Probability of Success[†*]			
		when the true treatment difference is 0mL (false positive rate)	when the true treatment difference is 60mL	when the true treatment difference is 86mL	when the true treatment difference is 100mL
Primary: FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25	325mL	19%	63%	81%	88%
	350mL	19%	61%	78%	85%
	400mL	21%	58%	74%	81%
Secondary: FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25	325mL	16%	60%	78%	86%
	350mL	18%	58%	76%	83%
	400mL	19%	55%	72%	79%

[†]The probability of success values reported for the secondary treatment comparison (FF/UMEC/VI 200/62.5/25 compared to FF/VI 200/25) are only relevant after obtaining a positive outcome for the primary treatment comparison (FF/UMEC/VI 100/62.5/25 compared to FF/VI 100/25).
*Results based on simulating 10,000 replicate studies and averaging the study results across replications.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

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

6.1.1. Participant Disposition

The overall participant disposition will be summarized for the Enrolled population, including the number and percentage of participants in each treatment group and overall, screened (All Participants Screened), randomized, ITT population. Additionally, the reasons for Screen Failure, Run-in Failure, will be summarized for the Enrolled Population.

Listings of failures prior to randomization will be generated.

The number and percentage of participants at each centre will be summarized. This will be repeated using the ITT population.

The number and percentage of participants who completed the double-blind study treatment as well as the number who stopped the study treatment prior to the end of the study will be summarized, along with the reasons for discontinuation of the study treatment, and these will also be listed. The reason of indirect impact of pandemic will be displayed separately in addition to the eCRF reported reasons.

The number and percentage of participants who completed the study as well as the number who withdrew early from the study will be summarized, along with reasons for early withdrawal from the study, and these will also be listed.

6.1.2. Demographic and Baseline Characteristics

Each of the following types of data will be summarized:

- Demographic data: age, sex, ethnicity, weight, height, body mass index (BMI)
  - Age will be also summarized in the categories of: <18, 18 to <65, 65 to <75, 75 to <85, ≥85
  - Body Mass Index (BMI) is calculated as weight (kg) / [height (m)]2, will be presented as for summary statistics with 1 decimal place.
- eCRF-Reported pre-study ICS dosage at screening
- Disease Duration (duration of asthma, onset age of asthma (rounded down to integer in year unit))
- Asthma medical history questionnaire: the subject's quick relief inhaler (rescue inhaler) provide symptom relief (no relief, a little relief, some relief, a great deal of relief, complete relief)
- Smoking history (smoking status of non-smoker or former smoker, and current smokers)
- Medical conditions
- Spirometry at Visit 1 and Visit 2
  - Pre- and post-bronchodilator for FEV1, FVC, and FEV1/FVC, reversibility by albuterol/salbutamol at Visit 1, and associated percent predicted values.
  - Pre-dose for FEV1, FVC at Visit 2, and associated percent predicted values.
  - Change in pre-dose FEV1 from Visit 1 to Visit 2 during run-in period.
  - At Visit 1, if the spirometry assessment is repeated for a given participant to meet the eligibility criteria on the reversibility, the repeated spirometry data will be used for that visit.
  - Reversibility will be summarized in the categories of: <15%, ≥15%, <400 mL, ≥400 mL

- ACQ-6 total score at screening and randomization (day 1) Cardiovascular history and cardiovascular risk factors.
    - Cardiovascular history includes the following medical condition: arrhythmia, congestive heart failure, coronary artery disease, myocardial infarction, cerebrovascular accidents.
    - Cardiovascular risk factors include the following medical condition: hypertension, diabetes mellitus, hypercholesterolemia.

6.1.3. Protocol Deviations

Important protocol deviations will be summarized in ITT population.

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 intervention details) are captured and categorised in the protocol deviations dataset (except for the PD of taking incorrect treatment).
- Participants who received an incorrect container will be captured as an important protocol deviation. The actual treatment in the incorrect container will be identified and quality controlled by S&P either as incorrect treatment or unplanned treatment per randomization schedule.
- This dataset will be the basis for the summaries and listings of protocol deviations.

No per-protocol analysis is planned for this study.

6.1.4. Concomitant Medications

Summaries will be provided for the asthma medications by

- At study entry
- On-treatment period
- Post-treatment period
- Post-study period

Summaries will be provided for the non-asthma medications by

- On-treatment period
- Post-treatment period
- Post-study period

Concomitant Medications will be coded using the GSKDrug dictionary. Asthma medication tables will be reported by Respiratory Medication Class (RMC) and ingredient. Non-Asthma medication tables will report by Anatomical Therapeutic Chemical (ATC) level 1 and ingredient. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classification of the ingredients.

6.1.5. Study Intervention Compliance

Dose counter data handling refers to section 4.5.1.

Treatment compliance of double blinded treatment period is derived as:

$$\text{Treatment compliance} = \frac{\text{Total number of doses taken}}{\text{Treatment stop date} - \text{treatment start date} + 1} \times 100\%$$

Overall compliance will be summarized and categorized as follows:

- < 50 %
- ≥50 % to < 80%
- ≥80 % to < 95 %
- ≥95 % to ≤105 %
- >105 % to ≤120 %
- >120 %.

If a participant receives a treatment other than the randomized treatment during the study, the compliance will still be calculated using data from all containers received and overall exposure start and stop dates.

If a participant completed treatment and did not administer the study treatment at the day of last clinic visit (i.e., Visit 4 [EOS Visit] or Early Withdrawal Visit [EW]) and date of last dose not collected in eCRF page “Treatment Discontinuation/Completion”, then the day of last clinic visit (i.e., Visit 4 [EOS Visit] or Early Withdrawal Visit [EW]) will be deemed as the last dose day.

6.2. Appendix 2 Electronic Clinical Outcome Assessment (eCOA) Compliance

The compliance of ACQ eCOA data will be assessed at clinical visits and will be derived at overall study and visit level for the endpoint of ACQ and reported across all participants and by treatment group.

6.2.1. Endpoint Level Compliance

The assessments of ACQ will be performed as detailed within Section 4.4.1.

The compliance for ACQ eCOA (i.e. availability of a score) will be reported for each analysis timepoint using a frequency table. The denominator will be the number of expected completed questionnaires (i.e., the number of participants remaining in the study at the given timepoint).

Endpoint-level compliance will be restricted to key eCOA endpoints within the study (ACQ-5, ACQ-6). eCOA compliance for key eCOA endpoints of ACQ-5 and ACQ-6 across all participants will be calculated separately. The target compliance is >=90% for each key endpoint. The study eCOA compliance will be reported for each treatment group and overall.

6.2.2. Study Level Compliance

An eCOA (ACQ) will be considered complete according to the conditions mentioned in section 4.4.1.

- The overall study level eCOA compliance will be assessed across all participants and across all visits between the date of the Screening visit through to the date of the participant's study completion or study withdrawal.

  The target compliance for the study level is >=90%. The study ACQ eCOA compliance will be reported for each treatment group.

  Overall study level ACQ eCOA compliance for the study is calculated as:

$$\frac{\text{Total number of complete eCOAs}}{\text{Expected number of complete eCOAs per participant} \times \text{Total number of particpants}} \times 100\%$$

- Overall visit level ACQ eCOA Compliance will be calculated across all ACQ eCOAs and across all participants for baseline (Day 1), Week 4 and Week 12. The target compliance is >=90%. The study ACQ eCOA compliance will be reported for each treatment group.

  Overall visit level ACQ eCOA compliance for the study is calculated as:

$$\frac{\text{Total number of complete eCOAs at that visit}}{\text{Expected number of complete eCOAs per participant} \times \text{Total number of particpants at the visit}} \times 100\%$$

6.3. Appendix 3 Data Derivations Rule

6.3.1. Planned and Actual Treatment

For participants who received the correct treatment throughout the study, the actual treatment will be the same as the planned treatment. For participants who received an incorrect treatment, the actual treatment will be derived as follows:

- If the number of doses on an incorrect treatment is less than the number of doses on the planned treatment then the actual treatment is assigned as planned treatment.
- If the number of doses on an incorrect treatment is greater than the number of doses on the planned treatment then the actual treatment is assigned as the incorrect treatment.
- If the number of doses on an incorrect treatment and planned treatment are the same, the actual treatment is assigned as the treatment with the UMEC and/or higher FF dose.
- If an incorrect container was dispensed and not returned, such that it is not possible to ascertain whether or not any doses were taken from the incorrect container, it will be assumed that the participant took all possible doses from this container (i.e., 30 doses in total).

6.3.2. Study Period

The study consists of a 1-week pre-screening period, a 3-week screening / run-in period, a 12-week treatment period, and a 1-week safety follow-up period.

Pre-screening: Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) must be completed prior to initiating any Visit 1 procedures.

Screening / run-in**:** Participants who meet all the eligibility criteria at screening (Visit 1), will enter the run-in period for 3 weeks in order to continue to assess the participant's eligibility for the study. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF/VI (100/25 μg via the ELLIPTA dry powder inhaler [DPI]), taken in the morning once daily during the 3-week run-in period. Rescue medication (albuterol/salbutamol) will be provided to use on an as-needed basis throughout the study. The 3-week run-in period is necessary in order to allow participants to become accustomed to using the ELLIPTA DPI as well as to assess the participant's eligibility for the study and collect baseline electronic diary (eDiary) data.

Treatment period: At the conclusion of the 3-week run-in period (Visit 2), all participants who meet the additional predefined criteria will be randomized 1:1:1:1 to receive either FF/UMEC/VI (100/62.5/25; 200/62.5/25 μg) or FF/VI (100/25; 200/25 μg) via the ELLIPTA DPI for the duration of the 12-week treatment period. Study treatment will be administered via the ELLIPTA DPI in the morning.

Safety follow-up: A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 4/end of study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study upon completion of all assessments and procedures for Visit 4/EOS and including a successful follow-up contact/visit.

For analyses of safety data and concomitant medications, during screening/run-in period, at study entry, on-treatment period, post-treatment and post-study period are defined as:

Study Phase	Definition
At Study Entry	Event Onset Date/Time < Visit 0 (Pre-screening Visit) Date and Event End Date/Time >= Visit 0 (Pre-screening Visit) Date - 2 Note: if the end date/time is missing, deem as ongoing.
Screening/Run-in Period	Visit 1 (Screening/ Run-in Visit) Date <=Event Onset Date or Assessment Date/Time < Randomized Treatment Start Date. Note: for participants who didn't receive any randomized treatment, the rule will be: Visit 1 Date <=Event Onset Date or Assessment Date/Time < Target Randomization Date.
On-Treatment	Randomized treatment start date <=Event Onset Date or Assessment Date/Time <=Randomized Treatment Stop Date +1 or any assessment with a missing or partial date unless there is evidence it was not on-treatment.
Post-Treatment[1]	Randomized Treatment Stop Date + 1 < Event Onset Date or Assessment Date/Time <=Last Scheduled Clinic Visit (i.e., Visit 4 [EOS Visit] or Early Withdrawal Visit [EW])[2] Note: if any participant does not receive a dose of randomized treatment then all post-baseline data prior to EW or EOS visit is considered as post-treatment.
Post-Study	Event Onset Date > Last Scheduled Clinic Visit (i.e., Visit 4 (EOS Visit) or Early Withdrawal Visit)[2] Note: for participants who continue in the study after IP discontinuation (i.e., where treatment discontinuation date < Visit 4 (EOS visit) date or EW visit date), the rule will be: Event Onset Date > Last Scheduled Clinic Visit (i.e., Visit 4 (EOS Visit) or EW Visit)[2]

[1]: Applicable only for participants who continue in the study after IP discontinuation.

[2]: If a participant is lost to follow up and does not have an EOS or EW visit, the study conclusion date will be used if available. If no study conclusion date is available, the last contact date will be used.

For analyses of concomitant medications at study entry, medications will be included if the start date prior to study entry (pre-screening visit [Visit 0]) and are either ongoing at Visit 0 or have a stop date within 2 days before Visit 0, on or after Visit 0. A medication will be classified into every period in which it was taken. For medications with partial start and stop dates, the medication will be classified into every period in which it could have been taken.

6.3.3. Study Day and Reference Dates

The safety reference date is the study intervention 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

In general, data will be reported according to the nominal time of clinic visits and assessments as specified in the protocol. For example, if a participant had recorded values for the Week 4 visit on the 22nd day of treatment, the data will be presented as Week 4 values in the summary tables.

The post-randomization clinic data collected at EW/ End of Study (EOS) visits in the eCRF and SDTM data will be mapped based on study day as follows:

Study days	**Target date for visit**	**Visit/Week**
15 to 56	29	Visit 3/Week 4
≥ 57	85	Visit 4/Week 12

If a participant has an EW visit on or before day 14 then the data collected at this study visit will be listed but excluded from visit-based summaries, figures and analyses.

Note:

- For laboratory there is no planned assessment at week 4 and so data that slots to week 4 will be excluded from summaries and analyses.
- After mapping visit for EW/ End of Study (EOS) visits, when there is more than one non-missing value within an assessment window for a given analysis or summary, the measure from the scheduled visit will take priority.

6.3.5. Multiple measurements at One Analysis Time Point

For safety parameters, participants having both high and low values relative to normal ranges at post-baseline on treatment visits will be counted in both the high and low categories of the 'worst-case post-baseline' row of related summary tables.

For ACQ assessment, if multiple measurements at one scheduled visit (i.e. visit 2, visit 3, visit 4), the non-missing record closest to the target study day will be used. If there are multiple records within the same distance from the target study day, the latest record will be used.

Visit/Week	**Target date for visit**
Visit 2/Baseline	1
Visit 3/Week 4	29
Visit 4/Week 12	85

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.

</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 intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.

Else if study intervention start date is not missing:

o If month and year of start date = month and year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.

Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.

Else if study intervention start date is not missing:

o If year of start date = year of study intervention start date, then

▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.

Else set start date = January 1.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Element</th><th colspan="2">Reporting Detail</th></tr>
<tr><td></td><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></td><td>Missing end day and month</td><td>No Imputation</td></tr>
<tr><td></td><td>Completely missing start/end date</td><td>No imputation</td></tr>
<tr><td>Concomitant Medications</td><td colspan="2">• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:</td></tr>
<tr><td></td><td>Missing start day</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = 1st of month.
Else if study intervention start date is not missing:
o If month and year of start date = month and year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date= 1st of month.
▪ Else set start date = study intervention start date.
Else set start date = 1st of month.</td></tr>
<tr><td></td><td>Missing start day and month</td><td>If study intervention start date is missing (i.e. participant did not start study intervention), then set start date = January 1.
Else if study intervention start date is not missing:
o If year of start date = year of study intervention start date, then
▪ If stop date contains a full date and stop date is earlier than study intervention start date, then set start date = January 1.
▪ Else set start date = study intervention start date.
Else set start date = January 1.</td></tr>
<tr><td></td><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>

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<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>No imputation</td></tr>
</table>
If an AE cannot be classified into any of 'during screening/run-in period ', 'on-treatment', or 'post-treatment' based on its imputed start and end dates, the AE will be classified to “on treatment”.
</td></tr>
<tr><td>Age</td><td>

Age will be calculated based on the Pre-Screening Visit date (or Screening, if pre-screening not performed).
Only year of birth is collected on eCRF. Day and Month of birth are imputed as 30 June. Age is derived using the date of the pre-screening visit.
All participants with imputed age of 17 or 18 years will be source data verified, and presence/ absence of protocol deviation on the inclusion criteria #1 will be taken into consideration in the derivation for the analysis variable age.
Age will be rounded down to integer.
Birth date will be presented in listings as ‘YYYY’.

</td></tr>
<tr><td>Study treatment start and stop date</td><td>

If the study treatment start date is missing, the Visit 2 (Day 1) date will be used.
If overall treatment stop date is missing or partial, it will be imputed as follows:
For participants who attended an Early Withdrawal visit, use the date of the Early Withdrawal visit
For participants who attended the last on-treatment visit, use the End of Study Visit date
For participants who died and did not attend the last on-treatment visit, use the date of death
For all other participants, use the last recorded exposure stop date

</td></tr>
</table>

6.3.7. Abbreviations & Trade Marks

6.3.7.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BDB	Bayesian Dynamic Borrowing
BMI	Body Mass Index
CI	Confidence Interval
CV	Cardiovascular
DBL	Database Lock
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
eDiary	Electronic Diary
EOS	End of study
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IP	Investigational Product
ITT	Intent to Treat
kg	Kilogram
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
µg	Microgram
m	Meter
MAR	Missing at Random
MedDRA	Medicinal Dictionary for Regulatory Activities
mL	Microliter
MMRM	Mixed-Model Repeated Measures
MNAR	Missing Not at Random
prn	As needed
PD	Protocol Deviation
QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula

Abbreviation	Description
QTcF	QT interval corrected for heart rate by Fridericia's formula
RMC	Respiratory Medication Class
SABA	Short-Acting Beta-2-Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoA	Schedule of Activities
SMQ	Standardized MedDRA Query
UMEC	Umeclidinium
VI	Vilanterol

6.3.7.2. Trademarks

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MedDRA

7. REFERENCES

Schmidli, H., Gsteiger , S., Roychoudhury , S., O'Hagan , O., Spiegelhalter , D. J., & Neuenschwander , B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics, 70: 1023-32.