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Title:	Meta-Analysis Plan for MID207941: A Study to Evaluate Risk Factors for Pneumonia and Chronic Obstructive Pulmonary Disease (COPD) Exacerbations in a COPD Population of Patients Treated with GW685698 + GW642444 (Fluticasone Furoate + Vilanterol); GW642444 (Vilanterol); CCI18781 (Fluticasone Propionate); GR33343 (Salmeterol); CCI18781+ GR33343 (Fluticasone Propionate + Salmeterol) and Placebo.

Compound Number: GW685698, GW642444, CCI18781, GR33343

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Description:

This document describes the reporting and analysis planned for the MID207941 meta-analysis.

The study is designed to evaluate risk factors for pneumonia and COPD exacerbations in the COPD population of the five contributing studies: HZC102870, HZC102970, SCO100250, SCO40043, and SCO30003.

Subject: COPD, pneumonia, COPD exacerbations, inhaled corticosteroids

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ABBREVIATIONS

BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
FF	Fluticasone Furoate
FP	Fluticasone Propionate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled Corticosteroid
ITT	Intent-to-Treat
SAL	Salmeterol
VI	Vilanterol

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1. INTRODUCTION

The purpose of this meta-analysis is to evaluate the most important risk factors, alone and in combination for pneumonia and chronic obstructive pulmonary disease (COPD) exacerbations in patients with COPD.

The analysis will indentify the subgroups of COPD patients which are most at risk for these events and quantify the probability of patients having those events.

Previous analyses of the separate studies [not yet published] have identified some similarities in risk factors for pneumonias and COPD exacerbations in this population and this meta-analysis is intended to provide a more definitive list of risk factors using a larger sample size, and hence additionally more events of interest.

2. OBJECTIVE(S) AND ENDPOINT(S)

2.1. Objective(s)

2.1.1. Primary Objectives

The primary objectives of this study are to evaluate

- Risk factors for pneumonia in the COPD population of the contributing studies
- Risk factors for moderate/severe exacerbations in the COPD patient population of the contributing studies

2.1.2. Exploratory Objective

Based on previous analyses of the separate studies [not yet published] we anticipate that body mass index (BMI) will be an important factor in understanding the risk of pneumonia, both as a main effect and in interaction with treatment (inhaled corticosteroid [ICS] vs. non inhaled-corticosteroid [non-ICS]). In these previous analyses, a single cut-off for BMI subgroups was used: (BMI $< 25 kg/m^2$ vs. BMI $\geq 25 kg/m^2$), this was chosen because the median BMI value in the studies was often close to $25 kg/m^2$. However, there exists literature suggesting that a BMI ≤ 21 kg/m^2 may be an important cut-off for examining the effect of BMI on the risk of a subsequent pneumonia. Therefore the secondary objective for this study is to fully characterise the effect of BMI on risk for pneumonia.

2.2. Endpoint(s)

- Time to first pneumonia
- Time to first moderate/severe exacerbation

3. DATA SOURCES/STUDIES INCLUDED

The following criteria will be used to select studies:

- Randomised, parallel-group, double-blind clinical trials in COPD with FF/VI or FP/SAL as a randomized study drug not in combination with another study drug
- Inclusion of a VI or SAL alone treatment arm
- Constant dose of FP or FF
- At least 52 weeks duration
- Minimum 100 subjects per treatment arm to ensure sufficient events
- Not conducted earlier than TORCH (as this was first study where pneumonia was noted)
- Not solely in moderate COPD patients

The following table lists all studies conducted with FF/VI or FP/SAL of at least 52 weeks duration and the reason for exclusion if excluded.

Study	SFC or FF/VI	Comparators	Duration	Reason for Exclusion
SCO30003 (TORCH)	SFC 50/500	Placebo, Salmeterol, FP	156 weeks	
SCO40043	SFC 50/250	Salmeterol	52 weeks	
SCO100250	SFC 50/250	Salmeterol	52 weeks	
HZC102972	FF/VI 50/25, 100/25, 200/25	Vilanterol	52 weeks	
HZC102871	FF/VI 50/25, 100/25, 200/25	Vilanterol	52 weeks	
SCO40036 (INSPIRE)	50/500	Tiotropium	104 weeks	No VI or SAL arm
SFCB3024 (TRISTAN)	SFC 50/500	Placebo, Salmeterol, FP	52 weeks	Pre TORCH
SCO40002 (COSMIC)	SFC 50/500	Salmeterol	52 weeks	FP withdrawn
SCO40041 (Bone Mineral Density Study)	SFC 50/250	Salmeterol	104 weeks	<100 subjects per arm
SUMMIT	FF/VI 100/25	Placebo, Vilanterol, FP	Mean Treatment Exposure 1.6-1.7 years	Moderate COPD only

This is therefore a meta-analysis of five randomised double blind parallel group studies. Treatment assignments will be pooled into two groups "ICS treated" and "non-ICS treated" based on whether the patient was randomised to an inhaled corticosteroid (ICS) treatment alone or in combination: FF in the HZC studies, or FP in the SCO studies.

All available on-treatment data will be used from each study.

The numbers in the intent-to-treat (ITT) population and assigned treatment arms in each of the contributing studies is given in Table 1.

Table 1

Study	ITT	FF/VI 200/25	FF/VI 100/25	FF/VI 50/25	VI 25	FP/SAL 250/50	SAL 50	FP 500	Placebo	Total ICS	Total non-ICS

										treated	**treated**
HZC102871	1622	402	403	408	409					1213	409
HZC102970	1633	409	403	412	409					1224	409
SCO100250	797					394	403			394	403
SCO40043	782					394	388			394	388
SCO30003	6112					1533	1521	1534	1524	3067	3045
Meta-analysis	10946	811	806	820	818	2321	2312	1534	1524	6392	4654

Further details can be found in the protocols and reporting analysis plans (RAPs) of the contributing studies.

4. PLANNED ANALYSES

4.1. Analysis Methods

The analyses will be based on a backwards selection process for covariates. A starting Cox model will be fitted to the data using all relevant covariates and covariates will be removed iteratively until the selected model is found.

4.2. Statistical Hypotheses

The comparisons of interest will all be tests of significance of the type III Wald statistic of covariates in a Cox model. The hypothesis tested is:

H_0: The estimated beta coefficient of the covariate is equal to zero (i.e. the covariate has no effect on the outcome)

H_1: The estimated beta coefficient of the covariate is non-zero (i.e. the covariate has an effect on the outcome)

5. ANALYSIS POPULATIONS

The intent-to-treat (ITT) population will be used, and will consist of the ITT populations from each of the contributing studies.

6. TREATMENT COMPARISONS

Treatment comparisons will be made by pooling patients into two groups “ICS treated” and “non-ICS treated” based on whether the patient was randomised to an FF/VI arm in the HZC studies, or either FP alone, or in combination with salmeterol: FP/SAL in the SCO studies.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

In using the backward selection process to select the most significant model covariates, inevitably concerns about multiple testing will arise. The purpose of this analysis is not confirmatory and so the control of the type I error level is not paramount. Any conclusions drawn from the final model will take into account the nature of the selection process in performing multiple hypothesis tests on model covariates.

In the final publication of results, reference will be made to the previous analyses of risk factors for pneumonia and COPD exacerbation which were performed separately on each study [not yet published]. These "by study" results will be used to assess the heterogeneity of studies used in this meta-analysis.

8. DATA HANDLING CONVENTIONS

8.1. Premature Withdrawal and Missing Data

No imputation of missing data will be performed for the purposes of this study.

8.2. Derived and Transformed Data

No additional derivations will be used.

8.3. Assessment Windows

Not applicable

8.4. Subgroup and Covariate Definitions

The covariates to be used in the primary analyses are all binary categorical variables measured at baseline: treatment assignment (ICS, non-ICS) age ($\leq$64, $\geq$65), sex, BMI ($<25kg/m^2$, $\geq 25kg/m^2$), GOLD status (I & II, III & IV), smoking status (current smoker, former smoker), exacerbation history in the previous year (<2, ≥ 2). Only covariates which are measured in all contributing studies are included.

In additional analyses two more binary covariates will be used: race (Asian, non-Asian), and the World Bank categorisation of country income group from the year in which the contributing study started (2000 for SCO30003, 2004 for the SCO exacerbation studies, and 2009 for the HZC exacerbation studies). The World Bank categorises countries into four groups: high income, upper-middle income, lower-middle income and low income, which for the purposes of this analysis will be regrouped further into high income and non-high income countries to give more reasonable sample sizes in the categories.

Note, that neither study nor region will be used as a covariate in the analyses. Study will not be used because the variable has no predictive value for the wider COPD population and this analysis is intended to provide useful indicators of risk in the wider COPD population. Region will not be used because of colinearity issues with the race covariate.

It is hoped that race and income group will account for some aspects which the study and region covariates would traditionally adjust for, namely differences in the standards of care in different countries.

8.5. Other Data Handling Conventions

Only on-treatment moderate/severe exacerbations and pneumonias will be considered for this analysis, and follow up time will be censored at the end of the on-treatment period (see individual study RAPs for definitions of the on-treatment period in each study).

9. ANALYSES

9.1. Study Population

Disposition, demography, baseline characteristics and exposure tables will be produced.

9.2. Efficacy and Safety Analyses

The analyses of risk factors for i) pneumonia and ii) exacerbations will be based on a) selecting the best fitting Cox models using a backwards selection procedure, and then b) presenting the hazard ratios and probabilities from the selected model.

9.2.1. Analysis of risk of pneumonia event based on seven common covariates

9.2.1.1. Backwards selection

The starting Cox model will contain covariates for treatment, age, BMI, exacerbation history, GOLD, sex, and smoking status and all possible (21) pairwise interactions of those main effects. Covariates will be iteratively removed from the model based on the type III Wald statistics of the covariate. The covariate with the largest statistic will be removed until in the final model all remaining covariates have a p-value > 0.1. However, main effects will not be eligible for removal during the selection procedure if there is an interaction term involving that main effect still remaining in the covariate list. (Thus the finally selected model may contain main effects with associated p-values > 0.1.)

9.2.1.2. Subgroup probabilities and hazard ratios

Once the final model has been selected, the model estimated probability of pneumonia during the first year will be presented together with a figure of the survival function for each subgroup combination of the covariates remaining in the final model. Hazard ratios for each of the covariates in the final model will also be presented. Although data from the full three years of the SCO30003 (TORCH) study will be used in the model, survival estimates from the Cox model will be presented up to one year only.

9.2.2. Analysis of risk of pneumonia event based on nine common covariates

This analysis will be as for the analysis of pneumonia based on seven common covariates, but will additionally include race, and the World Bank country income groups and all their interactions in the starting model for the backwards selection process.

9.2.3. Analysis of risk of exacerbation event based on seven common covariates

This analysis will be as for the analysis of pneumonia based on seven common covariates replacing the analysis variables of time to pneumonia with time to moderate/severe exacerbation

9.2.4. Analysis of risk of exacerbation event based on nine common covariates

This analysis will be as for the analysis of pneumonia based on nine common covariates replacing the analysis variables of time to pneumonia with time to moderate/severe exacerbation

9.3. Exploratory analyses

Examination of BMI effect and BMI by treatment effect in risk of pneumonia

In the primary analysis for risk of pneumonia, the BMI subgroup variable will be "cut" at 25kg/m^2 (<25kg/m^2, >=25kg/m^2), and based on previous analyses of pneumonia risk in the individual studies, it is anticipated that BMI and/or treatment*BMI, will be significant explanatory covariates of the risk of pneumonia. If this is indeed the case, in order to better understand the risk profile for patients with different BMIs, the following two models (or one model if the selected models are identical) will be rerun, using a BMI covariate with more than two modalities.

1. The final pneumonia Cox model selected based on seven common covariates

2. The final pneumonia Cox model selected based on nine common covariates

The BMI covariate will be "cut" as follows into groups which are roughly deciles of the data: (0, 20), [20, 22), [22, 23), [23, 24), [24, 25), [25, 26), [26, 28), [28, 30), [30, 33), 33+

Using these two models the effect (hazard ratios vs. BMI reference level) of BMI on pneumonia, using the lowest (0, 20) kg/m^2 group as the reference level, will be presented and plotted in any subgroups which interact with BMI

Additionally assuming an interaction between BMI and treatment is present, the treatment effect (hazard ratio for ICS vs. non-ICS) at each of the BMI subgroup levels.

10. REFERENCES

11. ATTACHMENTS

11.1. List of Trials

Data from the following trials will be used in this study: HZC102870, HZC102970, SCO100250, SCO40043, and SCO30003.