NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Incidence of selected adverse events in a population-based Danish cohort with atopic dermatitis treated with conventional systemic therapies: a matched case-cohort study.
Protocol number	B3211007
Protocol version identifier	1.0
Date	04 November 2025
EU Post Authorization Study (PAS) register number	1000000628
Active substance	Methotrexate L01BA01 / L04AX03
Medicinal product	Methotrexate [redacted]
Research question and objectives	Research questions to be addressed by this study are as follows: What is the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population? What are the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population? What is the identified incident rates of above adverse events compared to the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies?

	Primary Objective: The primary objective is to quantify the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population. Secondary Objective: The secondary objective is to quantify the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections,) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population. Tertiary Objective The tertiary objective is to compare the above identified incident rates of adverse events per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population with the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies (see section 9.7).
Country(ies) of study	Denmark
Author	[redacted]

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Atopic Dermatitis
AT	Arterial Thromboembolisms
ATC	Anatomical Therapeutical Chemical
CABG	Coronary Artery Bypass Grafting
CPR	Civil Personal Register (unique Danish personal ID number)
CNS	Central Nervous System
CV	Cardiovascular
DVT	Deep Vein Thrombosis
DNPR	Danish National Patient Registry
DMARDs	Disease-Modifying Antirheumatic Drugs
EC	Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HMA	Heads of Medicines Agencies
ICD	International Classification of Diseases
IQR	Interquartile Range
IR	Incidence Rate
IRB	Institutional Review Board
ITT	Intention-To-Treat

JAKi	Janus Kinase Inhibitors
MACE	Major Adverse Cardiovascular Events
NCSP	Nordic Medico-Statistical Committee Classification of Surgical Procedures
NMSC	Non-Melanoma Skin Cancer
PAS	Post Authorization Study
PCI	Percutaneous Coronary Intervention
PE	Pulmonary Embolism
PH	Proportional Hazards
PS	Propensity Score
PSO	Psoriasis
RA	Rheumatoid Arthritis
RWD	Real World Data
SAS	Statistical Analysis System
SD	Standard Deviation
SKS	Danish Classification of Health Care Procedures (Sundhedsvæsenets Klassifikations System)
SOP	Standard Operating Procedure
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VTE	Venous Thromboembolism

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3. ABSTRACT

Title: Incidence of selected adverse events in a population-based Danish cohort with atopic dermatitis treated with conventional systemic therapies: a matched case-cohort study.
Version 1.0, 04-NOV-2025, [redacted]

Rationale and Background: Conventional systemic treatments are commonly used as first-line immunosuppressive therapy for AD in Denmark, despite being prescribed off-label and lacking AD-specific safety data. Existing safety data on conventional treatments are largely derived from other conditions such as rheumatoid arthritis or psoriasis. Therefore, generating safety data specific to AD is needed to close the data gap.

Research question and objectives:
What is the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population?

What are the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population?

What is the identified incident rates of above adverse events compared to the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies?

PRIMARY OBJECTIVE:
The primary objective is to quantify the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population.

SECONDARY OBJECTIVE:
The secondary objective is to quantify the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections,) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population.

TERTIARY OBJECTIVE

The tertiary objective is to compare the above identified incident rates of adverse events per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis

(AD) patient population with the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies (see section 9.7).

Study Design: This is a retrospective observational cohort register study.

Population: Patients with AD verified by a dermatologist and a background population

Variables: Variables include diagnosis for AD (and relevant diagnosis to be excluded), treatment for AD, i.e. conventional systemic therapies (exposures) and advanced therapies (exclusion criteria), outcomes, i.e. adverse events of special interest, including MACE, malignancies (excluding and including non-melanoma skin cancer), serious infections, venous thromboembolism (deep vein thrombosis and pulmonary embolism), dyslipidemia, and herpes zoster, and medical history (key covariates), i.e. alcohol abuse, cardiovascular disease (including heart failure and coronary heart disease), diabetes, dyslipidemia, prior cancer, hypertension, and smoking status.

Data source: The Danish National Registries including the Danish National Patient Registry, the Danish Register of Medicinal Product Statistics, the National Cause of Death Registry, and the National Population Registry.

Study size: All patients meeting the inclusion criteria will be included for the current data analysis. Since this is a descriptive, retrospective study, no sample-size calculation is performed.

Data analysis: Descriptive statistics will summarize patient characteristics using frequencies for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables.

Incidence rates of outcomes will be reported per 10,000 person-years with 95% confidence intervals.

The groups will be compared using a Cox-regression models. The proportionality assumptions will be tested using Schoefeld test and plots. If the PH assumption is violated, we will allow time-varying effects by including covariate×log(time) interactions or using time-split intervals. Use of competing-risk models will be employed where relevant and feasible. The statistical analysis will be captured in a statistical report with aggregated data in tables. In the primary analyses, overlapping events will be attributed to the drug to which the patient has been exposed for the longest duration.

P-values may be reported when relevant for descriptive purposes and will not be adjusted for multiple testing; they are presented as descriptive statistics only, and no hypotheses are being tested.

A sensitivity analysis will be conducted requiring only one use of a drug to fulfil the inclusion criteria.

To evaluate the robustness of the method applied to handle overlapping events in the primary analysis, multiple sensitivity analyses will be performed, in which overlapping events will alternatively be assigned to (a) the most recently administered drug, (b) attributed to both drugs, or (c) excluded by censoring the patient at the time of the event. These results will be presented separately.

Furthermore, a sensitivity analyses will be conducted reporting incidence rates for the years 1995-2001, 2002-2008, 2009-2015, and 2016-2022.

As a sensitivity analyses, a cox regression model with inverse Probability Treatment Weighting will be conducted.

Milestones:

Start of data collection: 07 November 2025

End of data collection: 30 November 2025

Registration in the HMA-EMA Catalogues of RWD studies: 06 November 2025

Final study report: 31 December 2025

4. AMENDMENTS AND UPDATES

None

5. MILESTONES

Milestone	Planned Date
Start of data collection	07 November 2025
End of data collection	30 November 2025
Registration in the HMA-EMA Catalogues of RWD studies	06 November 2025
Final study report.	31 December 2025

6. RATIONALE AND BACKGROUND

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer. This study is not a commitment or requirement to any regulatory authority.

Conventional systemic treatments are the first step when initiating systemic immune suppression therapies for atopic dermatitis in Denmark. Although these therapies have been used for many years, they are prescribed off-label, resulting in a lack of published safety data in an AD population. In contrast, there is ample data on the safety of advanced therapies such as biologics and JAKis. Most published safety data on conventional systemic therapies instead come from other conditions including but not limited to RA or PSO. Hence, these therapies might exhibit a significantly different safety profile in AD patients compared to other patient populations. A literature search was conducted on September 16th, 2025 in Embase <1974 to 2025 September 12>, Ovid MEDLINE(R) ALL <1946 to September 15, 2025> for patients with M2S AD treated with conventional systemic treatments found a few reports of small case studies, while a search for studies including a similar amount of patients as in the proposed study (>5000 patients) did not detect any study. Obtaining safety data on the conventional systemic therapies is therefore essential for the treating healthcare professional to make an informed decision on choice of treatment. Obtaining safety data on the conventional systemic therapies is therefore essential for the treating healthcare professional to make an informed decision on choice of treatment.

The current protocol is designated as a PASS per CT34-POL Post-Authorization Safety Studies (PASS) for Methotrexat® "Lederle", that is approved for use for active rheumatoid arthritis in adult patients, for polyarthritic forms of severe, active juvenile idiopathic arthritis (JIA) when the response to non-steroidal anti-inflammatory drugs (NSAIDs) was inadequate, and for severe, refractory, disabling psoriasis that does not respond adequately to other forms of therapy such as phototherapy, PUVA therapy and retinoids, as well as severe psoriatic arthritis in adult patients, but not for AD. Regarding the safety profile of Lederle, the most common adverse events (≥1/100, <1/10) are loss of appetite, nausea, vomiting, abdominal pain, inflammation and ulceration of the mucosa of mouth and throat, stomatitis, dyspepsia, and increase in liver-related enzymes (ALAT [GPT], ASAT [GOT], alkaline phosphatase and bilirubin).

7. RESEARCH QUESTION AND OBJECTIVES

Research questions to be addressed by this study are as follows:

What is the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population?

What are the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population?

What is the identified incident rates of above adverse events compared to the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies?

Primary Objective:
The primary objective is to quantify the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population.

Secondary Objective:
The secondary objective is to quantify the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections,) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population.

Tertiary Objective

The tertiary objective is to compare the above identified incident rates of adverse events per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population with the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies (see section 9.7).

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective register study employing a matched cohort design. This study design was selected to reflect real world usage by utilizing the high-quality registries in Denmark with detailed information on patients with AD[20]. This allows for retrospective analysis of a large number of patients and gives the possibility for comparing with cohort matched control groups (see details below and in section 9.2): the database includes information about close to 13.000 adult patients with a hospital diagnosis of AD[12]. In addition, the database contains information about the general adult population estimated to 4.2 million in 2019[21]. Hence a retrospective study design is more feasible than a prospective design. By matching adult AD patients on conventional systemic therapy with two comparator cohorts – the general Danish population and dermatologist-verified AD patients not receiving systemic treatment – the study contextualizes adverse event rates and isolates the treatment's effect. The general population cohort provides background incidence rates, and the untreated AD cohort helps distinguish the baseline risk from AD itself versus any additional risk due to systemic therapy. Matching on key factors (e.g., age, sex, and cardiovascular risk factors) further enhances methodological rigor by reducing confounding, making the safety outcome comparisons more reliable and clinically meaningful[26].

Patients with a diagnosis of AD (Table I) are included using the inclusion and exclusion criteria specified in 9.2. AD patients will be matched with individuals from the general population and patients with AD not treated with a systemic to enable relevant comparisons to further investigate safety data in the AD population.

Primary endpoints

- Reporting of incidence rates for a composite endpoint of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)

Secondary endpoints

Reporting of detailed event-by-event incidence rates

- All-cause mortality
- Arterial thromboembolisms
- Venous thromboembolisms
- Dyslipidemia
- Herpes zoster
- NMSC
- Serious infections
- MACE [primary]
- Malignancies (excl. NMSC) [primary]

Tertiary Endpoints

- Comparison of the identified adverse events per individual conventional treatment (table II) with the following two matched groups:
    - a cohort-matched general Danish population
    - a cohort-matched patients with AD not receiving systemic treatment (Patients may only be included in one of the study groups).

8.2. Setting

Persons and place:
The Danish health-care system is public and tax funded. It offers equal access to health services throughout the primary, secondary, and tertiary sector. At birth or upon immigration, all Danish residents receive a unique personal identification number. An anonymized identifier based on this number is used across national databases, allowing for accurate linkage of patient data. The linked data can then be accessed via Statistics Denmark where anonymized grouped data can be requested.

Representativeness:
Statistic Denmark is comprised of data from the entire country. The database includes information about patients with a hospital diagnosis of AD. This number has recently been estimated to be close to 13.000 adult patients[12].
The aim of this study is to investigate a) the incident rate of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population, b) the incident rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections) per individual conventional systemic treatment in a dermatologist-verified adult atopic dermatitis (AD) patient population and c) compare the identified incident rates of above adverse events to the following two matched cohorts: The Danish background population AND Patients diagnosed with AD not receiving systemic therapies.

Only patients with moderate to severe AD are in scope of the conventional systemic treatments. Hence the cohort of interest will be representative of the moderate to severe AD patients diagnosed in hospital setting by dermatologists and who are candidates to receive conventional systemic treatment. For the comparison groups consisting of AD patients not receiving conventional systemic therapy, this group will be representative of patients diagnosed in hospital setting by dermatologists and who have not received conventional systemic treatment. The comparison group consisting of the Danish background population will be representative of the Danish adult population without AD diagnosed in hospital setting by dermatologists.

This will be specific for AEs that occur more frequently than one in 13.000 patients. A cohort of approximately 13,000 adult patients with atopic dermatitis is expected to be sufficient for evaluating major adverse cardiovascular events (MACE) in this non-interventional safety study. Danish registry-based studies[27, 28] have demonstrated that cohorts of similar or smaller size can detect meaningful differences in MACE incidence, especially among patients receiving systemic therapies. With expected MACE rates around 1.5% annually in AD populations, this sample size should yield over 100 events per year, enabling robust risk estimation and subgroup comparisons. This aligns with epidemiological evidence and supports the adequacy of the proposed study population for assessing cardiovascular safety.

Inclusion and exclusion criteria rationale:
The aim of this study is to investigate specific adverse events following treatment with conventional systemic therapies (see section 8). The inclusion and exclusion criteria (see section 9.2.1 for details) have been designed to ensure the highest likelihood that any observed adverse events can be attributed to treatment with a conventional systemic therapy aimed at treating AD.

Inclusion criteria rationale:
The objective is to increase the probability that the included patients have an accurate diagnosis (criteria 2) and are actively filling their prescriptions (criteria 3); this strategy may create a more selective cohort but seeks to ensure superior data quality.

Exclusion criteria rationale:
The aim is to ensure that the adverse events registered cannot be attributed to any current or previous cases of cancer (criteria 1), other treatments (criteria 2 and 3), or other inflammatory diseases and their treatments (criteria 4). Additionally, it ensures that systemic treatments are administered specifically for AD and not for any other condition (criteria 4).

Given the high number of AD patients in the registry combined with previous experience each treatment group it is expected to comprise around 1000 patients for the majority of treatments.

Time period
The study period runs from January 1st, 1995, through December 31st, 2022. In the main analyses, patients are included if they have been diagnosed with AD by a dermatologist in a hospital setting and received the same conventional systemic therapy twice (Table II).

Cohort entry (index date) for exposed:
1) Date of initiation of the second administration/filled prescription of the conventional systemic therapy for AD,
2) Last inclusion date is December 31st, 2021, to allow for a minimum of one year of follow-up.

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Age ≥18 years at prescription/administration of conventional systemic therapy
2. An ICD-10 diagnostic code for AD provided by a dermatologist (Table I)
3. Have filled/administered the same conventional therapy twice (Table II)

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Current or previous cancer prior to inclusion (except NMSC) (Table III)
2. History of biological therapy prior to inclusion (Table II)
3. History of JAK inhibitor prior to inclusion (Table II)
4. History of prespecified diseases that could be treated with the conventional drugs of interest i.e., RA, IBD, PsA, and PsO (Table I)

8.3. Variables

Table I. Diagnoses of diseases

Variable (Disease)	**Role**	**Data Source**	**Operational Definition** (AD ICD-10 diagnostic code)
Atopic dermatitis	Demographic characteristics, inclusion criteria	National Patient registry	L20.x
Inflammatory Bowel Disease	Demographic characteristics, exclusion criteria	National Patient registry	K50, K51
Psoriatic Arthritis	Demographic characteristics, exclusion criteria	National Patient registry	M07.0, M07.1, M07.2, M07.3
Psoriasis	Demographic characteristics, exclusion criteria	National Patient registry	L40
Rheumatoid arthritis[4]	Demographic characteristics, exclusion criteria	National Patient registry	M05.x and M06.x (except M06.1)

Table II. International Anatomical Therapeutical Chemical (ATC) codes and treatment procedure (SKS) codes.

Systemic treatment for AD (conventional disease-modifying antirheumatic drugs (DMARDs))

Variable (Exposure)	Role	Data Source	Operational Definition (ATC Code)	Operational Definition (SKS Code)
Cyclosporine	Treatment	Registry of Medicinal Products Statistics	L04AD01	BOHJ20
Methotrexate	Treatment	Registry of Medicinal Products Statistics	L01BA01 / L04AX03	BWHA115
Azathioprine	Treatment	Registry of Medicinal Products Statistics	L04AX01	BWHB83
Mycophenolic Acid	Treatment	Registry of Medicinal Products Statistics	L04AA06	BOHJ22B
Prednisolone	Treatment	Registry of Medicinal Products Statistics	H02AB*	MH02AB*

Systemic treatment for AD and other indications (biological therapy and targeted synthetic DMARDs)

Variable (Exclusion criteria)	Role	Data Source	Operational Definition (ATC Code)	Operational Definition (SKS Code)
Baricitinib	Treatment, exclusion criteria	Registry of Medicinal Products Statistics	L04AF02	BWHP106
Upadacitinib	Treatment, exclusion criteria	Registry of Medicinal Products Statistics	L04AF03	BWHP107
Dupilumab	Treatment, exclusion criteria	Registry of Medicinal Products Statistics	D11AH05	BOHJ18B8

Table III. Outcomes.

Variable (ICD-10 diagnostic code description)	Role	Data Source	Operational Definition (ICD-8 diagnostic code)	Operational Definition (ICD-10 diagnostic code)
Dyslipidemia	AE, sec. outcome	National Patient registry		E78 (pre-defined macro)
Herpes zoster[5]			053.00–053.9	B02
		MACE[6]		
Stroke	AE, part of primary outcome (MACE)	National Patient registry	NA	I61, I63, I64
Myocardial Infarction	AE, part of primary	National Patient registry	NA	I21, I22

	outcome (MACE)			
CV death (cause of death)[7]	AE, part of primary outcome (MACE)	National Patient registry	NA	Cause of Death: ICD10: I20-25, I60-61, I63-64, I69, G45.8-45.9, I71, I74, I11.0, I13.0, I13.2, I50, Z95, I46.1, I65, I66, I67.0, I67.2, I70.
		Malignancies		
Malignancies, excluding NMSC	AE, co-primary outcome (Malignancy)	National Patient registry	140-209 (except 173)	C00-C99, expect C44
NMSC	Exclusion criteria	National Patient registry	173	C44
Serious infections[8]	AE, sec. outcome	National Patient registry	Table V	Table V
Arterial thromboembolisms (AT) Venous thromboembolismDeep vein thrombosis (DVT) and pulmonary embolism (PE)[9,10]	AE, sec. outcomes	National Patient registry	DVT: 451 PE: 450.99 AT: 444	DVT: I801, I80.2, I80.3, I80.8, I80.9, I82.2, I82.3, I82.9 PE: I26 AT: I74 And anticoagulation therapy: ATC B01A

Table IV. ICD-8 and ICD-10 for medical history

Variable (ICD-10 diagnostic code description)	**Role**	**Data Source**	**Operational Definition** (ICD-8 diagnostic code)	**Operational Definition** (ICD-10 diagnostic code)	**Operational Definition** (Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures codes)
Alcohol abuse	medical history	National Patient registry	291, 303	F10.1–10.9 (pre-defined macro)	NA
Heart failure	medical history	National Patient registry	NA	I11.0, I13.0, I42, I50	NA
CVD Risk Factors[2]					

History of coronary heart disease[11]	medical history	National Patient registry	NA	I20-I25	PCI (KFNG00, KFNG02, KFNG02A, KFNG05, KFNG05A, KFNG10, KFNG12, KFNG20, KFNG22, KFNG30, KFNG40, KFNG96, KZFX01) or CABG (KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNH, KFNJ, KFNK, KFNW)
Diabetes	medical history	National Patient registry	250	E10-E14 (pre-defined macro)	NA
Dyslipidemia (within the past 5 years)	medical history	National Patient registry	NA	E78 (pre-defined macro)	NA
History of cancer	medical history	National Patient registry	140-209	C00-C96	NA
Hypertension	medical history	National Patient registry	400-404 (pre-defined macro)	I10.x-I15.x (pre-defined macro)	NA
Smoking history	medical history	National Patient registry	NA	Pre-defined macro	NA

Table V. ICD-10 Serious infection[7] (see table III, role for all: AE and Secondary Outcome; Data Source: National Patient Registry)

Serious infections	Operational Definition: **ICD-10**
CNS infections	A02.21, A06.6, A17.0, A20.3, A27.81, A32.1, A39.0, A80-A89, B00.3, B00.4, B01.0, B01.1, B02.0-B02.2, B05.0, B05.1, B06.0, B26.1, B26.2, B10.01, B37.5, B38.4, B43.1, B45.1, B46.1, B58.29, G00-G08

Gastrointestinal infections	A00, A01, A02.0, A02.8, A02.9, A03-A05, A06.0, A06.2-A06.4, A07-A09, A21.3, A22.2, A42.1, B05.4, B15-B19, B25.1, B46.2, K35, K37, K57, K61, K62.0, K65.0, K65.9, K67, K75.0, K81.0, K81.8, K81.9
Gynecological infections	N70.0, N70.9, N71.0, N71.9, N72, N73.0, N73.2, N73.3, N75.5, N73.8, N73.9, N74
Heart infections	A32.8, B33.21, B37.6, I00, I01, I30, I32, I33, I38-I41, I43.0
Hepatitis	B16, B17, B18
HIV	B20-B24
Musculoskeletal infections	A02.23, H05.029, M00-M03, M46.2, M46.3, M46.5, M46.6, M60.0, M65.0, M65.1, M71.0, M71.1, M86.0-M86.2, M86.8, M86.9, M90.0, M90.1, M90.2
Opportunistic infections	A02, A07.2, A07.3, A15-A19, A27.0, A31, A32, A40.3, A42-A44, A48.1, A48.1, A60.0, A81.2, B00-B02, B17.9, B25, B27.1, B37-B40, B44, B45, B55, B58, B59, B78, B95.3, G02.0, G02.1, J13, J17.1, J17.2, K23.0, K67.3, K93.0
Pulmonary infections	A48.1, A37, B39-B40, B01.2, B05.2, B25.0, B44, B58.3, B59, B95.3, J10-J22, J85, J86, U04
Sepsis	A02.1, A20.7, A22.7, A24.1, A26.7, A28.2B, A32.7, A40, A41, A42.7, B37.7, R65.0, R65.1, R65.9
Skin and subcutaneous tissue infections	A36.3, A60, B00.1, B00.2, B00.7, B00.9, B01.8, B01.9, B02.3-B02.9, B05.3-B05.9, B08, B09, B35, B36, L00-L05, L08, K11.3, K11.4, K11.6, K12.2, K06.8, K06.9, L30.3, M72.6
Tuberculosis	A19, K23.0, K67.3, K93.0, M01.1, M49.0, M90.0, N33.0, N74.1, N74.1
URTI	A18.6, A36.8, A36.9, H39.0, H39.1, H60.0-H60.3, H60.9, H61.0, H65.0, H65.1, H65.9, H66.0, H66.4, H66.9, H67.1, H70.0, H70.2, H70.8, H70.9, J01, J02, J06, J36
UTI	A54.0-A54.2, N80, N10, N12, N13.6, N15.1, N15.9, N16.0, N30.0, 30.3, N30.9, N34.0, N34.1, N34.2, N39.0, N41.0, N41.2, N45

8.4. Data Sources

The data used in this project will be retrieved via Statistics Denmark following a formal research request. Once approved Statistic Denmark can draw on data from registries under the Danish Health Data Authority.

Unique Identifiers and Linkage Mechanisms
Danish registries are linked at the individual level primarily by the Civil Personal Register (CPR) number, a unique 10-digit personal identification number assigned to every resident at birth or immigration[22]. The CPR number is used in all national databases that contain personal information, including health registers and socio-economic registers. This universal identifier functions as a common key that allows records from different databases to be matched for the same person with a high degree of accuracy. For example, a patient's hospital discharge in the National Patient Registry can be linked to that same person's prescription records in the Medicinal Product Statistics Register, and to their vital status in the Civil Registration System, by using CPR as the join field.

Other unique keys are used for non-personal linkages (e.g. a health facility ID, or family identifiers in certain datasets), but the CPR number is the cornerstone of data linkage. It enables both cross-sectional linkage (combining data across registers for a given year) and longitudinal linkage (tracking individuals over time)[3]. Because of CPR, "registers with information on health can be linked to other population registers containing information on, for example, education, income, housing, etc., at the individual level". This creates rich, multidimensional datasets for research, covering medical history, medication use, outcomes, and socio-demographics for each person.

Importantly, when data are prepared for research use, the actual CPR numbers are not revealed to analysts. Instead, Statistics Denmark (or the Danish Health Data Authority when relevant) replaces real CPRs with encrypted or pseudonymized IDs. In practice, each project gets a project-specific anonymous person identifier, so that researchers can link records internally within their dataset without ever seeing a real CPR number. This mechanism preserves the ability to link data accurately while protecting personal identity.

Registries utilized in this study:

The Danish National Patient Registry (DNPR) holds information on inpatient visits (since 1977) and outpatient visits (since 1995), along with data on medical procedures, including hospital-administered biologics and phototherapy. Diagnoses are recorded based on the International Classification of Diseases (ICD-8 from 1977 to 1993 and ICD-10 from 1994 onward). Hospital-administered procedures and treatments are registered using the SKS codes, while surgical procedures have been recorded according to the NOMECO Classification of Surgical Procedures (NCSP) since 1996.

The Danish Register of Medicinal Product Statistics contains information on all filled prescriptions at community pharmacies from 1995 onwards, using the Anatomical Therapeutic Chemical (ATC) classification system.

The National Cause of Death Registry holds information on the cause and date of death when applicable.

The National Population Registry contains demographic information, including vital status and gender.

Validation of registries and endpoints:

The Danish registries are widely used in epidemiological research and known for their high-quality longitudinal data and validity of these[21]. Input of data into the registries and the following use of this is managed by the Danish Health Data Authorities (Sundhedsdatastyrelsen); a public authority that follows national guidelines, laws and regulations. Specifically, the Danish Health Data Authorities manages all national health registries such as the CPR-registry, National Patient Registry, Hospital Medicines Registry etc.[23]. Use of these data for research is handled via Statistics Denmark, as describes below.

A recent study successfully validated the ICD-10 AD diagnosis code in the DNPR[14]. No formal validation studies of all study endpoints have been performed. However, the validity of cardiovascular diagnoses in the DNPR has been investigated and overall found to be high and sufficient for use in research since 2010[15]. In addition, other studies have used these registries to investigate similar endpoints in a similar population. E.g. a large population-based cohort study demonstrated that the IRs of VTE, DVT, and PE in 17,341 patients with AD were comparable with those in the general population[13].

8.5. Study Size

Study size and power calculations
All patients meeting the inclusion criteria will be included for the current data analysis. Since this is a descriptive, retrospective study, no sample-size calculation is performed.

8.6. Data Management

The raw data is already collected in structured form. The investigators will independently extract the data needed for the current retrospective based on the criteria set out in the protocol (section 9) using a unique identifier. All outcome analyses will be performed using SAS, R, and python.
The investigators operate in a secure, environment hosted at Statistics Denmark. Statistics Denmark's information security policy, which establishes the framework of the security work in Statistics Denmark and complies with the information security standard ISO 27001:2022 (Statistic Denmark Security Policy). The server is Windows-based and offers SAS 9.4, R 4.1.3, and python 3.7.4. The data are held at secure facilities by Statistics Denmark. All communication lines are encrypted, and security measures are updated on an ongoing basis, including ISO 2700x according to requirements from the Agency for Digitization ("Digitaliseringsstyrelsen") and the Center for Cyber security[24]. Due to national data security

requirements, only results in the final analyzed report form can be provided to Pfizer (no access can be granted to source/raw data files or coding/logs). As for oversight, there will be regular interaction between Pfizer study lead and vendor to verify study progress and support with issue solving. Vendor management is supported by the Pfizer study manager to assure compliance and adherence to all processes and documentation required per Pfizer SOPs.

8.7. Data Analysis

Raw data processing:
The raw data can be accessed remotely and online via The Secure Research Platform hosted in Statistics Denmark. Once a data request is submitted, Statistics Denmark will provide results in form of aggregated data. These results are organized as tables with columns and rows. Each column represents a variable (e.g., age, gender), and each row represents an observation or unit (e.g., dermatology verified AD patients receiving systemic treatment). The data may be numerical, textual, or categorical, depending on the type of variable.

Methods used to correct inconsistencies or errors:
If data points are missing for some individuals these cannot be added at a later point as the data received are anonymized and the source not identifiable. Any missing data will be noted in the analysis and added as limitations if it impacts the results and results presented. In case of too few patients or events in one drug group to carry out the planned analysis per group, the analysis can be carried out by combining drug classes.

Treatment series
Treatment series are defined as periods of time in which a patient is considered on active treatment. The allowable gap between administrations of the same drug is 150 days to aggregate the treatment series. If the gap exceeds 150 days, patients are considered to have initiated a new treatment series. The allowable gap is based on the common gap of 90 days between each filled prescription, with an additional extension of 60 days to mirror the design of ORALSURV, which allowed for up to 2 months of discontinuation for safety issues.

The duration of active therapy following the last filled prescription or administration is set at 120 days, reflecting the standard 90-day prescription interval plus an additional 30 days, as outlined by Fleischmann et al. [1]. Each treatment series is considered separately, as concomitant therapies were allowed in the ORALSURV study design.[2]

Follow-up and exposure and censoring
Patients are followed from the index date until the earliest occurrence of one of the following: the event of interest, the study closing date (30 December 2022), initiation of a

biological therapy or JAK inhibitor, death, the development of a condition that would qualify for one of the treatments of interest (Table 1), or migration.
When using treatment series, exposure time is calculated and cumulated based on the specific therapy received. Except for the event of interest, any of the previously mentioned cases will result in censoring.
Additional analyses will be conducted on an intention-to-treat basis.

Events
During the treatment series, an adverse event can be adjudicated to the ongoing treatment. In the intention-to-treatment (ITT) study design, the event can be adjudicated to the treatment initiated at the index date.

If a patient is receiving overlapping treatments, any adverse event occurring during both therapies will be adjudicated to the therapy the patient has been on for the longest duration. Such events are referred to as overlapping events.

In the primary analyses, for overlapping events, the event is assigned to the drug the patient has been on the longest.

Multiple sensitivity analyses will be conducted to address overlapping events:

- The event is assigned to the most recent drug.
- The event is attributed to both drugs.
- The event is attributed to neither drug and the patient is censored.

Serious infections are defined as those requiring hospital admission for more than one day (Table V), and infections with HIV, hepatitis B or C, tuberculosis, or infections resulting in death.

Matching:
Logistic regression will be used to estimate propensity scores (PS). The logit function may include, among others, age, sex, index date (prescription date of conventional systemic therapy), and the presence of at least one cardiovascular risk factor. However, we intend to use clinical judgment to determine which variables will be added based on standardized differences. For matching, we are considering nearest-neighbor (greedy) matching with a 1:1 to 1:4 ratio—likely with replacement[16]. We intend to use a caliper of ±0.01 but have also considered 0.2 × SD of logit(PS). Depending on performance, “optimal” matching could also be considered instead[17]. The model with the best properties will be applied[18]. Alternative

approaches for handling matching and assessing model performance are discussed (among others) here[19, 20].

Patient characteristics:
Descriptive statistics will be presented to describe patient characteristics performed for all groups:

a) dermatologist-verified adult patient population with atopic dermatitis (AD) receiving conventional systemic treatments as per inclusion/exclusion criteria,
b) cohort-matched general Danish population
c) cohort-matched patients with AD not receiving systemic treatment (see section above for matching criteria).

Categorical covariates will be described by frequency distribution while continuous covariates expressed in terms of their mean and standard deviation or median and interquartile range (IQR) as appropriate. The descriptive statistics will be captured in a statistical report with aggregated data in tables.

Between group comparisons for baseline characteristics:
Pearson's chi-square test will be used for dichotomous categorical variables, t-test will be used for continuous variables, and the Mann-Whitney U test for non-parametric variables. The statistical analysis will be captured in a statistical report with aggregated data in tables.

Primary endpoint statistical analysis:
Incidence rates of major adverse cardiovascular events (MACE) and malignancy (excluding non-melanoma skin cancer (NMSC)) will be presented per 10,000 person-years at risk with 95% confidence intervals. The incidence rates will be reported for each group separately: a) a dermatologist-verified adult patient population with atopic dermatitis (AD) receiving conventional systemic treatments as per inclusion/exclusion criteria, b) cohort-matched general Danish population and c) cohort-matched patients with AD not receiving systemic treatment (see section above for matching criteria). For group a, the incident rates will be presented per individual conventional systemic treatment (see table II).
In cases where patients received two systemic treatments or more during the data collection period, each treatment series will be analyzed independently. The statistical analysis will be captured in a statistical report with aggregated data in tables.
In the primary analyses, overlapping events will be attributed to the drug to which the patient has been exposed for the longest duration.

Secondary endpoint statistical analysis:
Incidence rates of additional adverse events of special interest (All-cause mortality, Arterial thromboembolisms, Venous thromboembolisms, Dyslipidemia, Herpes zoster, NMSC, Serious infections) will be presented per 10,000 person-years at risk with 95% confidence intervals. The incidence rates will be reported for each group separately (Groups a) a dermatologist-verified adult patient population with atopic dermatitis (AD) receiving conventional systemic treatments as per inclusion/exclusion criteria, b) cohort-matched

general Danish population and c) cohort-matched patients with AD not receiving systemic treatment (see section above for matching criteria)).
For group a, the incident rates will be presented per individual conventional systemic treatment (see table II).
In cases where patients received two systemic treatments or more during the data collection period, each treatment series will be analyzed independently. The statistical analysis will be captured in a statistical report with aggregated data in tables.
In the primary analyses, overlapping events will be attributed to the drug to which the patient has been exposed for the longest duration.

Tertiary statistical analysis:
Comparison of the identified adverse events per individual conventional treatment (table II) with the following two matched groups: a cohort-matched general Danish population and a cohort-matched patients with AD not receiving systemic treatment (see section above for matching criteria).

The groups will be compared using a Cox-regression models. The proportionality assumptions will be tested using Schoefeld test and plots. If the PH assumption is violated, we will allow time-varying effects by including covariate×log(time) interactions or using time-split intervals. Use of competing-risk models will be employed where relevant and feasible.
The statistical analysis will be captured in a statistical report with aggregated data in tables.
In the primary analyses, overlapping events will be attributed to the drug to which the patient has been exposed for the longest duration.

P-values may be reported when relevant for descriptive purposes and will not be adjusted for multiple testing; they are presented as descriptive statistics only, and no hypotheses are being tested.

A sensitivity analysis will be conducted requiring only one use of a drug to fulfil the inclusion criteria.

To evaluate the robustness of the method applied to handle overlapping events in the primary analysis, multiple sensitivity analyses will be performed, in which overlapping events will alternatively be assigned to (a) the most recently administered drug, (b) attributed to both drugs, or (c) excluded by censoring the patient at the time of the event. These results will be presented separately.

Furthermore, a sensitivity analyses will be conducted reporting incidence rates for the years 1995-2001, 2002-2008, 2009-2015, and 2016-2022.

As a sensitivity analyses, a cox regression model with inverse Probability Treatment Weighting will be conducted.

Analyses will be conducted using SAS 9.4, Python v3.11.5, and R v4.4.1

8.8. Quality Control

Denmark provides universal healthcare coverage funded primarily through general taxation. Services are free at the point of care for all residents. The country is divided into regions and their responsibilities are defined by the Danish Health Act (Sundhedsloven). Regional authorities manage public hospitals, including staffing, budgeting, and infrastructure. Hospitals often rely on regional SOPs rather than site-specific ones. This centralized governance ensures consistency in quality management, business continuity, and regulatory compliance across institutions.
The Danish Healthcare system aligns with European and international standards, making it a reliable partner for global clinical research and pharmaceutical collaboration. Denmark maintains over 60 national health registries (Danish Registries EMA Data source ID 42187), governed by the Danish Health Data Authority (HMA-EMA catalogues: Institution ID 3331256 https://catalogues.ema.europa.eu/institution/3331256) and 150 socioeconomic registries. These registries are population-based, interlinkable via the Civil Registration Number (CPR), and renowned for their completeness, longitudinal depth, and high data validity. Data are anonymized or pseudonymized before use, and strict safeguards ensure confidentiality and compliance with GDPR.
Statistics Denmark is the primary source of official statistics in Denmark, covering a broad range of areas relevant to public health, including population demographics, health statistics, and economic data.

The requirement for official statistics follows on the Act on Statistics Denmark, which provides the formal framework for official statistics in Denmark (appendix 1, Statistics Denmark's Information Security Policy). In addition, the statistics must meet requirements developed in international cooperation. Official statistics must also satisfy quality requirements formulated in the European Statistics European Code of Practice, which includes transparency about methods and production routines.

Detailed technical documentation covering the primary backup infrastructure and associated fallback environments is held by Statistics Denmark and is not distributed to external institutions. External parties receive the information contained in Statistics Denmark's Information Security Policy (appendix 1), which summarises the available safeguards without exposing sensitive configuration details. All backup and recovery controls are implemented within Statistics Denmark's ISO/IEC 27001-certified information-security management system, ensuring they meet internationally recognised standards for confidentiality, integrity, and availability and the requirements from the Danish Agency for Digitisation and the Danish Centre for Cyber Security (links to the compliance with GDPR, Data Confidentiality Policy at Statistic Denmark 2024 and Statistic Denmark Information Security Policy 2025: Information security and data confidentiality - Statistics Denmark).

Statistics Denmark register (log) which data sets each employee uses and follows the directions from the Data Protection Agency. External users, e.g. research scientists, must be approved and only have access to information where civil registration numbers (CPR numbers) etc. have been replaced with serial numbers that do not allow you to identify people.

Bispebjerg Hospital is a part of the Capital Region of Denmark. It is registered in the HMA-EMA- catalogues under Institution ID3331470. Currently it is a partner in the following studies: EUPAS4072 (ongoing, non-voluntary PASS) and EUPAS34845 (ongoing, voluntary PASS). The data is retrieved specifically from specifically the National Patient Register (Landspatientregisteret) (EMA Data source ID: 1111181, Landspatientregisteret (National Patient Register) | HMA-EMA Catalogues of real-world data sources and studies) and Statistics Denmark.

In the Hospitals under the Capital Region, the safety and quality areas are governed by the overarching Unit for Quality, Research, and Patient Safety. Their tasks include, among other, responsibilities related to the national quality program, patient safety, pharmaceuticals, hygiene, clinical guidelines, quality databases, etc. They support quality work at the region's hospitals in collaboration with the region's IT organization, the clinical (specialty) councils, other administrative units, the executive management, and the political committees. A main task is to facilitate work on quality and patient safety in the region and to create a basis for decision-making that benefits the entire healthcare system. They govern work on clinical quality databases, Support the region's document management system and the development of regional and cross-regional guidelines (VIP), Support the work related to the National Quality Program, including learning and quality teams (LKT) and support patient safety efforts in relation to the Health Platform (Sundhedsplatformen).

Locally, the continued data storage, and subsequent management and analyses will be conducted according to the Department of Dermatology, Bispebjerg Hospitals standard operating procedures and in compliance with the Capital Region (Region Hovedstaden). All study documents (protocol, report, publications) will be reviewed by the primary investigator (i.e., Dr. Simon Francis Thomsen). The Department of Dermatology, Bispebjerg Hospital will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permissions necessary to conduct this study.

A quality management system is in place locally to ensure the procedure for the preparation, approval, implementation, and revision of Standard Operating Procedures and guidelines within the research unit, and to ensure that the unit's other documents, e.g., worksheets for specific trials, are document-controlled and archived in accordance with national legislation in the area (appendix 2, Kvalitetssystemet, Hud-og Sårafdelingens forskningsenhed).

The Code of Conduct for Responsible Research (appendix 3) outlines the University of Copenhagen's Code of Conduct for Responsible Research, which includes clear rules and procedures for handling suspicions of research misconduct and other breaches of responsible conduct of research. It describes mechanisms which are designed to ensure that all reports of research misconduct are taken seriously and investigated thoroughly while protecting the rights and confidentiality of the individuals involved. They include 1) Direct

Reporting, 2) Research Integrity Officer, 3) Anonymous Reporting and 4) Whistleblower Protection[25].

8.9. Limitations of the Research Methods

This study is based on data from Denmark, which introduces certain limitations regarding the generalizability of the findings. The Danish population is relatively homogenous in terms of ethnicity and socioeconomic structure, which may limit the direct applicability of results to more diverse populations. Additionally, Denmark has a high standard of living and a universally tax-funded healthcare system that ensures equal access to medical care. While this provides a robust setting for epidemiological research, it may not reflect healthcare access, quality, or utilization patterns in countries with different healthcare models. These contextual differences should be considered when interpreting the results and comparing them to findings from other regions or healthcare systems.

Diagnosis, comorbidities, medical history and outcomes will be identified using the ICD-8 and -10 diagnosis codes, which might be subject to potential miscoding. However, this is partly mitigated by using dermatologist verified AD diagnosis. Based on clinical experience, outcomes of this severity are unlikely to be over- or underreported. However, the events can be misdiagnosed and improperly entered in to the registries.

Typically, prescription of a medication does not necessarily indicate that the medication was taken as prescribed. Similarly over-the-counter medications will not be captured in the databases, and the effect of these cannot be elucidated.

The investigated medications are used for multiple indications, therefore it is possible that the medications, e.g. prednisolone, was prescribed for another diagnosis than AD. However, this is attempted to be counterbalanced, as patients with concurrent diagnoses where the investigated treatments also were used, were excluded from the study.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

According to Danish legislation (" Lov om videnskabsetisk behandling af sundhedsvidenskabelige forskningsprojekter") observational studies not involving primary analysis of human tissue are exempt from ethical review (§14, section 2). In this non-interventional study ethical review is therefore not needed. No waiver was received. The study will be registered in the Capital Regions inventory, which constitutes the necessary legal approvals.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp
- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Following the end of the study and analyses, a study report will be prepared. Afterwards, a manuscript will be prepared based on the results stemming from this study for submission in a peer-reviewed journal. The manuscript will be drafted by the principal investigator and will contain a description of the objectives of the study, the methodology and its results and conclusions. Pfizer will be offered the opportunity to review and comment on the manuscript prior to submission. Pfizer employees that fulfill the ICMJE criteria will be offered to co-author the publication.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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13. LIST OF TABLES

Tables – see section 9.3 for the full list

14. LIST OF FIGURES

None

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	Appendix 1	04/07/25	Statistics Denmark's Information Security Policy
2	Appendix 2	04/07/25	QMS, skin and wound research department (In Danish:

			Kvalitetssystemet, Hud-og Sårafdelingens forskningsenhed)
3	Appendix 3	04/07/25	the University of Copenhagen's Code of Conduct for Responsible Research

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

For protocols not submitted in the EU/EEA or UK, this annex is not required.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

Document Approval Record

Document Name:	B3211007_NIS Protocol_AD conventional safety_04Nov2025_clean
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Signed By:	Date(GMT)	Signing Capacity
[redacted]	07-Nov-2025 17:06:00	Final Approval
[redacted]	11-Nov-2025 17:27:23	Manager Approval