1. Title Page

Title	TARGET-EU: Comparison of single-device vilanterol/fluticasone furoate with other single-device inhaled corticosteroid and long-acting beta agonist combinations in the risk of pneumonia in adolescents with asthma.
Research question & Objectives	The primary objective is to assess whether vilanterol/fluticasone furoate increases the risk of pneumonia compared to other fixed dose combinations of an inhaled corticosteroid and long-acting beta-2 adrenoceptor agonist (ICS+LABA) in a single-device in adolescent asthma patients.
Protocol version	2.0
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Study registration	**Site:** https://catalogues.ema.europa.eu/node/4893/administrative-details **Identifier:** EUPAS1000000989 *This study is part of the TARGET EU study with registration details:* **Site:** https://catalogues.ema.europa.eu/node/4440/administrative-details **Identifier:** EUPAS1000000539
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Conflict of interest	None

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2. Abstract

Vilanterol and fluticasone furoate (V+FF) single-device combination is approved for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product of long-acting beta-2 adrenoceptor agonist and inhaled corticosteroid (LABA and ICS) is indicated, i.e., if adequate symptom control is not achieved with ICS and SABA, or adequate control is achieved combining ICS with LABA. In a meta-analysis of 7034 patients from 11 asthma trials, the incidence of pneumonia in V+FF (25/100µg) was 9.6/1000 person-years, compared to 8.0/1000 person-years in placebo-treated patients. Incidence of pneumonia was higher, 18.4/1000 patients, with higher fluticasone furoate dose (V+FF 25/200µg). Most of the pneumonia events were managed in outpatient settings, and no risk factors increasing the risk of pneumonia were identified in studies with asthma.[1] These trials included adults and adolescents and thus there are no specific estimations on whether pneumonia risk is increased in vilanterol+ICS combination treatment specifically in adolescent asthma. There are also no previous comparisons of V+FF and other ICS+LABA single-device combinations in this population.

The main objective of this observational cohort study is to assess whether vilanterol+fluticasone increases the risk of pneumonia compared to other single-device ICS+LABA combinations in adolescent patients with asthma already treated with ICS. An active comparator new-user design is used to compare the risk of pneumonia in adolescents with asthma between initiators of V+FF and initiators of other single-device ICS+LABA combination therapies during a two-year follow-up. We will employ two European national databases routinely used for research purposes: Finnish national healthcare registers and Clinical Practice Research Database (CPRD) from UK. Both data sources include inpatient and outpatient diagnosis and procedure data. The Finnish data covers dispensations in outpatient settings whereas CPRD captures prescriptions in outpatient settings.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
27 February 2026	1.0			
3 June 2026	2.0	7.3.1 Definition of time 0 for entry to the study population - context and rationale	The following text was added: *"The study is conducted as a single-entry study, meaning that if a person has multiple qualifying entries, only the first one is considered."*	The change clarifies that subjects can contribute only once to the study.
		Table 10	Split *"end of observation data"* into *"Date of final data capture in data source"* and *"End date of individual observation in the data source (e.g., migration or de-registration from the practice)"* End of exposure: *Censoring at end of exposure occurs when the participant had no subsequent dispensing/ prescription within 30 days after the calculated end of the previous dispensing's/ prescription's duration, with follow-up ending 30 days after the final prescription coverage period."* Treatment switch: "*Censoring occurs at the dispensing/prescription of the other ICS+LABA combination."*	The definition of end of observation was not sufficiently specific, as it could occur through two distinct mechanisms. Specification how the end of exposure is defined and occurrence of censoring at end of exposure. Specification of switching event and occurrence of censoring at that event,

		Table 11	*"Number of Outpatient visits"* changed to *"number of primary care visits".* Variable type of ICS dose changed from *"continuous"* to *"categorical"*	Specification of healthcare setting. The variable in the database is categorical.
		Annexes	Addition of the study code list as annex	Inclusion of the study code list for programming activities to identify eligibility criteria, exposures, outcome, covariates, etc. , which was missing.

4. Milestones

Table 1. Milestones

Milestone	Date
Study protocol for RWD study	8 August 2025
Preliminary results RWD study	April 2026
Final Study report	10 June 2026

5. Rationale and background

What is known about the condition: Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. In 2016, the Pharmaceutical Risk Assessment Committee of European Medicines Agency concluded that the association between ICS and pneumonia observed in COPD patients is likely causal.[2] Since then, this association has been reported in asthma cohorts, including a cohort study of adolescents and young adults (age 12-35 years).[3] Pneumonia has been included in the pre-specified adverse events in asthma RCTs, but there are no specific estimates on pneumonia risk in adolescents with asthma. Higher pneumonia rates for patients on V+FF combination

treatment in comparison to ICS have been reported in trials on adolescent and adult asthma patients.[1,4] The number of adolescent patients in these trials was limited, thus the risk increase in this population is not known.

What is known about the exposure of interest: Vilanterol is an ultra-long-acting beta 2-adrenoceptor agonist indicated for COPD and asthma. Fluticasone furoate is a corticosteroid, available in nasal and inhaled administration forms with different indications. V+FF combination treatment is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of ICS+LABA combination is appropriate (adequate symptom control not achieved with ICS and as-needed short-acting beta2-agonists or patients already adequately controlled on ICS+LABA combination)

Gaps in knowledge: It is not known whether the V+FF combination pertains to higher pneumonia risk than other single device ICS+LABA combinations.

What is the expected contribution of this study? This study will evaluate the risk of pneumonia in V+FF initiators in comparison to other ICS+LABA single-device treatments in representative real-world settings among adolescents with asthma who are already on ICS treatment.

6. Research questions and objectives

The overall aim is to assess whether the risk of incident pneumonia differs between V+FF combination initiators compared with initiators of other single-device combination treatments.

6.1. Primary Estimand 1

Table 2. Primary Estimand (Estimand 1)

	Target Trial	Target Trial Emulation	Comment
Population	Adolescent patients with asthma already treated with ICS	Adolescent patients with asthma already treated with ICS	
Treatment Conditions	Intervention:vilanterol-fluticasone furoate Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention: vilanterol-fluticasone furoate Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention and control identified from prescriptions in electronic health records/national prescription databases using ATC/DM+D codes.Exposure based on first observed prescription after one-year washout.

Endpoint	Time to pneumonia	Time to pneumonia, identified with ICD-10/Read codes using electronic health records/national registers (diagnoses from primary and secondary care)	Majority of events in trials are outpatient-treated -> OP diagnosis data in TTE necessary and available for both data sources. Emulated using validated code lists.
Summary Measure	Hazard ratio	Hazard ratio	
Intercurrent events and strategies to handle them	Same for both treatment conditions	Intercurrent events are handled according to pre-specified strategies of the hypothetical target trial	Inaccuracies in estimation of timepoint of discontinuation are anticipated due to reliance on prescription data.
	Discontinuation: while on treatment	Treatment discontinuation is defined as a gap of more than 30 days between the coverage of consecutive prescriptions for the index therapy (ATC/DM+D code). Switches are considered as a specific form of discontinuation and defined as initiation of another ICS+LABA treatment during continuous treatment of the index therapy.	
	Add-on/rescue medications: treatment policy	Add-on/rescue medications, including dose adjustments of ICS or LABA of the index therapy, are determined by prescriptions of these medications during continuous treatment with index therapy.	Whilst add-on and rescue medication relies on the accuracy of prescribing records, the impact of such inaccuracies is less important because in treatment policy approach individuals are followed regardless of whether they experience the intercurrent event.
	Death (any cause): while alive	Death dates are identified from population register or electronic health records.	Deaths are expected to be rare in this patient population, and there is a possibility of misclassification (some of the deaths may be due to pneumonia). Information on causes of death is not available in both database instances.

Research question targeted by the estimand: What is the HR of pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the study treatments. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients use the medicine. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Deaths are a rare intercurrent event in the young study population and causes of death information are not available from both study sites. In addition, pneumonia deaths in this population are likely preceded by admission so outcome misclassification is likely to be rare.

6.2. Supplementary Estimand 2

Table 3. Estimand 2

	Target Trial	Target Trial Emulation	Comment
Population	As in Estimand 1		
Treatment Conditions	As in Estimand 1		
Endpoint			
Summary Measure	Difference in restricted mean survival time	Difference in restricted mean survival time.	
Intercurrent events and strategies to handle them	As in Estimand 1		

Research question targeted by the estimand: What is the difference in restricted (at two years) mean survival time to pneumonia for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the medicines of interest. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients use the medicine. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Deaths are a rare intercurrent event in the young study population and causes of death information are not available from both study sites. In addition, pneumonia deaths in this population are likely preceded by admission so outcome misclassification is likely to be rare.

6.3. Supplementary Estimand 3

Table 4. Estimand 3 (for Finland only)

	Target Trial	Target Trial Emulation	Comment
Population	As in Estimand 1		
Treatment Conditions	As in Estimand 1		

Endpoint	Time to pneumonia diagnosis or pneumonia death	Time to pneumonia diagnosis of death due to pneumonia, identified with ICD-10 codes using national registers (diagnoses from primary and secondary care and causes of death).	Causes of death added as a source of case ascertainment.
Summary Measure	Hazard ratio	Hazard ratio	
Intercurrent events and strategies to handle them	Otherwise as in Estimand 1, except Pneumonia death: composite. Non-pneumonia death: while alive	Death dates and causes of death are identified from the causes of death register.	Deaths are expected to be rare intercurrent events, and there is a possibility of misclassification. For this estimand, pneumonia cases ascertained from causes of death register in addition to primary and secondary healthcare data. In addition, instead of any cause death, the intercurrent event of death is restricted to non-pneumonia deaths.

Research question targeted by the estimand: What is the HR of pneumonia, including pneumonia deaths, for V+FF vs. other ICS+LABA combination in adolescent asthma patients who were on ICS treatment within the year preceding the initiation, while alive and on treatment (i.e., before treatment discontinuation or switching to another ICS+LABA combination), regardless of using other add-on or rescue medications?

Rationale for handling of intercurrent events: The risk of pneumonia is a safety concern plausible when patients are exposed to the medicines of interest. While-on-treatment strategy for switches and discontinuations estimates the effect of treatment exposure during the period when patients remain adherent. Treatment policy strategy for other add-on medications and rescue medications such as biologicals reflects usual clinical practice. Ascertaining pneumonia cases also from causes of death register and including non-pneumonia deaths as an intercurrent event assists in evaluating the impact of misclassification bias on estimand 1.

7. Research methods

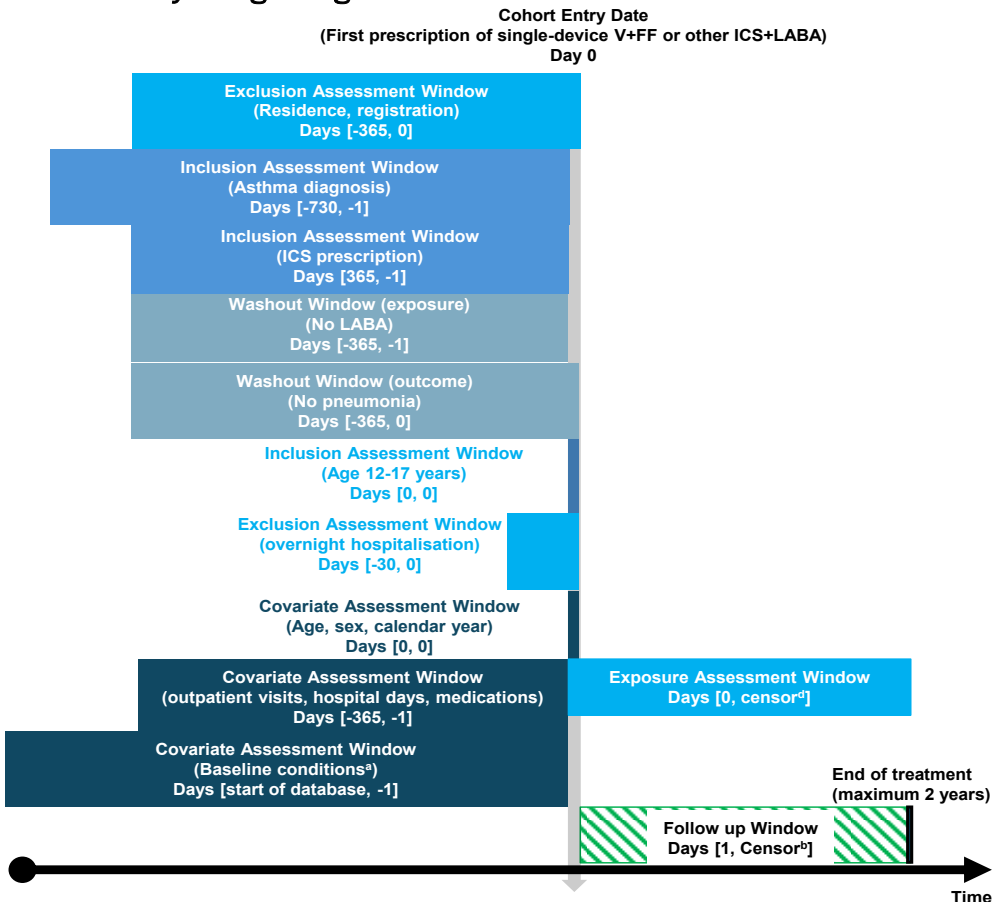
7.1. Study design

Research design (e.g. cohort, case-control, etc.): Active comparator new user cohort design

Rationale for study design choice: The active comparator study design reduces risk of bias from unmeasured confounding by indication and is optimal for the target trial emulation framework. Using another single-device ICS+LABA combination treatment reduces indication bias, and restriction to single-device treatments ensures similar compliance between the treatment arms. The comparison treatments are clinically relevant and commonly prescribed alternative to V+FF.

The new-user design ensures easily identifiable and comparable time 0 between treatment arms as the follow-up starts with treatment initiation. This avoids immortal time bias, which can occur if follow-up starts before the actual initiation of therapy.

7.2. Study design diagram



a. Baseline conditions included: diabetes, rheumatological diseases,malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, inhaled corticosteroids (dose), leukotriene receptor antagonists, antibiotics, pneumococcal vaccination, influenza vaccination

b. Earliest of: outcome of interest (pneumonia), switching or discontinuation of study drugs, death, emigration, end of treatment.

LABA = long-acting beta-2 adrenoceptor agonist
ICS = inhaled corticosteroid

7.3. Setting

This study is conducted using routinely collected electronic health records from 2014 to 2023. The study is set primarily in primary care, drawing on longitudinal data from general practices with linkage to hospital data. Data are sourced from two European countries, the United Kingdom (Clinical Practice Research Datalink [CPRD]) and Finland (Finnish national registries), providing population-based and representative coverage of real-world clinical care.

7.3.1 Definition of time 0 for entry to the study population - context and rationale

Time 0 is the date of initiation of V+FF or other single-device ICS+LABA combination treatment. This is when the adolescent asthma patients who fulfil the eligibility criteria enter the study population and it mimics the timing of initiation of therapy at randomisation in the target trial. The study is conducted as a single-entry study, meaning that if a person has multiple qualifying entries, only the first one is considered.

Table 5. Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure: single-device V+FF	Date of incident prescription/ dispensation for V+FF (time 0)	Single	Incident	[-365, -1]	OP	ATC DM+D	n/a	LABA (any formulation)		Investigator review of ATC/DM+D codes
Comparator: other single-device ICS+LABA	Date of incident prescription/ dispensation for ICS+LABA (time 0)	Single	Incident	[-365, -1]	OP	ATC DM+D	n/a	LABA (any formulation)		Investigator review of ATC/DM+D codes

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.3.2 Study inclusion criteria - context and rationale

We require one year of residence or registration in the relevant database prior to time 0 to ensure that the study participants have observable time in the data where contact with the healthcare system will allow capture of clinical codes to measure inclusion and exclusion criteria and covariates. We restrict the population to adolescents aged 12-17 years to evaluate pneumonia risk in adolescent asthma population. All participants are required to have a dispensed (Finland) or written (UK) ICS prescription within the year preceding time 0 to ensure they have a step up of asthma treatment (from maintenance ICS and as needed SABA). All participants are required to have at least one dispensation (Finland) or written prescription (UK) of V+FF or other ICS+LABA single-device combination treatment.

Table 6. Operational Definitions of Inclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
At least one dispensation or written prescription of V+FF or other single-device ICS+LABA		[0, 0]	OP	ATC DM+D	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Observable time	Continuous residence/ registration in database	[-365, 0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		n/a
Age 12-17 yrs		[0, 0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		n/a
Asthma diagnosis	Based on diagnostic and special reimbursement codes	[-730, -1]	Any	ICD-10, special reimbursement, Read	Any	Exposure: single-device V+FF Comparator: other single-device ICS+LABA	references [5,6]	
ICS treatment	Based on record of prescription	[-365, -1]	OP	ATC DM+D	n/a	device V+FF Comparator: other single-device ICS+LABA		

	and/or dispensing							

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.3.3 Study exclusion criteria - context and rationale

We exclude participants with overnight hospitalisation within 30 days prior to day 0 to exclude those with possible asthma exacerbations, that are directly recorded in the applied real-world data sources, and to avoid incorrect specification of day 0 as they may have been administered ICS+LABA while in hospital, because information in hospital-administered treatments is not available in both study sites. Records with missing values for key demographic variables (e.g., age or sex) are excluded from the analysis as information for these individuals is not provided by the database maintainers at the data extraction stage.

Table 7. Operational Definitions of Exclusion Criteria

Criterion	Details	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Previous pneumonia	Based on diagnostic codes	[-365, 0]	Any	ICD-10 Read/SNOMED	Any	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Overnight hospitalisation	Based on recorded hospital stay	[-30, 0]	IP	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		

[1]IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2]See appendix for listing of clinical codes for each study parameter
[3]Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4 Variables

7.4.1 Exposure - context and rationale

The use of an active comparator of other single-device ICS+SABA combination treatment will allow us to compare initiators who are in need of a similar line of therapy and at a similar stage of asthma severity, reducing confounding by indication. Restriction to single-device treatment ensures similar compliance between the treatment groups.

Algorithm to define duration of exposure effect:

The study medications are single-inhalation once-daily administration so fixed assumptions method using one dose/day based on dispensed amount is used to construct treatment episodes. A 30-day grace period between calculated duration of prescriptions is used to account for noncompliance. For the last prescription, duration is calculated based on the dispensed amount and a carryover period of 30 days is added. This is based on the half-life of ICS (2-3days) and possible delay in clinical manifestation and diagnosis of pneumonia.

Table 8. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Exposure	Single-device V+FF based on record of prescription and/or dispensing	[-365, -1]	[0, censor]	OP	ATC DM+D	n/a	All study populations	Prescriptions measured in one year prior to first use	reference[7]	Investigator review of available products in study countries
Comparator	Other single-device ICS+LABA based on record of prescription and/or dispensing	[-365, -1]	[0, censor]	OP	ATC DM+D	n/a	All study populations	Prescriptions measured in one year prior to first use	reference[7]	Investigator review of available products in study countries

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.2 Outcome - context and rationale

Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. Pneumonia also increases the risk of asthma exacerbations in all age groups, and ICS increase the risk of pneumonia also in adolescents. Pneumonia has been included in the pre-specified adverse events in asthma RCTs, but there are no specific estimates on pneumonia risk in the adolescent

population. Most pneumonia cases are treated in outpatient settings, therefore we include both in- and outpatient diagnoses as well as data from primary and secondary healthcare.

Table 9. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Pneumonia	Diagnosis date from primary or secondary healthcare. In estimand 3 death date from causes of death register is used in addition to diagnosis date.	Yes	Time-to-event	[-365, 0]	OP, IP	ICD-10 Read SNOMED	any	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		investigator review of codes

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.3 Follow up - context and rationale

The investigated medications are intended for long-term period of use as asthma is a chronic condition. However, significant changes in asthma severity and symptoms occur in puberty, and a significant proportion of even severe asthma cases are resolved.during adolescence,[8] supporting the restriction of trial duration to two years. A duration of 2 years is expected to be sufficient for capturing enough pneumonia events.

Table 10. Operational Definitions of Follow Up

Follow up start	Day 1	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	First occurrence of pneumonia
Date of death	Yes	Date of any death (estimands 1,2) Date of non-pneumonia death (estimand 3)
Date of final data capture in data source	Yes	Censor at database end; administrative censoring
End date of individual observation in the data source (e.g., migration or leaving the practice	Yes	Censor at date of emigration or known deregistration; Non-administrative censoring
Day X following index date *(specify day)*	Yes	Day 730; administrative censoring
End of study period (specify date)	Yes	31-Dec-2023
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	Yes	Fixed assumption method (1 dose per day) with 30-day grace period. Censoring at end of exposure occurs when the participant had no subsequent dispensing/prescription within 30 days after the calculated end of the previous dispensing's/prescription's duration, with follow-up ending 30 days after the final prescription coverage period.
Date of switch from exposure *(specify algorithm)*	Yes	Initiation of another ICS+LABA combination during continuous treatment of the index therapy based on prescription data. Censoring occurs at the dispensing/prescription of the other ICS+LABA combination.
Other date *(specify)*	No	

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

7.4.4 Covariates - context and rationale

The study covariates were chosen based on previous literature on risk factors for pneumonia, asthma severity and outcomes in asthma. These include age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose before the index date, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination. In addition, calendar year is used to account for possible time trends, and number of outpatient admissions and hospital days are used as proxies for overall comorbidity.

Table 11. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Age	(cohort entry date - date of birth) in years. Accuracy for DOB varies between databases (year/month/exact date)	Continuous	[0,0]	n/a	n/a	n/a	Exposure: single-device V+FF Comparator: other single-device ICS+LABA		
Sex	men, women	Binary	[0,0]	n/a	n/a	n/a	as above		
Calendar year		Continuous	[0,0]	n/a	n/a	n/a	as above		
Season	month or as 4 categories	Categorical	[0,0]	n/a	n/a	n/a	as above		
Number of primary care visits		Continuous	[-365,-1]	OP	n/a	n/a	as above		
Number of hospital days		Continuous	[-365,-1]	IP	n/a	n/a	as above		
diabetes		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED ATC DM+D	any	as above		

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
rheumatological diseases		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
malignancies		Binary	[-start of database,-1]	IP	ICD-10 Read SNOMED	any	as above		
other immunological conditions		Binary	[-start of database,-1]	IP	ICD-10 Read SNOMED	any	as above		
cardiovascular diseases		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED ATC DM+D	any	as above		
intellectual disability		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
congenital malformations		Binary	[-start of database,-1]	OP,IP	ICD-10 Read SNOMED	any	as above		
psychotropic drugs		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
Asthma exacerbations	Number of asthma-related overnight hospitalisations	Continuous	[-365,-1]	IP	ICD-10, Read SNOMED	main	as above		
oral corticosteroids		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
biologicals		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
SABA		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
Inhaled corticosteroids (dose)	obtained from the latest prescription before the index date	Categorical	[-365,-1]	OP	ATC DM+D	any	as above		
leukotriene receptor antagonists		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
antibiotic use		Binary	[-365,-1]	OP	ATC, DM+D	any	as above		

Characteristic	Details	Type of variable	Assessment window	Care Settings [1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
pneumococcal vaccination		Binary	[-365,-1]	OP	ATC DM+D	any	as above		
influenza vaccination		Binary	[-365,-1]	OP	ATC DM+D	any	as above		

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.5 Core Emulation Table - Design Summary

Table 12. Comparison of Target Trial and Proposed Target Trial Emulation Design Elements (Estimand 1)

	Target Trial	Target Trial Emulation	Comment
Inclusion criteria	1. age 12-17 years at randomisation 2.diagnosis of asthma 3.step-up to ICS+LABA combination necessary because asthma symptoms not adequately controlled with current treatment	1. age 12-17 years at initiation V+FF or comparison medication 2. asthma diagnosis within 730 days before initiation 3. previous ICS treatment within 365 days of initiation 4. a first prescription of V+FF or other single-device ICS+LABA combination treatment The target trial is emulated using data on people included in EHR/national registers.	Emulation study population is restricted to new users of the medicines of interest. The necessity for adding LABA to current treatment is assumed to represent a step-up from having symptoms insufficiently controlled with low-dose ICS (with/without SABA) but symptoms or disease control cannot be directly evaluated from patient records.
Exclusion criteria	1. previous pneumonia diagnosis within the previous year	1.ICD-10/Read diagnosis of pneumonia in primary care/secondary care EHR 365 days before initiation of study therapy	Inaccuracies in diagnostic coding can affect the ability to capture the exclusion criteria in the emulation study

	2.LABA treatment within the previous year 3.hospitalisation within 30 days prior to randomisation.	2.ATC/DM+D code for LABA in dispensing data in 365 days before initiation of study therapy 3.Overnight hospitalisation in 30 days before initiation of study therapy	
Setting	Treatment in outpatient setting, outcomes from in- and outpatient care	Electronic healthcare record data sources capturing prescriptions/dispensations, outcomes, and covariates capturing treatment in outpatient setting, outcomes from in- and outpatient care	
Method of Assignment to Trial Intervention	Randomisation	Assignment reflects clinical need.	Randomisation cannot be directly emulated. In the statistical analysis, inverse probability of treatment weighting following propensity score calculation will be used to balance baseline covariates to emulate randomisation.
Study treatment conditions	Intervention: vilanterol- fluticasone furoate. Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate)	Intervention: vilanterol- fluticasone furoate. Control: other single-device ICS+LABA combinations (not vilanterol-fluticasone furoate) Medications are identified using ATC/DM+D codes.	Intervention and control identified from prescriptions or dispensing in electronic health records/national prescription databases using ATC/DM+D codes. Exposure based on first observed written (UK) or dispensed (Finland) prescription.
Time *(when follow up begins and ends):*	Starts at randomisation, ends at pneumonia, death, treatment discontinuation, study withdrawal, loss to follow-up, or trial end (two years after randomisation), whichever occurs first	Starts at initiation of V+FF or comparator, ends at pneumonia, death, treatment discontinuation, loss to follow-up or two years since treatment initiation, whichever occurs first	In estimands 1 and 2, all deaths regardless of cause are intercurrent events. In estimand 3, non-pneumonia deaths are intercurrent events, but pneumonia deaths are included as pneumonia. First prescription/dispensation is used as a proxy for initiation.
Outcome (including operational definition)	Pneumonia	Pneumonia diagnosis in primary or secondary care based on ICD-10/Read/SNOMED code (primary diagnosis)	Causes of death are not available from CPRD. Therefore, primary analyses (estimands 1 and 2) are conducted with any death as an intercurrent event. Most of the fatal pneumonia events in this population are expected to be preceded by pneumonia hospitalization, therefore the fatal

			cases are likely to be captured with the EHRs. To evaluate the impact of potential misclassification, pneumonia deaths are included in the outcome for estimand 3, which will only be estimated using Finnish data.
Intercurrent Events and strategies to handle them	1. Treatment discontinuation 2.Add-on/rescue medications 3.Death, any cause (estimands 1-2) Non-pneumonia death (estimand 3)	1. Assessed based on dispensing (dispensing dates, ATC/DM+D codes and dispensed quantity): while on treatment strategy 2. Identified with dispensing information (ATC/DM+D codes): treatment policy strategy 3. Identified from population register or EHR: while alive strategy Identified from causes of death register: while alive strategy	Treatment start and end dates must be estimated in the datasets as precise times are not provided
Loss to follow up	Patients who fail to return for the required study visits and his/her health condition and vital status remains unknown despite multiple attempts to contact them.	Patients with known deregistration or emigration date or database end. Measured directly in data sources	Information on emigration/registration end dates are available in both data sources. Real-world proxy used to define loss to follow-up;

Estimand 2

Same as estimand 1 but difference in restricted mean survival time instead of hazard ratio is used as the summary measure.

Estimand 3 (Finland only)

Same as estimand 1 but pneumonia cases ascertained from causes of death register in addition to primary and secondary healthcare data. In addition, instead of any cause death, the intercurrent event of death is restricted to non-pneumonia deaths.

7.6 Data analysis

For estimand 1, the main estimand supporting decision making, the primary analysis is an IPTW-weighted Cox proportional hazards model.

Sensitivity analyses will be performed to assess the robustness of the results to assumptions made in the primary analysis.

Supplemental analyses include diagnostic and descriptive assessments to support the main analysis. These cover crude and IPTW-adjusted Kaplan-Meier curves, crude Cox models, event counts, incidence rates, weight and propensity score distributions, covariate balance before and after weighting, censoring and intercurrent event patterns, proportional hazards diagnostics, and positivity checks.

A Cox regression model will be fitted separately to data from each data source. The estimated HRs from Finland and CPRD will be combined with a random effects meta-analysis of log hazard rations with IPTW. Combined HR and 95% CI, in addition to country-specific estimates will be reported. Potential sources of heterogeneity between data sources will be described, and we will assess qualitatively relevant differences in the estimates. In addition, the estimate agreement between the data sources will be assessed as outlined by Franklin et al.[9]

7.6.1 Analysis plan overview

Overview

The analyses are conducted within a target trial emulation framework to estimate the effect of initiating single-device V+FF vs. other single-device ICS+LABA on the risk of incident pneumonia.

For **Estimand 1**, the main estimand supporting decision making, the primary causal effect summary measure is the hazard ratio for time to incident pneumonia, estimated using an inverse probability of treatment weighted (IPTW) Cox proportional hazards model. The Cox model will be fitted separately within each data source (Finnish registers and CPRD), and the resulting hazard ratios will be combined using a random-effects meta-analysis; potential sources of heterogeneity will be described qualitatively, including structural differences (e.g., coding systems, population coverage) and measurement differences (e.g., recording practices) and their implications (e.g., residual confounding or misclassification).

Sensitivity analyses will assess robustness of the primary findings to key assumptions, including inverse probability of censoring weighting (IPCW), tipping point analysis, and probabilistic bias analysis for non-differential exposure misclassification (details in Section 7.6.5).

Two supplemental estimands are also defined: **Estimand 2**, estimating treatment effects using restricted mean survival time (RMST) derived from an IPTW-weighted Weibull accelerated failure time (AFT) model and **Estimand 3** (in Finnish data only), investigating time to first pneumonia diagnosis or pneumonia death with same statistical analysis methods as in Estimand 1. In addition, supplemental analyses (e.g., crude and IPTW-adjusted Kaplan–Meier curves, crude Cox models, event counts and incidence rates, propensity score and weight distributions, covariate balance before and after

weighting, censoring and intercurrent event patterns, proportional hazards diagnostics and positivity checks) will be conducted to support interpretation of the main analysis.

7.6.2 Primary Estimand Analysis

i. Objective

To estimate the hazard ratio of incident pneumonia in initiators of V+FF versus other single-device ICS+LABA.

ii. Exposure contrast

single-device V+FF vs. other single-device ICS+LABA

iii. Outcome

Time to first pneumonia diagnosis

iv. Software

R.

v. Handling of intercurrent events

Handle intercurrent events according to the following strategies:

- Treatment discontinuation (both or an individual component): Apply a while-on-treatment strategy
- Treatment switching: Apply a while-on-treatment strategy.
- Add-on or rescue medications: Apply a treatment policy strategy
- Death: Apply a while-alive strategy

For the intercurrent events handled with a “while…” strategy, data will be excluded after the occurrence of the intercurrent event.

For intercurrent events handled with a treatment policy strategy data after the occurrence of the intercurrent event will be included in the analysis.

vi. Outcome Modelling

A Cox proportional hazards model, weighted by inverse probability of treatment (IPTW), will be used to estimate the effect of initiating V+FF versus other single-device ICS+LABA. on time to first pneumonia diagnosis

Start of follow-up: date of treatment initiation for single-device V+FF or other single-device ICS+LABA

- Timescale: time since index date
- Endpoint: first occurrence of pneumonia
- Censoring:
    - Non-administrative censoring: Loss to follow-up
    - Administrative censoring: End of study follow-up in the absence of pneumonia (maximum two years)
    - Model covariate: Treatment group (single-device V+FF or other single-device ICS+LABA)

Assumptions of KM

- Non-informative Censoring:
- For Crude KM curves: Censoring is assumed to be independent of the outcome, conditional on treatment and survival up to the time of censoring.
- For IPTW-adjusted KM: Censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the treatment weights
- Times of events and censoring are known and correctly recorded
- Independence between observations

Assumptions of Cox Model

Proportional Hazards:

- The hazard ratio is assumed to be constant over time.

Non-informative Censoring:

- Censoring is assumed to be independent of the outcome, conditional on the treatment, survival up to the time of censoring and indirectly baseline covariates used to estimate the treatment weights
- Times of events and censoring are known and correctly recorded

- Independence between observations

Diagnostics for Cox Model

Proportional hazards assessed using log(-log) survival plots or Schoenfeld residuals

vii. Confounding Adjustment

Inverse Probability of Treatment Weighting (IPTW)

To adjust for baseline confounding, inverse probability of treatment weighting will be used. Propensity scores, defined as the probability of initiating single-device V+FF or other single-device ICS+LABA inhibitor, will be estimated using logistic regression The model will include baseline covariates selected a priori as potential confounders due to their identification as risk factors for the outcome (age, sex, season, diabetes, rheumatological diseases, malignancies, cardiovascular diseases, intellectual disability, congenital malformations, psychotropic drugs, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose before the index date, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, calendar year of initiation, number of primary care admissions and hospital days). Restricted cubic splines will be used to model continuous variables.

Stabilised weights will be calculated by dividing the marginal probability of receiving the treatment actually received (i.e., the overall proportion treated in the study population) by the individual's estimated propensity score (i.e., the conditional probability of receiving their observed treatment). Weights will be truncated at the 1st and 99th percentiles to limit the influence of extreme values.

Weight truncation reduces the influence of individuals with highly improbable treatment assignments, but it does not resolve propensity score non-overlap. Therefore, if regions of the propensity score distribution show insufficient overlap, we plan to restrict analyses to the overlapping region (trimming) or apply overlap weights.

Truncated stabilised IPTW weights will then be applied in the Cox proportional hazards model (weighted likelihood) to estimate the marginal treatment effect of V+FF vs. other ICS+LABA combination on time to first pneumonia.

Standard errors will be estimated using robust (sandwich) variance estimators.

Assumptions Underlying IPTW

- **No unmeasured confounding** (all relevant baseline confounders are included in the propensity score model).
- **Positivity** (each individual has a non-zero probability of receiving either treatment, given their covariates).
- **Correct model specification** (the propensity score model is correctly specified [functional form, covariate inclusion]).

- **Consistency** (each individual's potential outcome under the observed treatment equals their actual outcome).

Diagnostics for IPTW

- Evaluation of weight distribution before truncation in different treatment groups
- Evaluation of baseline covariate distribution in different treatment groups before and after trimming
- Covariate balance: Check that baseline characteristics are balanced across treatment groups after weighting.
- Evaluate standardized mean differences (SMDs): SMDs < 0.1 will be considered acceptable.
- Positivity check: Plot the distribution of PS (histograms) and graphically evaluate overlap.
- Describe baseline covariate distribution before and after PS based population trimming.

viii. Missing Data handling

Missing Exposure Data: We assume that missing dispensing or prescription records for V+FF or other ICS+LABA reflect true treatment discontinuation after the end of previous dispensing/prescription, and not incomplete data capture or prescriptions issued outside the database.

Missing Outcome Data: The Cox proportional hazards model implicitly assumes censoring occurring at random, meaning that censored participants contribute time at risk up to the time of censoring and their censoring is unrelated to the outcome, conditional on model covariates and survival up to the time of censoring (i.e., outcome data is missing at random under these assumptions). The absence of an outcome event during the observed follow-up is interpreted as no occurrence of pneumonia.

Missing Covariate Data: The absence of a disease diagnosis code will be interpreted as the absence of the corresponding condition. All covariates in this study are either completely recorded (e.g. age and sex), or are binary variables based on coded medications or diagnoses. Absence of codes for medication or disease diagnoses is assumed to mean the absence of the corresponding medication or condition.

As such, there will be no missing data for covariates, exposure or outcome.

7.6.3 Supplemental Estimand (2) Analysis

i. Objective

Estimate the effect of initiation single-device V+FF vs. other single-device ICS+LABA on the risk of pneumonia

ii. Exposure contrast

single-device V+FF vs. other single-device ICS+LABA

iii. Outcome

Time to incident pneumonia diagnosis

iv. *Software*

R.

v. Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)

Same as 7.6.2

vi. Outcome Model

IPTW weighted Accelerated Failure Time (AFT) model, followed by estimation of Restricted Mean Survival Time (RMST) at fixed time point of two years

Covariate in the model will include treatment group.

Start of follow-up: Date of treatment initiation.

Timescale: Time since index date

Endpoint: Time from treatment initiation to incident pneumonia

Censoring and missing outcome data:
Non-administrative: loss to follow-up
Administrative: two-year study end

Model Assumptions:

- Survival times follow a Weibull distribution
- Non-informative censoring (conditional on included covariates and survival up to time t)

- Log-linear relationship between covariates and log survival time

Diagnostics:

- Log(-log(S(t))) vs log(t) should be linear Q-Q plot of residuals

To estimate the RMST at two years from the Weibull AFT model, we first use the model to obtain the predicted survival curve for each treatment group. The RMST is then calculated as the average survival time up to a fixed time point, which corresponds to the area under the survival curve between time zero and two years. Confidence intervals are estimated with bootstrapping (1000 samples, percentile-based 95% confidence intervals constructed from these 1000 bootstrap estimates).

- Fit the Weibull AFT model, which gives the shape and scale of the survival curve for each group.
- From this model, generate the predicted survival probability at each time.
- Integrate (i.e., add up) the survival probabilities from time 0 to 2 years. The result is the expected survival time lived within those windows.
- Compare the RMST values between treatment groups to obtain the difference in average survival time over two years.

vii. Confounding adjustment

Same as 7.6.2; IPTW will be incorporated into the AFT model to obtain estimates of RMST at year 2

viii. Missing Data Handling

Same as 7.6.2

7.6.4 Supplemental Estimand (3) Analysis

i. Objective

Same as 7.6.2

ii. Exposure contrast

Same as 7.6.2

iii. Outcome

Time to incident pneumonia diagnosis or pneumonia death.

iv. Software:

R.

v. Handling of intercurrent events (explaining how follow-up is handled post intercurrent event)

Same as 7.6.2 except non-pneumonia death instead of any death is used as an intercurrent event and handled with a while-alive strategy.

vi. Outcome Model

Same as 7.6.2

vii. Confounding adjustment

Same as 7.6.2

viii. Missing Data Handling

Same as 7.6.2

7.6.5 Sensitivity Analyses

Table 13. Sensitivity analyses – Varying conditions of the censoring at random assumptions using Inverse Probability of Censoring Weighting (IPCW)

Analysis Methods	This analysis will examine the impact of varying assumptions about the censoring-at-random condition. In the primary analysis we assumed censoring independent of the outcome, ***conditional*** on treatment group and survival up to the time of censoring (i.e., outcome data is missing at random conditional on observed exposure and outcome). In the IPCW analysis, we use inverse probability of treatment weights and inverse probability of censoring weights. This analysis assumes censoring is independent of the outcome, with all common causes of both the outcome and censoring being accounted for. Follow-up will be divided into equal 30-day intervals. At the start of each interval, we will update the information available on each study participant and assess whether they remain followed or have been censored (due to nonadministrative reasons). If they remain under observation, they contribute to the risk set for that interval. The time-specific weight component for each participant at each interval is calculated as the inverse estimated probability of remaining uncensored, given a set of baseline and time-updated covariates that could affect both censoring and the outcome

	Characteristics that could affect both censoring and the outcome include: baseline (age,sex, calendar year of initiation, number of outpatient admissions and hospital days) and time varying covariates (time since index treatment initiation, asthma exacerbations, oral corticosteroids, biologicals, SABA, SAMA, inhaled corticosteroids dose, leukotriene receptor antagonists, antibiotic use, pneumococcal vaccination, influenza vaccination, upper respiratory tract infections, antihistaminic use/allergic dermatological conditions) The time-specific weight component is calculated separately for each interval, and then these weight components multiplied together across all intervals of follow-up to give each participant's cumulative weight. The denominator probability will be estimated using pooled logistic regression models fit to the person-interval dataset. The model outcome is whether the participant was censored in that interval. Time will be modelled flexibly using restricted cubic splines. We will truncate the weights at prespecified percentiles (1st and 99th). The stabilised IPCW will be applied as time-varying weights in the Cox model for time to incident pneumonia. As the inverse probability of treatment weights (IPTW) are also used, the final analysis weights will be the product of IPTW and IPCW.
Assumptions	• Censoring is conditionally independent of the outcome given covariates (i.e., non-informative censoring/censoring at random, conditional on other covariates beyond those in the outcome model); outcome does not directly influence its own missingness Correct model specification and positivity (every individual has a non-zero probability of remaining uncensored at each time point given their covariates).
What is Being Varied?	The condition of the censoring at random assumption.
Why (Objective)	• To assess the robustness of the treatment effect estimate to violations of the censoring at random assumption. If results are stable across scenarios, confidence increases that findings are not driven by selection bias due to censoring.
Strengths	• IPCW adjusts for measured predictors of censoring. Offers a principled method for recovering unbiased estimates under nonrandom censoring.
Limitations	• IPCW is sensitive to model misspecification. • Cannot account for unmeasured factors affecting censoring. • Weighting can increase variance, especially if weights are unstable Sensitivity analyses rely on varying the assumptions of the primary analysis, but for censoring these assumptions cannot be verified from the observed data; their plausibility can be discussed, yet ultimately remains unknown.

Table 14. Sensitivity analyses – Informative Censoring

<table>
<tr><td>Analysis Methods</td><td>

Best/worst case scenarios. The goal is to assess the impact on the estimated treatment effect of selected censoring non-at-random assumptions. The assumptions chosen represent the 4 extremes of a tipping point sensitivity analysis.
For non-administrative or treatment discontinuation/switching- censored individuals, repeat the analysis under four scenarios, assuming within each treatment group that a) all censored individuals had the outcome of interest at the censoring date and b) no censored individuals had the outcome of interest by the end of the study. This equates to the following scenarios

<table>
<tr><th>Scenario</th><th>Exposed Group (V+FF)</th><th>Unexposed Group
(Other ICS + LABA)</th><th>Interpretation</th></tr>
<tr><td>1</td><td>Best case (lowest event rate)</td><td>Worst case (highest event rate)</td><td>Maximally favors V+FF</td></tr>
<tr><td>2</td><td>Worst case (highest event rate)</td><td>Best case (lowest event rate)</td><td>Maximally favors Other ICS + LABA</td></tr>
<tr><td>3</td><td>Best case</td><td>Best case</td><td>Optimistic for both groups</td></tr>
<tr><td>4</td><td>Worst case</td><td>Worst case</td><td>Pessimistic for both groups</td></tr>
</table>
</td></tr>
<tr><td>Assumptions</td><td>

All or none of the censored individuals had the outcome of interest
.

</td></tr>
<tr><td>What is Being Varied?</td><td>

The assumption made in the primary analysis that censoring is non-informative given treatment group and survival up to the time of censoring.

</td></tr>
<tr><td>Why (Objective)</td><td>

To assess the robustness of the treatment effect estimate to violations of the non-informative censoring assumption made in the primary analysis.
If results are stable across scenarios, confidence increases that findings are not driven by selection bias due to informative censoring.

</td></tr>
<tr><td>Strengths</td><td>

Enables the exploration of alternative assumptions about censoring.
Does not assume a certain structure of informative censoring.
Sets bounds on the extent of maximum possible bias due to informative censoring

</td></tr>
<tr><td>Limitations</td><td>

Best/worst case scenarios are extreme assumptions

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

Table 15. Sensitivity analyses – Non-Differential Exposure Misclassification

Analysis Method	Probabilistic Bias Analysis using Monte Carlo Simulation at the summary level measure. The final effect estimate from the main analysis will be used as the input for this analysis. The aim is to evaluate the potential impact of exposure initiation misclassification at index date (all prescriptions in CPRD may not be dispensed (primary adherence) or eventually used (secondary adherence), and all dispensations in the Finnish data may not be eventually used). This sensitivity analysis addresses misclassification of treatment initiation only (i.e., at index date), not exposure discontinuation or adherence during follow-up. • Probability distributions will be specified for the sensitivity and specificity parameters of exposure (i.e., treatment initiation) classification Plausible parameter ranges for prescription-based exposure measurement in real-world data (based on literature review of studies mainly assessing ICS use in adolescents); the adherence over the course of treatment was 49-71%[10] . However, as we are assessing initiations of ICS+LABA which typically represent intensification of treatment, we expect the adherence to be higher, around 70-90%. Sensitivity: 0.70-0.90 o (lower bound reflects non-initiation after prescribing; upper bound reflects high adherence) Specificity: 0.95-0.99 o (high specificity expected, as those without prescriptions are unlikely to be truly exposed) • In each Monte Carlo iteration, a single pair of sensitivity and specificity values will be drawn from the prespecified distributions and applioed to both treatment groups, reflecting the assumption of non-differential misclassification. This approach avoids introducing artificial random differences in initiation of medication use between treatment arms while allowing uncertainty in the overall degree of misclassification to be propagated. [11,12]. These values will be used to probabilistically adjust the pooled hazard ratio for exposure misclassification using established bias-adjustment methods for dichotomous exposure classification. • Repeating this process across many iterations (e.g., 10,000) will generate a distribution of bias-adjusted hazard ratios. Final uncertainty will be represented by the percentile-based 95% confidence interval from the distribution of simulated bias-adjusted hazard ratios, which is derived from the empirical distribution of bias-adjusted point estimates across all Monte Carlo iterations and incorporates uncertainty from sampling variability, and exposure misclassification, rather than from confidence intervals calculated within individual iterations Although not verifiable, misclassification is assumed to be non-differential with respect to outcome. The limitations of this assumption will be acknowledged.
Assumptions	• Non-differential misclassification: exposure error is unrelated to the outcome. • Sensitivity and specificity are correctly specified and constant across individuals, over treatment arms. • The primary outcome model is correctly specified.
What is Being Varied?	• The assumption of accurate exposure measurement via prescribing • Simulate variation in sensitivity and specificity to generate corrected exposure measurement. • Assess how misclassification could bias the estimated hazard ratio.
Why (Objective)	• Evaluate whether the findings are robust to exposure misclassification.

	• Determine whether plausible levels of misclassification could meaningfully alter the estimated treatment effect.
Strengths	• Explicitly incorporates uncertainty in exposure classification. • Produces a distribution of corrected effect estimates, not just a point estimate.
Limitations	• Requires accurate or defensible assumptions about Se and Sp. • Limited to non-differential misclassification.

7.6.6 Core Emulation Table – Estimation summary

Table 16. Core Emulation Table: Estimation Summary

Estimand 1 (primary estimand)

	Target Trial	**Target Trial Emulation**	**Comment**
Analysis Method	Cox Proportional Hazards model	IPT-weighted Cox model to estimate HR	IPTW used to emulate randomisation in observational data Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported

			extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring given treatment group and not experiencing the event up to the time of censoring; censored participants contribute partial information under Cox models	Noninformative given treatment group, survival up to the time of censoring and model covariates	
Statistical Model Assumptions	Proportional hazards Non-informative censoring Correct specification of the Cox model (functional form and covariates)	Same, and in addition: • **IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency	To correctly model the propensity score, the model should include all risk factors of the outcome. However, this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).
Sensitivity Analyses	Sensitivity analysis under the CNAR assumption will be carried out.	Sensitivity analyses with IPCW to determine whether results are sensitive to alternative assumptions about censoring, i.e. censoring at random conditional on additional baseline and time-varying covariates. Best/worst case scenario analysesQBA for exposure misclassification	

Estimand 2

	Target Trial	Target Trial Emulation	Comment
Analysis Method	AFT model followed by estimation of restricted mean survival time	IPT-weighted AFT followed by estimation of restricted mean survival time	IPTW used to emulate randomisation in observational data.

			Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring given treatment group and not experiencing the event up to the time of censoring;; censored participants contribute partial information	Same	
Statistical Model Assumptions	Survival times follow Weibull distribution Non-informative censoring Log linear relationship between covariates and log linear survival time	Same, in addition **IPTW Assumptions**: no unmeasured confounding, positivity, correct model specification, consistency	To correctly model the likelihood of exposure, the model should include all risk factors of the outcome. However, this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in

			adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).
Sensitivity Analysis	None	None	

Estimand 3

	Target Trial	Target Trial Emulation	Comment
Analysis Method	Cox Proportional Hazards model	IPT-weighted Cox model to estimate HR	Cox model selected to reflect treatment policy estimand; IPTW used to emulate randomisation in observational data. Trimming of PS represents a departure from the target trial but is considered best practice when using propensity score methods in emulation. By removing study participants in regions of non-overlap, the analysis is restricted to a population where treatment assignment is comparable across groups. As a result, the estimated effect no longer applies to the entire population but to this more comparable subset. If some study participants have an extremely low probability of receiving one of the treatments, valid causal contrasts cannot be identified for them. Without trimming, effect estimates in these regions rely on unsupported extrapolation, making the results unstable and potentially biased.
Missing Data Assumptions and Methods to Handle	Assumes noninformative censoring; censored participants contribute partial information under Cox models	Same; administrative censoring used	
Statistical Model Assumptions	Proportional hazards Non-informative censoring	Same, in addition • **IPTW Assumptions**: no unmeasured confounding, positivity, correct model	To correctly model the likelihood of exposure, the model should include all risk factors of the outcome. However,

	Correct specification of the Cox model (functional form and covariates)	specification, consistency No Unmeasured Confounding for Censoring	this assumption is difficult to test in practice and has been addressed in this study by expert opinion-based risk factor list, confirmed by review of previous studies on pneumonia risk in adolescents, and previous studies on these medications and pneumonia in adults. Positivity assumption ensures there are comparable individuals for different values of propensity scores (or combination of risk factor values).

7.7Data sources

7.7.1 Data sources - context and rationale

Rationale for selection and feasibility:

Finnish national registers and CPRD were selected as data sources for this study because they offer large, high-quality, population-based electronic health records with national coverage in Finland and the UK, respectively. Both sources provide the required data elements to operationalise the study design, including demographics, primary and secondary healthcare diagnoses, prescriptions and mortality data. Finnish national registers on dispensed prescriptions, primary and secondary healthcare contacts and causes of death are linkable through the National Hearth and Data Permit authority Findata, while CPRD offers linkage of written prescriptions to hospital and mortality records through NHS Digital. Both databases have previously been used in studying pneumonia incidence and risk factors as well as the utilization and outcomes of different asthma medications. They have been used in regulatory studies and are known to support the emulation of clinical trial eligibility criteria and endpoints. Their extensive follow-up time (median ~7 years for existing instance of Finnish registers and ~6–13 years for CPRD) makes them suitable for assessing the outcomes outcome. Data extraction and feasibility assessments confirm that the study variables are available with sufficient completeness and temporal coverage to support the research objectives.

Strengths of data source(s):

Finnish registers cover the entire population of Finland (ca. 5.5M), and provide high completeness and reliability for critical variables such as date of birth, sex, specialized and primary healthcare admissions including diagnostic codes (ICD-10), and all dispensed prescriptions (ATC codes) and mortality including causes of death. Data for most registers are updated annually, for some of them continuously.

CPRD covers over 19 million patients in total, with 16.5 million current acceptable patients in Aurum and nearly 3 million in GOLD. The data are updated frequently (monthly for GOLD, quarterly for Aurum), and mortality, prescribing, and diagnosis information are available with high completeness. CPRD includes validated linkages to secondary care. Both databases support validated outcome definitions and have been widely used in pharmacoepidemiological studies.

Limitations of data source(s) (with potential impact on study results):

For both databases, dose information of ICS is not routinely available and as the pneumonia risk associated with ICS is dose-dependent this can potentially introduce bias to the results. However, the ICS component of study treatment is fixed, and add-on ICS treatments are handled with a treatment policy approach, reflecting the use of these medications in routine clinical settings. Further, the necessity of introducing additional ICS during the combination treatment can be considered as an association mediator. Information on possible pneumonia risk factors, which are household-related related risk factors (such as exposure to smoking, crowded housing, parental socioeconomic position) is missing, but we attempt to capture this with comorbidity proxies. Both databases miss information on asthma severity, which is captured by proxies (such as asthma-associated hospitalisations, use of add-on or rescue medications). For CPRD, cause of death is not available and therefore misclassification of outcome is possible. This is assessed by conducting an additional estimand in Finnish data (estimand 3), in which pneumonia is ascertained also from the causes of death register. For CPRD, month of birth is available for individuals aged ≤16 years and year of birth for 17-year-olds, which may slightly impact precision in age-based eligibility criteria.

Data Quality:

The registers are maintained by different organisations and authorities in Finland (Finnish Institute of Health and Welfare THL, Social Insurance Institution of Finland Kela, Statistics Finland, DVV) and data requests are centralised to Finnish Social and Health Data Permit Authority Findata. Data providers (such as healthcare organisations and pharmacies) submit data to register maintainers, who conduct initial quality control. Instructions and SOPs are partially publicly available (https://dvv.fi/en/population-information-system , https://stat.fi/meta/til/ksyyt_en.html , https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions , https://www.kanta.fi/en/research-and-knowledge-management) All research data are pseudonymized before being released for research use and all individual-level data are accessible only in audited remote use envionments,

CPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. Data from participating general practices are extracted monthly (GOLD) or quarterly (Aurum) and undergo multi-level validation and quality checks. The CPRD provides data through its secure Trusted Research Environment or via multi-study licenses. Full metadata and SOPs are available at https://www.cprd.com/data-access and https://www.cprd.com/data-quality

Databases' suitability and case-studies' feasibility assessment for this case study followed three key steps: I) Data sources' systems and processes characterisation, using the EMA checklist to evaluate foundational aspects and their maturity; II) Metrics for data quality for each data source (data reliability), based on published research and open-access catalogues; and III) Fitness-for-use evaluation (data relevance), assessing database suitability for each case study based on question-specific determinants. Steps 1 and 2 are database-specific, while step 3 is both database- and case-specific, i.e. it can only be assessed in view of the specific research question to be addressed. From the previous steps, two tables containing qualitative information (I and III) and one including some quantitative metrics will be created (II). The overall feasibility of the case-studies using the candidate data sources will be determined by critically analysing the collected information. Additional insights will be gathered from DEAPs. All the information will be gathered in a report accompanying the generated tables, with our narrative assessment.

Table 17. Overall feasibility assessment summary for the Finnish registers and CPRD used in CS5 (Vilanterol/fluticasone furoate in the risk of pneumonia in adolescents with asthma)

RWD source	Sample size estimation from the hypothetical trial protocol	Feasibility assessment *(yes/yes, with limitations/no)*	Rationale for the feasibility assessment	Limitations identified during the feasibility assessment and categorisation	Description of potential impact of the identified limitations on the study results
CPRD	With an approximate estimated sample size of 26,750 individuals (based on a 1:1 ratio between treatment arms, with 13,375 participants in each), and considering that CPRD includes data from approximately 4.4 million inhabitants (as of 2014), the target cohort size is anticipated to be achievable. In the UK, asthma affects approximately 7.2 million individuals—about 8% of the population—with up to 5.4 million currently receiving any treatment. This translates to approximately 281,600 subjects. Teenager population in CPRD is 200,949, and the prevalence of asthma in UK teenagers is 15.2%, this translates in 30,544 astmathic teenagers in CPRD. The target sample size is anticipated to be reached.	Yes	Elements with high criticality are available and fairly reliable. Data recency of 3 months before extraction, reasonably enough for the research question. Sample size is achievable.	1.Potentially major: Hospitalisation data is not available for the core data source. 2.Potentially major: Not registered date of death. 3.Minor: Dispensing is not available, only prescription. 4.Minor: Diagnostic codes are available for 86% subjects attending emergency room.	1.The DEAP is able to perform data augmentation (linkage) to retrieve hospital admission and discharge diagnoses to detect the outcomes of this case-study. 2.For exact date of death or the cause of death data augmentation (linkage) is needed to the ONS death registration data. 3.As this database only has prescription data, it is unknown if patients took the prescription, and so, if they discontinued it. However, treatment duration is available, from which this data may be estimated. 4.Diagnostic codes are reported to be available for 86% of subjects in the emergency room; however, the missing cases we expect to capture them from hospitalisation records or primary care records, since the severity of this disease may justify an admission and/or the follow-up with the GP, or change of baseline treatment.

Finnish registers	With an approximate estimated sample size of 26,750 individuals (based on a 1:1 ratio between treatment arms, with 13,375 participants in each), and considering that Finland has a population exceeding 5 million (380,000 individuals aged 12-17y, 10.5% with asthma). Despite there is up to 18,293 users of vilanterol-fluticasone furoate among the 233,261 patients with chronic asthma or similar chronic obstructive pulmonary diseases as of 2021, there is no specific data available for teenage users. Since the number of teenage users is expected to be smaller than the target sample size, we anticipate that reaching the desired sample may not be feasible.	Yes, with limitations on sample size acquisition	Elements with high criticality are available and fairly reliable. Data recency is variable depending on the data sets used, but for the current case, a few months are reasonably enough for the research question. The time elapsed from when a user requests the data to when they actually receive it is 4-12 months. **Sample size might be difficult to be reached**.	1.Potentially major: limited sample size. 2.Minor: No in-hospital drug use available. 3.Minor: Duration of hospitalisation is not readily available. 4.Minor: Exacerbations inhospital are not available. 5.Minor: Duration of treatment and end of treatment are not directly available.	1. Limited sample size in Finnish registers might lead to underpowered analyses for this population. This can be mitigated by meta-analysing the results together with CPRD. 2.Duration of hospitalisation can be calculated from the admission and discharge dates. 3.Inhospital exacerbations can be inferred from admission, discharge and primary care diagnoses that are readily available. 4.End of treatment episodes may be derived based on dispensing date and dispensed amount.

Table 18. Metadata about data sources and software

	Data 1 (Finnish registers)	Data 2 (CPRD)
Data Source(s):	Finnish national registers	CPRD GOLD and CPRD Aurum
Study Period:	2017–2023	Expected: 2014–2023 (final dates TBD based on most recent data release)
Eligible Cohort Entry Period:	2017–2023	Expected: 2014–2024 (final dates TBD)
Data Version (or date of last update):	June 2024	CPRD GOLD: November 2024 CPRD Aurum: September 2024

Data sampling/extraction criteria:	Persons with asthma diagnosis aged 12-17, receiving at least one prescription for vilanterol/fluticasone furoate or another single device ICS+LABA combination ≥1 year lookback and two years follow-up	Persons with asthma diagnosis aged 12-17, receiving at least one prescription for vilanterol/fluticasone furoate or another single device ICS+LABA combination ≥1 year lookback and two years follow-up
Type(s) of data:	Primary and secondary care admission data dispensed prescriptions, causes of death, demographics	Primary care EHR, linked secondary care data (HES, ONS), prescriptions, lab values, demographics, outcomes
Data linkage:	Deterministic linkage with unique personal identification numbers	Yes: deterministic linkage with HES, ONS mortality, NCRAS, etc. (linkage via NHS number, DOB, postcode, sex)
Conversion to CDM*:	Yes: OMOP and CONCEPTION	Yes: OMOP CDM, also CONCEPTION CDM
Software for data management:	R and Python, analyses in audited remote use environment	EMIS Web for Aurum, Vision for GOLD; analyses via CPRD secure TRE or local TRE

7.8 Data management

The study will be conducted in a distributed manner using the UMCU, ARS Toscana and VAC4EU tools, procedures, and pipeline. Figure 1 specifies the data sets (D) and transformation processes (T), programming follows this pipeline, with involvement of different types of experts.

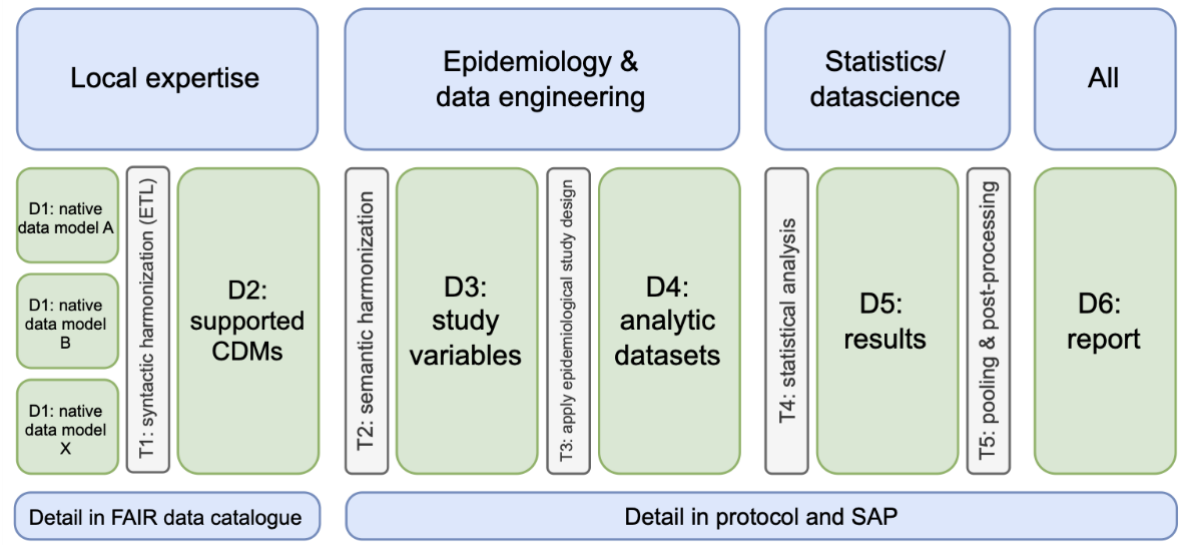


Figure 1. Data Management from the data transformation perspective

D1: Original data can be in any native format

The RWD-RWE pipeline used by VAC4EU starts with data banks that are controlled by the Data Expert and Access Partner (DEAP) and can be in any format. Data always stays local and never leaves the secure environments of the DEAPs. The ETL (extract, transform, load, see below for more details under 'T1') design is shared in a searchable FAIR VAC4EU catalogue. The VAC4EU FAIR Molgenis data catalogue is a meta-data management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

T1: Syntactic harmonisation (ETL)

T1: Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the ConcePTION common data model (CDM) (see section 'D2: Common data model'). To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al (2021):

- DEAPs are asked to share the data dictionaries of their data banks (selected tables and variable names/structure)
- Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in FAIR data catalogue (Molgenis).

D2: Common data model

For this project, the CDM (D2) is the ConcePTION common data model. The CDM version that is used is v2.2, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/SNOMED or MEDCODEID values).

T2: Semantic harmonisation

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more phenotype algorithms are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data such as the dose of vaccines, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of the creation of study variables, semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine-readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DEAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable (65,66).

D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, and outputs of functions that define smoking. Multiple functions/packages exist within the VAC4EU, for different study variables.

T3: Application of epidemiological design

In the T3 step epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU community (e.g. matching).

D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

T4: Statistical analysis

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

D5: Results

D5 is the set of estimates, tables or aggregate data that is transferred from the DEAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DEAP's site will be uploaded to the UMCU DRE for post-processing, pooling and visualisation (Figure 1). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU. The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely [ref]. UMCU is responsible for data processing and data security.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.

Uploading files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

T5: Post-processing/pooling

In this step, the result from different DEAPs is pooled and converted into tables and figures for reporting.

7.9 Quality control

All key study documents such as the hypothetical trial protocol, target trial emulation protocol and study reports will undergo senior scientific and editorial review.

Data quality

For all data sources and for each data instance we will conduct *INSIGHT* level 1-2 quality checks, detailed statistical analysis plans for the indicators are available on the public repositories:

- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level1 Hoxhaj, V. (2023). UMC-Utrecht-RWE/INSIGHT-Level1: https://doi.org/10.5281/zenodo.10035167
- https://github.com/UMC-Utrecht-RWE/INSIGHT-Level2 Hoxhaj, V., & van den Bor, R. (2023). UMC-Utrecht-RWE/INSIGHT-Level2: https://doi.org/10.5281/zenodo.10035169

Briefly, level 1 verifies Data Completeness and level 2 Data Consistency.

Level 1 – Data Completeness

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspellings and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats
- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

Level 2 – Data Consistency

Real data is not random but follows certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth
- Event dates after date of death
- Event dates out of observation periods
- Subjects having an observation but not present in the PERSONS table
- Observations associated with a visit id and occurred before/after the visit start/end date
- Subjects younger than 12 years old reported as parents
- Age at the observation period older than 115 y old Data

Code Quality

These coding practices define how the TARGET programming team collaborates to write clean, reliable, and reproducible code for the VAC4EU Real-World Evidence (RWE) Analytical Pipeline. They aim to ensure clarity, consistency, and maintainability across all case studies within the project.

Coding conventions

To ensure clarity, consistency, and maintainability across the project, the following conventions will be applied to all codebases within the project:

- Consistent style: Code follows a consistent and readable style (see the tidyverse style guide for R).

- Meaningful names: Use clear, descriptive names for variables, functions, and files to convey their purpose.
- Modular code: Break down code into small, reusable functions where possible.
- No hardcoded paths: Use configuration files or relative paths to ensure portability.

Following these conventions makes the code easier to understand, test, and reuse across case studies and teams.

Documenting Code

Code documentation is used to promote good coding practices and ensure our work is understandable, maintainable, and reproducible. To achieve this, we will:

- Use descriptive comments that explain the purpose and rationale behind code sections, focusing on why something is done, not just what.
- Clearly document function inputs, outputs, and side effects, using standardized formats (e.g., roxygen2 in R) where appropriate and supported.
- Write meaningful variable and function names to make the code as self-explanatory as possible.

Version Control

We use Git and GitHub to manage version control. These tools support good coding practices by enabling collaboration, tracking changes, accessing a project's history, and ensuring code quality through review and documentation.

A dedicated GitHub organisation has been created for the project (https://github.com/target-roc19). Each case study is managed in its own repository within this organisation. Repositories are structured consistently across case studies, to reinforce modularity. Access to repositories is controlled through teams.

During development, all repositories remain private to ensure confidentiality. Once the project is finalised, relevant repositories will be made public and assigned a digital object identifier (DOI) via Zenodo to support transparency, reproducibility, and reuse by the wider research community.

To maintain code quality and clarity, we follow the git and GitHub guidelines below.

- Always use pull requests (PRs): never push directly to the main branch.
- Open an issue before creating a new branch. Ideally, one PR resolves one issue to keep changes focused and reviewable.
- Every PR must be reviewed by at least one other person before merging.
- The PR author merges the PR after it has been reviewed and approved.
- Write clear, descriptive commit messages.
- Write informative PR descriptions, including:
  - A concise title
  - Links to related issues

- A summary of the changes

Continuous Integration

Continuous Integration (CI) is set up to automatically check code quality and run tests whenever changes are pushed to the repository or submitted through a pull request (PR). The CI workflow ensures that the package adheres to predefined style guidelines and that all automated tests pass before changes are merged.

Coding Template

Every case study follows the general coding template used across all code in the TARGET project. The folder structure is organised as follows:

case-study-template

|____data

| |____D2_cdm

| |____D3_study_variables

| |____D4_analytic_datasets

| |____D5_results

| |____D6_report

|____docs

|____logs

|____run

|____tests

|____transformations

| |____T2_semantic_harmonization

| |____T3_study_design

| |____T4_statistical_analysis

| |____T5_processing_results

|____CHANGELOG.md

|____LICENSE

|____README.md

Project Data Structure and Storage

The data folder follows the Real-World Evidence pipeline structure. Data conforming to the common data model is stored in the D2_cdm folder.

Results from transformations T2, T3, T4, and T5 are saved in the respective folders:

- D3_study_variables
- D4_analytic_datasets
- D5_results
- D6_report

Each dataset is associated with a codebook, explained in more detail below.

All data remain securely stored on the Data Expert and Access Partners (DEAPs) servers and are never transferred externally. For testing purposes, dummy datasets are created. These fall into two categories:

- Unit test data: Small, predefined input and output pairs used to test individual transformation steps. These are stored in the tests folder, not in data, and can support automated testing.
- Pipeline test data: Larger, more complex dummy datasets used to test whether the full pipeline runs as expected. These may be included in the repository only if they remain below GitHub's 100 MiB file size limit and will otherwise be shared via SharePoint.

Logging System

When the pipeline is executed, log files are saved in the logs folder. These logs are especially helpful when running the code in the DEAPs environment, as they help trace and diagnose potential errors. We recommend using the logger R package to handle logging throughout the pipeline. A sample logging setup can be found in the logger.R script located at the root of the project directory.

Executing the Analytical Pipeline

The run folder contains scripts used to execute each transformation step in the pipeline.

- A central script, run_pipeline.R, orchestrates the full pipeline from start to finish.
- Subscripts (e.g., run_T2.R or similar) are available to run individual transformation steps separately.

Typically, the run_pipeline.R script is the main entry point used by a DEAP to execute the full pipeline. Before running it in the DEAP environment, the pipeline may need to be adapted to local settings. This can be done using a configuration file that defines variables required to tailor the pipeline to a specific DEAP. Please note that configuration files should not include sensitive information.

Such a file might include variables like:

- The name of the DEAP
- The path to the local data instance
- The path to any required external resources

Testing and Quality Assurance

The tests folder contains scripts to test the analytical pipeline. Tests will be used to ensure code behaves as expected and remains stable over time. By systematically checking inputs, outputs, and edge cases, tests help catch errors early and make future changes safer. We use the testthat R package to structure and run unit tests.

Continuous integration (CI) is used to automate testing. With CI, tests are automatically run each time code is pushed to the repository (e.g., via GitHub Actions). This helps identify issues immediately, ensures that new changes do not break existing functionality, and supports better collaboration by enforcing consistent code quality across contributors.

Modular Data Transformation Workflow

The transformations folder follows the Real-World Evidence pipeline structure. It contains the source code for all transformation steps, which is typically written in R. Each subfolder corresponds to a specific step in the pipeline (e.g., T2_semantic_harmonization, T3_study_design, T4_statistical_analysis, T5_processing_results) and includes the relevant scripts and helper functions for that step.

During the T2 step, a database is usually created (e.g., using DuckDB). This database can be queried using SQL, and it is recommended that all SQL queries be saved as clearly named, standalone SQL script files to ensure readability and reusability.

The purpose of the transformations folder is to structure and modularise the processing logic, making it easier to maintain, test, and reuse across different case studies. By organising code by transformation step, teams can work in parallel, increasing efficiency.

Changelog

A changelog will be kept for all notable changes in the project. Changelogs help track the evolution of the project over time, making it easier for collaborators to understand what has changed between versions. We follow the structure and best practices outlined in Keep a Changelog.

Codebooks

Before developing code, codebooks are created to describe each dataset (D) within the pipeline. A codebook is a comprehensive document that outlines the structure, contents, and metadata of a dataset. It serves as a detailed reference guide for anyone working with the data and plays a crucial role in guiding the development of the analytical pipeline by clearly defining both the inputs and expected outputs.

All codebooks are summarized in a central index file, which provides a high-level overview of the pipeline's structure. For each codebook, the index file includes:

- A brief description of its purpose,
- A list of the scripts used to generate the corresponding dataset,
- A description of the input datasets and input parameters required.

The datasets D2, D3, D4, and D5 are typically subdivided into multiple smaller transformation steps, each detailed within their respective codebooks. These smaller transformation steps ensure that each part of the pipeline is clearly scoped and well-documented.

In addition to supporting development, codebooks help ensure quality control by making transformation logic transparent and verifiable, and they enhance reproducibility by documenting exactly how data is structured and used throughout the analytical pipeline.

Deployment

The analytical pipeline is delivered to DEAPs as a GitHub release, tagged with a version number. Versioning follows the format: vYYYYMMDD.XX, where the date indicates the release date and XX denotes the sub-version or revision number.

Any deployment issues can be reported via the GitHub repository using the issues feature, where the programming team responsible for the R code will collaborate with the local DEAP to resolve them as needed.

Reproducibility

It is recommended to locally use the renv R package to maintain the R version and version of packages for reproducibility purposes.

At this time, however, using renv reliably across different systems and environments remains challenging. For this reason, we currently recommend its use only in local development setups.

We are actively monitoring developments in the R ecosystem related to cross-platform reproducibility. As soon as a more stable and portable solution becomes available, we will revisit this guidance and promote broader adoption.

Licensing

The code will be made available under an open source license.

README Guidelines

Each case study repository includes a README that covers the following points:

- Project Overview: brief summary of the study goals and key research questions.
- Background: context and rationale for the study.
- Repository Structure: Outline of main folders and their contents.
- Data Overview: Description of data sources, formats, and data privacy considerations.
- How to Run: Instructions for running the pipeline and key scripts, plus where outputs are saved.
- Testing: How to run tests to verify code functionality.
- Contributing: Guidelines for code contributions and issue tracking.
- License: Information about the code license.
- Contact: Who to reach out to for help or questions.

7.10 Study size and feasibility

According to sample size calculation for the target trial based on hypothesis testing, a total of 26,750 subjects (13,375 per group) would be needed for a 2-year study with 1% loss to follow-up, to detect a hazard rate difference of 0.0027 (control group hazard 0.0108, experimental group hazard 0.0135, HR 1.25) with 80% power at a 5% significance level, using a conditional test for hazard differences under an exponential survival model. The expected number of events is 635 (283 in the comparison group and 352 in the experimental group).

Estimation of precision

In this non-interventional study, no hypothesis test will be performed. The focus is on the precision of the estimated treatment effect. Assuming the study size in each RWD source will be similar to the sample size of the target trial, the precision (based on the 95% CI) for a HR from a Cox proportional hazards model, the standard error (SE) of the log(HR) is derived from the total number of events. An additional calculation with 20% lower event rate (508 events) is conducted to evaluate the precision if the event rate is lower than expected.

Assumptions

- Equal allocation to treatment groups.
- Large-sample normal approximation for log(HR).
- Symmetric CI on the log scale.

Table 19. Confidence interval widths under different events counts

Scenario	Number of Events	Hazard Ratio (HR)	log(HR)	Standard Error (SE)	Margin of Error	Lower CI (HR)	Upper CI (HR)	CI Width	Precision (upper 95%CI limit/HR -1)
Scenario 1	635	1.25	0.22314355	0.05612135	0.10999785	1.12	1.40	0.28	12%
Scenario 2	508	1.25	0.22314355	0. 06274558	0.12298134	1.11	1.41	0.30	12.8%

8. Limitation of the methods

A key limitation of emulating a target trial using real-world data is that it may not be possible to fully reproduce all features of the target trial. These limitations are inherent to the target trial emulation approach.

Exposure Misclassification: UK CPRD data ascertains exposure based on prescription records, which do not capture whether the prescriptions were dispensed (primary adherence) or whether the patients took their medications as intended (secondary adherence). As a result, some individuals categorized as “exposed” may not have received the intended pharmacological effect. Finnish data includes dispensed prescriptions, thus avoiding the problem with primary adherence. These limitations are acknowledged as a source of non-differential exposure misclassification, which would bias effect estimates toward the null. A probabilistic bias analysis will be implemented at the summary level to assess the impact of varying levels of sensitivity and specificity in exposure classification, based on published estimates of prescription adherence.

Outcome misclassification: Both data sources capture pneumonia diagnoses from primary and secondary healthcare which is necessary as majority of pneumonias can be managed within primary care settings. Pneumonias are identified with diagnosis codes, as the identification with e.g. treatment or diagnostic procedure codes is not feasible because these would not be specific to pneumonia. Acute bronchitis and pneumonia may have symptomatic overlap, but symptoms are typically stronger in pneumonia and X-ray is an essential part of pneumonia diagnostics. Therefore, it is likely that a vast majority of suspected pneumonia cases would be confirmed in a more detailed diagnostic assessment, particularly in a population with more severe consequences of pneumonia. Causes of death are not available for the CPRD instance, which could lead to outcome underascertainment. Majority of the fatal pneumonia cases are expected to have a preceding hospitalization event so the misclassification is unlikely

to be significant. However to evaluate the impact of potential misclassification, pneumonia deaths are included in the outcome for estimand 3, which will only be estimated using Finnish data. Due to the active comparator design, the misclassification of outcome is expected to be nondifferential between the groups. However, the amount of misclassification is expected to be small. Unfortunately, there are not yet any validation studies on the pneumonia diagnosis codes in these data sources.

Violation of the Proportional Hazards Assumption: The Cox proportional hazards model assumes that the relative treatment effect is constant over time, which may not be appropriate. This assumption is explicitly tested using Schoenfeld residuals and log-log survival plots. In addition, a supplemental analysis is conducted using an accelerated failure time (AFT) model with a Weibull distribution to estimate restricted mean survival time (RMST) at fixed time point of two years.

Nonrandom censoring: If patients who are censored are systematically different in terms of their pneumonia risk (e.g., inadequate treatment response, higher initiation rate of rescue medications, comorbidities), this could bias the estimated treatment effect. We examine the impact if varying the assumption about the censoring-at-random condition by implementing inverse probability of censoring weighting (IPCW). IPCW estimates the probability of remaining uncensored over time conditional on both baseline and time-varying covariates. These probabilities are then used to reweight individuals in the outcome model, thereby creating a pseudo-population where censoring is independent of the outcome, conditional on the included covariates. In addition, a tipping point sensitivity analysis is conducted to assess how strong the association between censoring and outcome would need to be to change the study's conclusions.

Data Source Heterogeneity: Finnish data and CPRD differ in healthcare systems, coding practices, and linkage availability, which may introduce heterogeneity in effect estimates. Analyses will be performed separately within each data source using harmonized definitions under the Conception CDM framework.

Missing covariate data: Topic-specific limitations include the lack of information on asthma severity. Therefore, we cannot adjust for e.g. FEV_1, eosinophil counts and symptom severity. We use comorbidity- and prescription-based proxies for these. In addition, information on household-level potential pneumonia risk factors is missing, but it is unlikely these confounders would be affecting the treatment choice.

9. Protection of human subjects

This is a non-interventional study using secondary data collection and does not pose any risks for individuals. Each data source research partner will apply for an independent ethics committee review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants. Patient information This study involves data that exists in an anonymized structured format and contains no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Patient personal data will be

stored at DAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access. DAPs will implement appropriate technical and organisational measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, DAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

10. Reporting of adverse events

Not applicable. EU legislation states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health records, it may not be feasible to make a causality assessment at the individual case level. Further, according to the International Society for Pharmacoepidemiology Guidelines for GPP. “Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines.” For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health records, systematic reviews, or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarized in the study report, where applicable. According to the EMA Guideline on GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, “All adverse events/reactions collected as part of [non-interventional postauthorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of [individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report.” Module VIII – Post-Authorization Safety Studies echoes this approach.

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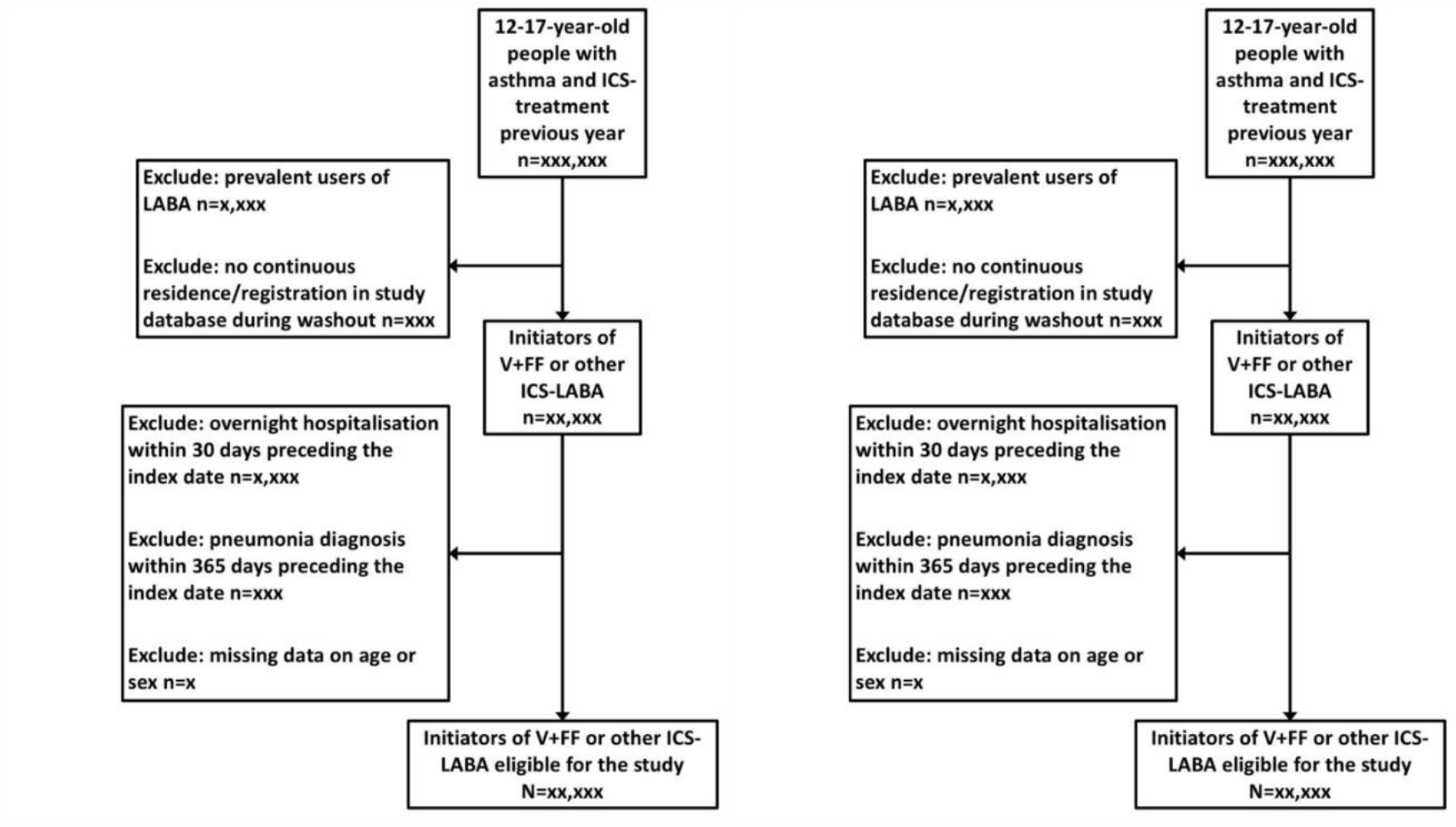
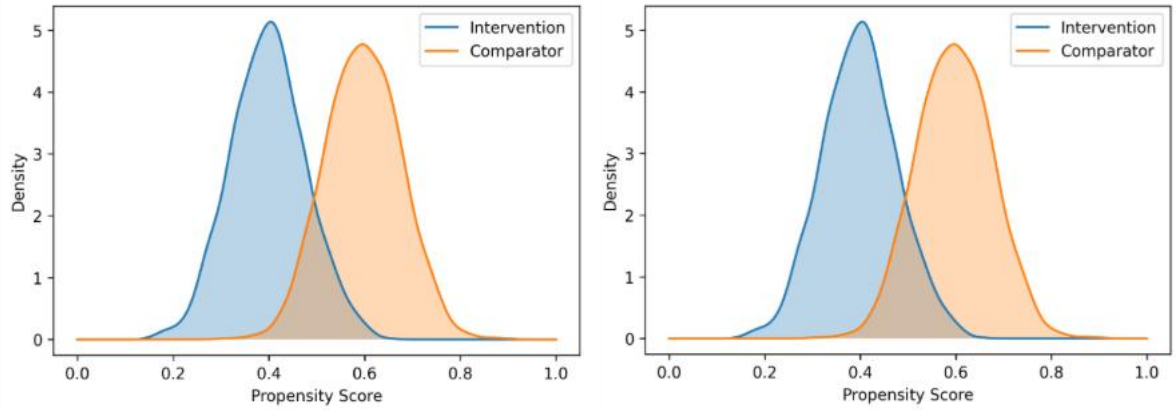
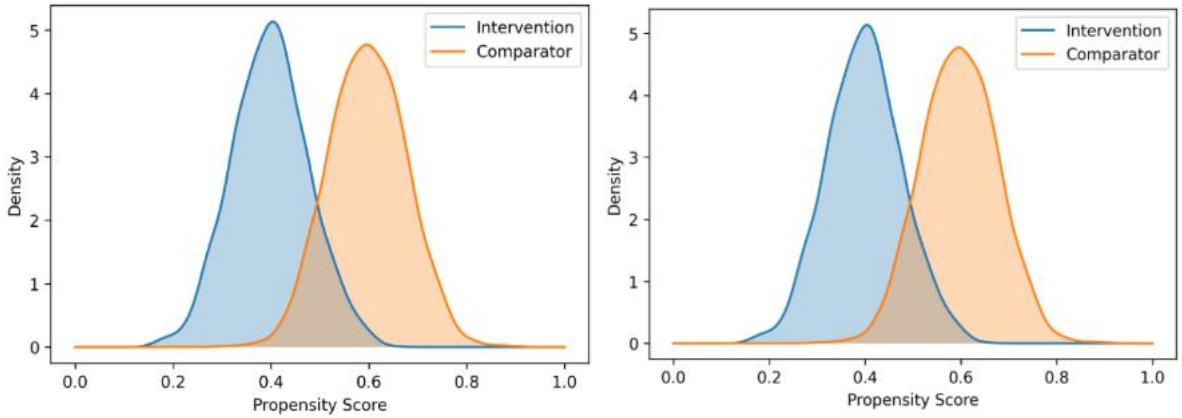


Figure 1 Flowcharts of participant exclusion in Finnish registers and UK Clinical Practice Research Datalink.

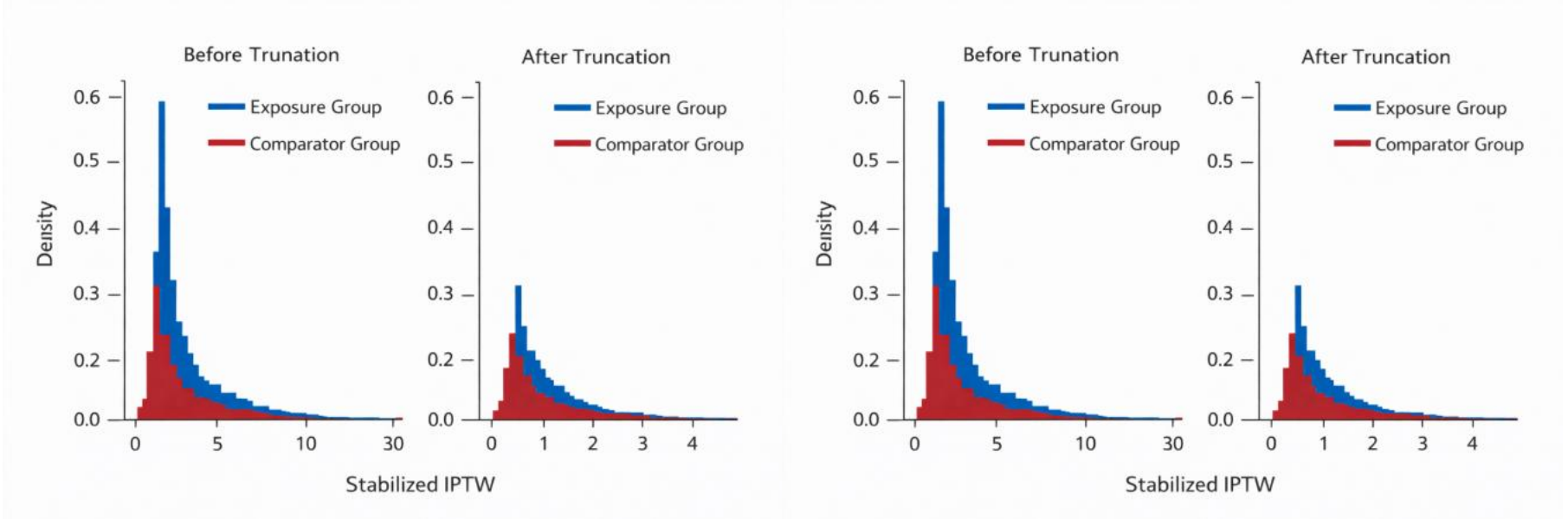
Before Truncation



After Truncation



Supplementary Figure 1. Distribution and overlap of propensity scores by treatment group, intervention V+FF, comparator= other single-device ICS+LABA before propensity score truncation in a) Finland b) UK CPRD and after truncation in c) Finland and d) UK CPRD.



Supplementary Figure 2. Density of stabilised IPT weights before and after 1% and 99% truncation by treatment group (intervention V+FF, comparator= other single-device ICS+LABA) in a) Finland b) UK CPRD.

Table 1. Standardised mean differences for baseline covariates before and after weighting (stabilized IPT weights with 1% and 99% truncation)

	Before weighting			**After weighting**		
Characteristic	V+FF (n =)	Other ICS+ LABA (n =)	aSD	V+FF (n =)	Other ICS+ LABA (n =)	aSD
Demographics						
Age at index, median (IQR)						
Sex, n (%)						
Women/Girls						
Men/Boys						
Other						
Season, n(%)						
winter						
spring						
summer						
autumn						
Comorbidities, n(%)						
Diabetes						
Rheumatological diseases						
Malignancies						
Cardiovascular diseases						

Intellectual disability						
Congenital malformations						
Psychotropic drugs						
Asthma exacerbations						
Healthcare use during washout, median (IQR)						
n of hospital days						
n of outpatient visits						
Medication use during washout, n (%)						
Oral corticosteroids						
Biologicals						
SABA						
SAMA						
Leukotriene receptor antagonists						
Antibiotic use						
Pneumococcal vaccination						
Influenza vaccination						
Inhaled corticosteroid dose (median, IQR)						

Table 2. Crude and IPT-weighed hazard ratios for time to first pneumonia in adolescent asthma patients initiating with vilanterol-fluticasone furoate single device combination treatment compared with initiators of other single device inhaled corticosteroid- long-acting beta agonist (ICS+LABA) combination treatments.

	No. of persons	No. of pneumonia events	Person-years of follow-up	Pneumonia rate (100 person-years), 95% CI)	Unadjusted HR, 95% CI	IPT-weighted HR, 95% CI*
Finland						
Comparison (other ICS+LABA)	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	1.00 (reference	1.00 (reference
Vilanterol-fluticasone furoate	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
UK CPRD						
Comparison (other ICS+LABA)	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	1.00 (reference	1.00 (reference
Vilanterol-fluticasone furoate	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
Combined Finland and UK CPRD						
Comparison (other ICS+LABA)	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	1.00 (reference	1.00 (reference
Vilanterol-fluticasone furoate	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx

*stabilised weights with 1% truncation, covariates include *list of final covariates*

Table 3. Comparison of hazard ratios and 95% Cis from main analysis and sensitivity analyses accounting for nonrandom censoring by IPC-weighting and "best" and "worst case" scenarios, sensitivity analyses for nondifferential exposure misclassification by QBA.

	main estimand IPT-weighted*	Sensitivity analysis 1a: IPT- and IPC-weighted**	Tipping point scenario 1	Tipping point scenario 2	Tipping point scenario 3	Tipping point scenario 4	Sensitivity analysis 2: nondifferential exposure misclassification, IPT-weighted*
Finland							
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference
Vilanterol-fluticasone furoate	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
UK CPRD							
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference
Vilanterol-fluticasone furoate	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
Combined Finland and UK CPRD							
Comparison (other ICS+LABA)	1.00 (reference)	1.00 (reference	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference
Vilanterol-fluticasone furoate	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx

*stabilised weights with 1% truncation, covariates include *list of final covariates*

** weighted for baseline *list of final covariates* and time varying *list of final covariates* covariates

Table 4. Difference in restricted mean survival time (RMST) at two-year follow-up for incident pneumonia in adolescent asthma patients initiating with vilanterol-fluticasone furoate single device combination treatment compared with initiators of other single device inhaled corticosteroid- long acting beta agonist (ICS+LABA) combination treatments.

	RMST (years)	Difference in RMST, 95% CI unadjusted	Difference in RMST, 95% CI IPT-weighted*	IPT- and IPC-weighted difference in RMST, 95% CI**
Finland				
Comparison (other ICS+LABA)	x.xx			
Vilanterol-fluticasone furoate	x.xx	x x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
UK CPRD				
Comparison (other ICS+LABA)	x.xx			
Vilanterol-fluticasone furoate	x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx
Combined Finland and UK CPRD				
Comparison (other ICS+LABA)	x.xx			
Vilanterol-fluticasone furoate	x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx

*stabilised weights with 1% truncation, covariates include *list of final covariates*

** weighted for baseline *list of final covariates* and time varying *list of final covariates* covariates

Supplementary Table 1. Follow-up time, intercurrent events, and reasons for censoring by treatment group (dapagliflozin vs DPP-4 inhibitors) for primary estimand in Finnish registers and UK CPRD

	V+FF		ICS+LABA	
	N (%)	Median time to censoring event (IQR, min, max)	N (%)	Median time to censoring event (IQR, min, max)
FINLAND				
Person-months of follow-up				
Median (IQR)				
Min, max				
Reasons for Censoring				
Treatment discontinuation				
Death				
Disenrollment or migration				
Pneumonia				
End of data instance				
UK CPRD				
Person-months of follow-up				
Median (IQR)				
Min, max				
Reasons for Censoring				
Treatment discontinuation				

Death				
Disenrollment or migration				
Pneumonia				
End of data instance				

Supplementary Table 2. Crude and IPT-weighed hazard ratios for time to first pneumonia in adolescent asthma patients initiating with vilanterol-fluticasone furoate single device combination treatment compared with initiators of other single device inhaled corticosteroid- long acting beta agonist (ICS+LABA) combination treatments in Finland. Pneumonia is ascertained from causes of death register in addition to primary and secondary healthcare registers.

	No. of persons	No. of pneumonia events	Person-years of follow-up	Pneumonia rate (100 person-years), 95% CI)	Unadjusted HR, 95% CI	IPT-weighted HR, 95% CI*	IPT- and IPC-weighted HR, 95%CI**
Finland							
Comparison (other ICS+LABA)	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	1.00 (reference)	1.00 (reference)	1.00 (reference)
Vilanterol-fluticasone furoate	xxxxx	xxx	xxxxxx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx	x.xx, x.xx-x.xx

*stabilised weights with 1% truncation, covariates include *list of final covariates*

** weighted for baseline *list of final covariates* and time varying *list of final covariates* covariates

Appendices

Appendix 1. Codelists

Appendix 2. Hypothetical Target Trial Protocol

Appendix 1. Codelists

This document provides access to the Zenodo entry for the **Case Study 5** with title *"TARGET-EU: Comparison of single-device vilanterol/fluticasone furoate with other single-device inhaled corticosteroid and long-acting beta agonist combinations in the risk of pneumonia in adolescents with asthma"* (EUPAS1000000989).

Metadata related to this case study, including the corresponding code lists, can be accessed through Zenodo: CS5_Codelist.

EMA/2020/46/TDA/19
Specific Contract 01

Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks (TARGET-EU)

Hypothetical Target Trial Protocol WP3
EU PE&PV research network

Case Study 5:
Comparison of single-device vilanterol/fluticasone furoate with other single-device inhaled corticosteroid and long-acting beta agonist combinations in the risk of pneumonia in adolescents with asthma

WP 3 Leads: Prof. Olaf Klungel & Prof. Ian Douglas
Case study Lead(s): Prof. Anna-Maija Tolppanen and Prof. Lies Lahousse

1. PROTOCOL SUMMARY

1.1 Protocol Synopsis

Primary and secondary objectives and endpoints

The primary objective is to assess whether vilanterol-fluticasone furoate increases the risk of pneumonia compared to other fixed dose combination single-device inhaled corticosteroid and long-acting β2-agonist (ICS+LABA) combination treatments in adolescent asthma patients.

Overall Design

Intervention model: Parallel group, active comparator, safety trial	Trial intervention assignment method: Parallel group 1:1 randomisation.
Trial Intervention: single-device vilanterol fluticasone furoate combination (V+FF)	Population Type: adolescent patients
Control Type: single-device active comparator	Population Diagnosis or Condition: asthma
Active comparator: other ICS+LABA combination single-device treatment	Population age: 12-17 at randomisation

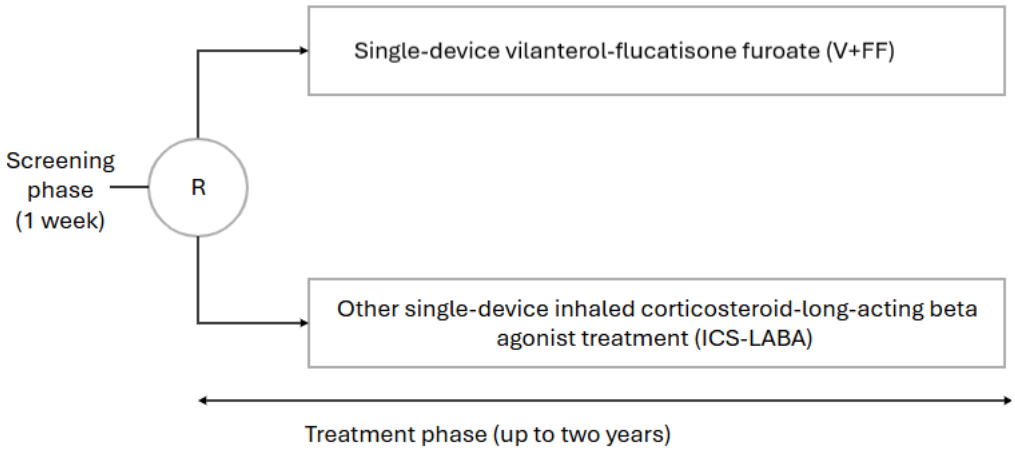
Number of arms: 2

Blinding: open label

Number of participants: 109,808 patients (i.e., 54,904 per arm)

Arms and duration: 1:1 randomisation is used. Patients are followed up to a maximum of two years after the randomisation day.

1.2 Trial Schema



2. INTRODUCTION

2.1 Purpose of the trial

V+FF combination is approved for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (LABA and ICS) is appropriate, i.e., if adequate symptom control is not achieved with ICS and SABA, or adequate control is achieved with ICS+LABA combination.

In a meta-analysis of 7034 patients from 11 trials in asthma patients, the incidence of pneumonia in V+FF (25/100µg) was 9.6/1000 person-years, compared to 8.0/1000 person-years in placebo-treated patients. Incidence of pneumonia was higher, 18.4/1000 patients, with higher fluticasone furoate dose (V+FF 25/200µg). Most of the pneumonia events were managed in outpatient settings, and no risk factors increasing the risk of pneumonia were identified in studies with asthma.[1] These trials included adults and adolescents and there were no specific estimations on whether pneumonia risk is increased in vilanterol+ICS combination treatment specifically in adolescent asthma. There are also no previous comparisons of V+FF and other ICS+LABA combinations in this population.

3. TRIAL OBJECTIVES, ENDPOINTS, ESTIMANDS

3.1 Main Objective of the Trial

The main objective of the trial is to assess whether vilanterol+fluticasone increases the risk of pneumonia compared to other single-device ICS+LABA combinations in adolescent asthma patients.

3.2 Primary Endpoint

The primary endpoint is the time to first pneumonia occurrence during follow-up.

Table 1. Estimand Table

	Estimand 1 ***(Primary estimand)***	**Estimand 2** ***(Supplementary estimand)***
Population	Adolescent patients with asthma	Adolescent patients with asthma
Treatment Conditions	Intervention: Vilanterol/fluticasone furoate	Intervention: Vilanterol/fluticasone furoate

	Estimand 1 ***(Primary estimand)***	**Estimand 2** ***(Supplementary estimand)***
	Control: other ICS + LABA (not Vilanterol/fluticasone furoate)	Control: other ICS + LABA (not Vilanterol/fluticasone furoate)
Endpoint	Time to first occurrence of pneumonia	Time to first occurrence of pneumonia
Summary Measure	Hazard ratio	Difference in Restricted Mean Survival Time
Intercurrent events and strategies to handle them*	Same for both treatment conditions Treatment Discontinuation: while on treatment Add-on/rescue medications (such as SABA, leukotriene receptor antagonists, biologicals, LAMA (as a single or component of triple therapy if the ICS+LABA components consistent with original assignment) and oral corticosteroids: treatment policy Non-pneumonia death: while alive	Same for both treatment conditions Treatment Discontinuation: while on treatment Add-on/rescue medications (such as SABA, leukotriene receptor antagonists, biologicals, LAMA (as a single or component of triple therapy if the ICS+LABA components consistent with original assignment) and oral corticosteroids: treatment policy Non-pneumonia death: while alive

3.3 Rationale for why selected strategies to handle intercurrent events are chosen

The intercurrent events of interest are the truncating event of death due to other cause than pneumonia and the following treatment-modifying events i) treatment discontinuation or ii) initiation of rescue or add-on medications. For non-pneumonia death, we use the while-alive strategy. For treatment discontinuation, we use while on treatment strategy to allow the estimation of biological effects under treatment adherence. For add-on/rescue medications, we use treatment policy (necessity of these medications is part of the treatment condition).

3.4 Research question targeted by the estimand

Estimand 1: What is the hazard ratio of pneumonia for initiating vilanterol/fluticasone furoate combination compared to other ICS+LABA combinations in adolescent asthma patients while the patients remain alive and adherent to the assigned treatment.

Estimand 2: What is the difference in restricted mean survival time for pneumonia between vilanterol/fluticasone furoate combination and other ICS+LABA combinations in adolescent asthma patients while the patients remain alive and adherent to the assigned treatment.

4. TRIAL DESIGN

4.1 Description of trial design

This is a pragmatic, randomised, open-label trial in adolescent asthma patients whose asthma is no longer adequately controlled with inhaled ICS and SABA and initiation of LABA is required.

Description of the Intervention Model

We will perform a parallel group trial with an active comparator, expecting to recruit 13,375 patients for the V+FF arm and 13,375 for the comparator arm which contains other single-device ICS+LABA combination treatments.

Patients will be randomised to either V+FF or another ICS+LABA combination and will start their assigned treatment immediately after randomisation.

Patients will receive their assigned treatments during the entire follow-up, and they will be followed up to a maximum of two years.

Description of Trial Duration

The overall duration for an individual patient in the trial is expected to be a maximum of two years of follow-up after randomisation.

Description of Method of Assignment to Trial Intervention

Simple 1:1 randomisation will be used to assign the trial intervention. Randomisation occurs at the moment when all inclusion criteria for the study have been met (and no exclusion criteria present).

4.2 Rationale for trial design

Rationale for intervention model

The parallel group design was chosen because we want to compare the risk of pneumonia between V+FF initiators to that of other ICS+LABA combinations in patients who need to initiate LABA for sufficient symptom control. With this contrast we can evaluate whether treatment with V+FF pertains a larger

pneumonia risk in adolescent asthma population compared to other single-device ICS+LABA combination treatments. The comparator group is restricted to single-inhaler treatments to ensure comparable adherence between the treatment arms.

Rationale for duration

The investigated medications are intended for long-term period of use as asthma is a chronic condition. However, significant changes in asthma severity and symptoms occur in puberty, and almost half of severe asthma cases were resolved during a three-year follow-up in a cohort of adolescent asthma patients, [2] which supports the restriction of trial duration to two years. The sample size calculation with a duration of 2 years suggest that the duration is sufficient for capturing pneumonia.

Rationale for Endpoints

Pneumonia is a severe infection, and its impact on patients with asthma can be particularly harmful due to underlying conditions. Pneumonia also increases the risk of asthma exacerbations, also in the younger population. ICS increase the risk of pneumonia also in adolescents. Pneumonia has been included in the pre-specified adverse events in asthma RCTs [3], but there are no specific estimates on pneumonia risk in the adolescent population.

Rationale for comparator

The comparison treatment was chosen based on Global Initiative for Asthma 2023 personalised management recommendations for adults and adolescents track 2, which recommends initiation of low-dose maintenance ICS+LABA if adequate symptom control is not achieved with ICS and SABA. The comparison of V+FF to other ICS+LABA combinations allows the assessment of possible excess risk of pneumonia associated with V+FF. This comparison is also justified from the disease severity point of view.

4.3 Start and End of Trial

Start of trial will be enrolment of first patient meeting eligibility criteria after the eligibility screening period. The end of trial will be two years after final patient is randomised.

5. TRIAL POPULATION

5.1 Inclusion Criteria

To be eligible for trial participation, an individual must meet all the following:

1. age 12-17 years at randomisation

2. Documented clinical history of asthma
3. step-up to ICS+LABA combination necessary because asthma symptoms not adequately controlled with current ICS-treatment

Exclusion Criteria

1. previous pneumonia diagnosis within one year prior to randomisation.
2. LABA treatment within one year prior to randomisation.
3. hospitalisation within 30 days prior to randomisation.

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of trial intervention

Both the intervention (V+FF) and comparison treatment are administered with a single inhaler. The duration of treatment will be up to two years, the maximum follow-up time justified by the restriction of study to treatment of adolescent asthma.

The control treatments include any of the following fixed dose, single device ICS+LABA combinations:

- formoterol and budesonide
- formoterol and beclomethasone
- formoterol and mometasone
- formoterol and fluticasone
- salmeterol and budesonide
- salmeterol and fluticasone propionate
- indacaterol and mometasone

Switch from the originally assigned single-device treatment to another in the control group (e.g. from formoterol and budesonide to formoterol and fluticasone) are considered as treatment discontinuations. Dose adjustments during the trial are permitted at the discretion of the treating physician.

6.2 Participant Assignment

Participant assignment to the intervention or the control arm will be done by simple 1:1 randomisation. Randomisation occurs once all inclusion criteria have been met (without the presence of any exclusion criteria).

6.3 Concomitant Therapies

Allowed: Add-on/rescue medications (such as SABA, leukotriene receptor antagonists, biologicals, LAMA (as a single or component of triple therapy if the ICS+LABA components consistent with original assignment) and oral corticosteroids.

Prohibited: switch to another ICS+LABA combination (both arms)

7. DISCONTINUATION OF TRIAL INTERVENTION AND LOSS TO FU

7.1 Discontinuation of trial intervention

- Possible reasons for discontinuation: adverse event or intolerable adverse effects, lack of treatment response.
- Patients are allowed to discontinue from the randomised treatment at any time.

7.2 Withdrawal from the study

Patients are at any time free to withdraw their informed consent and stop participation in the study.

7.3 Loss to Follow-up

A patient will be classified as lost to follow-up only if he/she has failed to return for the required study visits and his/her health condition and vital status remains unknown despite multiple attempts to contact him/her.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis Set:

Estimand 1 & 2

- Exclude data after the occurrence of treatment modifying intercurrent events: treatment discontinuation
- Include data before death

8.2 Analyses

Analyses supporting Estimand 1

Statistical Model, and method of analysis

- Cox Proportional Hazards model:
  - Endpoint: time from randomisation to occurrence of pneumonia
  - Censoring: loss to follow-up (non-administrative censoring), treatment-modifying intercurrent events (administrative censoring of switch to another ICS+LABA combination), non-pneumonia death (administrative censoring), study end without pneumonia (administrative censoring)
  - Covariates: Treatment group (V+FF vs other ICS+LABA)

- Data after treatment discontinuation will not be included in the analysis.

Assumptions & diagnostics

- Proportional hazards
  Schoenfeld residuals and log(-log) plots
- Non-informative censoring

  Assessment of censoring patterns for contextual information
- Correct specification of the model (functional form and covariates)
  Assess model diagnostics

Reporting

– Tables summarising event risks (event counts), incidence rates (e.g. per 100 person-years or 1000 person-years)
  - Hazard ratios (HR) with 95% Confidence Intervals
  - Report HR (and 95% CI) for each year of follow-up
  - Descriptive Kaplan-Meier curves for time-to-pneumonia in each treatment arm.

Analyses supporting Estimand 2

Statistical Model, and method of analysis

- *Accelerated failure time model with Weibull distribution*
  - Endpoint: time from randomisation to occurrence of first pneumonia
  - Censoring:
    - loss to follow-up (non-administrative censoring),
    - treatment-modifying intercurrent events (administrative censoring),
    - non-pneumonia death (administrative censoring),
    - study end without pneumonia (administrative censoring)
  - Covariates: Treatment group (V+FF vs other ICS+LABA)

Assumptions

- Survival times follow Weibull distribution

    - Diagnostic: Plot log(-log(S(t))) vs log(t): should be linear if Weibull holds.
- Censoring is non-informative
    - To provide contextual information: compare baseline characteristics of censored vs uncensored individuals.
- Log linear relationship between covariates and log linear survival time
    - Diagnostic: Q-Q plot of residuals normally distributed

Reporting

- Mean (95% CI) pneumonia free time in V+FF group and mean (95% CI) pneumonia free time in ICS+LABA group over all
    - two years of follow up (restricted mean survival time)

8.3 Handling of intercurrent events

Primary estimand

- Treatment discontinuation: censor participant, follow-up ceases
- Non-pneumonia death: censor participant, follow-up ceases

8.4 Handling of Missing Data

- Censored time to event data (handled by the model, contributes partial information)
    - Implicitly assumes censoring occurs at random

8.5 Sensitivity analyses

Sensitivity analysis under the CNAR assumption and Kaplan-Meier–based restricted mean survival time will be carried out.

8.6 Supplemental analysis

HR with 95% Confidence Intervals for each of the two consecutive years.

8.7 Sample size determination

A total of 26,750 subjects (13,375 per group) would be needed for a 2-year study with 1% loss to follow-up, to detect a hazard rate difference of 0.0027 (control group hazard 0.0108, experimental group hazard 0.0135) with 80% power at a 5% significance level, using a conditional test for hazard differences under an exponential survival model.

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