NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS Information

Title	Herpes zoster and other opportunistic infections in patients with inflammatory bowel disease in Norway – associations with immunosuppressive treatment
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Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	**Primary objective:** Determine the incidence rate of HZ, including rate of recurrent events, rates of disseminated HZ and complications (eg, postherpetic neuralgia) and the incidence rate of other

	OI (eg, *C. difficile*, CMV, fungal infections) in adult Norwegian IBD patients. Secondary objectives are to: • Determine the association between medical treatment (glucocorticoids, thiopurine, anti-TNF, anti-TNF+thiopurine, vedolizumab, ustekinumab and tofacitinib) and incidence of HZ and other OI. • Estimate the proportion of HZ events managed in general practice vs in hospitals. • Estimate the proportion of patients that are receiving anti-viral therapy for HZ events.
Country(-ies) of study	Norway
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
AE	adverse event
ATC	anatomical therapeutical classification
CD	Crohn's disease
CMV	cytomegalovirus
DDD	defined daily dose
ECCO	European Crohn's and Colitis Organization
HIV	human immunodeficiency virus
HZ	Herpes zoster
IBD	inflammatory bowel disease
ICD	international classification of disease
ICPC	international classification of primary care
IL	interleukin
JAK	janus kinase
KUHR	Kontroll og utbetaling av helserefusjoner (Norway Control and Payment of Health Reimbursement)
MSIS	Norwegian Surveillance System for Communicable Diseases
NIS	non-interventional study
NorPD	Norwegian Prescription Database
NOZOIBD	Norwegian study on herpes zoster and other opportunistic infections in IBD
NPR	Norwegian Patient Registry
OI	opportunistic infection
PASS	Post-Authorization Safety Study
PY	patient years
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Herpes zoster and other opportunistic infections in patients with inflammatory bowel disease in Norway – associations with immunosuppressive treatment (NOZOIBD)

Version and date of protocol: version 1.0, 04 May 2020

Pfizer NI Study Lead: Arne Yndestad, Senior Medical Advisor I&I, Pfizer Norway

Rationale and background. Patients with inflammatory bowel diseases (IBD), ie, ulcerative colitis (UC) and Crohn's disease (CD) have chronic intestinal inflammation. Current immunosuppressive treatment regimens can control inflammation, but also increase the risk of infections, including herpes zoster (HZ) and other opportunistic infections (OI). There is a need for studies that examine the burden of HZ and OI in a real-world setting.

Research question and objectives. Thestudy aims to quantify the incidence rates of HZ and other OI, including their association with immunosuppressive treatment, in adult Norwegian IBD patients. The primary objectives are to determine the incidence rate of HZ, including rate of recurrent events, rates of disseminated HZ and complications (eg, postherpetic neuralgia) and the incidence rate of other OI in adult Norwegian IBD patients. Secondary objectives are to: (i) determine the association between immunosuppressive treatment and incidence rates of HZ and other OI, (ii) estimate the proportion of HZ events in IBD patients managed in general practice versus in hospitals and (iii) estimate the proportion of patients receiving anti-viral therapy for HZ events.

Study design. Non-interventional retrospective observational study. Designated as a Post-Authorization Safety Study (PASS) and conducted voluntarily by Pfizer.

Population. Adult patients with IBD in Norway (approximately 55,000 patients).

Variables. Exposure variables are diagnosis of UC or CD and immunosuppressive drugs (ie, glucocorticoids, thiopurines, methotrexate, anti-TNF, anti-TNF and thiopurine combined, vedolizumab, ustekinumab and tofacitinib). Outcome variables are: diagnosis of HZ or other OI, antiviral treatment and management of HZ by primary or secondary healthcare.

Data sources. Patient-level deidentified data from Norwegian Patient Registry (NPR), Norwegian Surveillance System for Communicable Diseases (MSIS), Norway Control and Payment of Health Reimbursement (KUHR) and Norwegian Prescription Database (NorPD). Data will include patients who received at least 1 diagnosis of IBD during the study period 2008-2019 in the NPR.

Study size. The study will include all patients in Norway with a diagnosis code of IBD in NPR in 2008-2019, approximately 55,000 patients (expected distribution: 60% UC and 40% CD).

Data analysis. Categorical variables will be described with the number of values, percentages and as incidence rate/1000 patient-years. Data will also be calculated according to age categories. To assess the association between immunosuppressive treatment and incidence of HZ or other OI, the Sponsor will do a Cox regression with both fixed and time-dependent covariates. This entails following the patients from their first IBD diagnosis to their first diagnosis of HZ or other OI, adjusting for other covariates (age, gender, treatment [both current and prior]). The results will be presented as multivariable adjusted hazard ratios and survival plots.

Milestones. Start date of data collection: 01 September 2020; End data of data collection: 02 January 2021; Start date of data analysis: 02 January 2021; Date of final study report: 02 November 2021.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	01 September 2020
End of data collection	02 January 2021
Registration in the EU PAS register	10 May 2020
Final study report	02 November 2021

7. RATIONALE AND BACKGROUND

Inflammatory bowel disease (IBD), ie, Crohn's disease (CD) and ulcerative colitis (UC), are life-time diseases characterized by continuous or relapsing intestinal inflammation.[1] Chronic inflammation, intestinal lesions and malnutrition puts IBD patients at increased risk of infections.[2] Great progress has been made in the treatment of IBD in the past 2 decades, and a patient with a healing mucosa and disease remission have a reduced infectious risk. However, management of IBD involves treatment with drugs with immunosuppressive properties and an accompanying increased risk of infections, including opportunistic infections (OI), ie, infections that take place because of a weakened immune system. Thus, central in the clinical decision making in IBD is evaluation of the benefit-risk balance associated with long-term treatment with immunosuppressive drugs.

Drugs currently used in moderate to severe IBD, including glucocorticoids, thiopurines, methotrexate, anti-TNF agents (ie, infliximab, adalimumab and golimumab), the anti-integrin vedolizumab, the IL-12/IL-23 blocker ustekinumab and the JAK inhibitor tofacitinib, all have immunosuppressive properties. However, these drugs affect the immune system through different mechanisms and this is reflected in different infections associated with their use. Thiopurines increase the risk of viral infections, while TNF inhibitors are associated with bacterial infections, and the more recently introduced janus kinase (JAK) inhibitor, tofacitinib, appears to increase the risk of herpes zoster infection.[1,3]

Data on the incidence of HZ and other OI in real-world clinical management of IBD is limited. A recent retrospective cohort study of US veterans estimated the incidence rate of HZ in UC and CD patients on 5-ASA monotherapy to be 8.0 per 1000 patient-years (PY) and 6.8 per 1000 PY., respectively, compared to 3.2 per 1000 PY. in non-IBD controls.[4] In line with other studies from North America,[5,6] this indicates that the disease itself (in absence of immunosuppressive treatment) increases the risk of HZ. The same study found that exposure to thiopurines, the combination of anti-TNF agents and thiopurines and prednisone (short-term or cumulative) were associated with further increased risk of HZ.[4] A recent multicenter retrospective cohort study from Spain estimated a lower incidence of HZ (3.9/1000 PY).[7,8] Notably, there appears to be geographical differences, in particular within Europe, in the incidence of HZ in the general population.[9] Norway, a country where varicella vaccination is not introduced to the national program, has an incidence of approximately half of that observed in the rest of the world.[8] However, it is not known to

what extent the HZ risk in IBD patients associates with the HZ risk in the general population, ie, whether relative risk for HZ in IBD patients is the same, higher or lower.

The risk of serious infections and OI in IBD patients according to treatment exposure was recently estimated by Kirchgesner et al, using data from French administrative health databases.[10] Thiopurines, anti-TNF agents and in particular their combination, were all associated with increased risk of both bacterial and viral OI. However, this study did not report specifically on HZ.

ECCO, the European Crohn's and Colitis Organisation, and other gastroenterological societies recommend that all cases of HZ in IBD patients are managed by specialty health care. Patients are advised to promptly receive anti-viral treatment, preferably valaciclovir or famiciclovir in uncomplicated cases or intravenous therapy with acyclovir in complicated cases, such as disseminated HZ.[2,11,12] This is partly to decrease the risk of complications such as postherpetic neuralgia.[11,12] HZ is generally managed in primary health care. It is not known to what extent uncomplicated cases of HZ in Norwegian IBD patients are managed by gastroenterologists and to what extent the patients are receiving anti-viral treatment.

Thus, although there are some reports on the incidence of HZ and OI in IBD patients, there is a need for more studies that describe the burden of these infections in IBD in a real-world setting, their association with immunosuppressive therapy and how these infections are managed in the national health care systems. Data from such studies could advise clinicians in their decision of treatment strategy and also inform financial stakeholders about the total economic burden of IBD.

This is a non-interventional retrospective observational cohort study of adult Norwegian patients with IBD (approximately 55,000 patients). The study will use secondary structured data to identify IBD patients that receive a diagnosis of HZ or other OI and the association between these infections with immunosuppressive treatment regimens.

The non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The study aims to quantify the incidence rates of HZ and other OI, including their association with immunosuppressive treatment, in adult Norwegian patients with IBD.

Primary objectives:

- Determine the incidence rate of HZ, including rate of recurrent events, rates of disseminated HZ and complications (eg, postherpetic neuralgia) and the incidence rate of other OI (eg, *C. difficile*, CMV, fungal infections) in adult Norwegian IBD patients.

Secondary objectives:

- Determine the association between immunosuppressive treatment (glucocorticoids, thiopurine, methotrexate, anti-TNF, anti-TNF and thiopurine combined, vedolizumab, ustekinumab and tofacitinib) and incidence rates of HZ and other OI.

- Estimate the proportion of HZ events in IBD patients managed in general practice versus in hospitals.

- Estimate the proportion of patients that are receiving anti-viral therapy for HZ events.

9. RESEARCH METHODS

9.1. Study Design

This is a non-interventional retrospective observational cohort study of adult patients (≥18 years) in Norway with IBD (approximately 55,000 patients). The study will use secondary structured data to identify IBD patients that have received a diagnosis of HZ or other OI and the association between these infections with immunosuppressive treatment regimens.

Primary endpoints are incidence rates of HZ, including rate of recurrent events, rates of disseminated HZ and complications (eg, postherpetic neuralgia) and the incidence rates of other OI.

Secondary endpoints are (i) association between immunosuppressive treatment (glucocorticoids, thiopurine, methotrexate, anti-TNF, anti-TNF+thiopurine, vedolizumab, ustekinumab and tofacitinib) and incidence of HZ and other OI, (ii) the proportion of HZ events in IBD patients managed in general practice versus in hospitals, and (iii) proportion of patients that are receiving anti-viral therapy for HZ events.

To be able to address the study objectives, real world patient-level data from the Norwegian Patient Registry (NPR), Norwegian Surveillance System for Communicable Diseases (MSIS), Norway Control and Payment of Health Reimbursement (KUHR) and Norwegian Prescription Database (NorPD) will be combined.

Linkage of the 4 central health registries is necessary to address several of the study objectives. Uncomplicated cases of HZ are generally managed in primary health care in Norway (identified in KUHR), but could also be managed in specialty health care (identified in NPR together with complicated cases of HZ). Events of HZ in IBD patients should according to guidelines be treated with an anti-viral agent, ideally valaciclovir, but acyclovir could potentially also be prescribed (identified in NorPD). These data will allow estimation of the incidence rates of uncomplicated and compicated HZ, the proportion of HZ events managed in general practice and in hospitals, and the proportion of patients that are receiving anti-viral therapy for uncomplicated HZ events.

A significant strength of the current study design is that it captures the entire Norwegian IBD population, their interaction with primary and secondary health care related to HZ and other OI and their historical and current drug dispensation. Limitations of the study design are discussed in Section 9.9.

9.2. Setting

The study population includes all patients in Norway registered with IBD (ICD code K50 or K51) and aged ≥18 years in NPR in the time period between 2008 and 2019 that do not meet any exclusion criteria. Exposure to immunosuppressive treatment (co-medication, duration, and dosing) will be identified in the registries (NPR for hospital administered treatment and NorPD for drugs dispensed by pharmacies directly to patient).

Follow-up time is very likely to differ significantly among the included patients and will be handled appropriately in the statistical analyses.

9.2.1. Inclusion Criteria

All patients who are registered with at least 1 diagnosis of IBD (ICD-code K50 or K51) and aged ≥18 years in NPR during the study period 2008-2019.

9.2.2. Exclusion Criteria

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

1. A single hospital discharge diagnosis of IBD (ICD-code K50 or K51) and no pharmacy claim for IBD medication (eg, 5-ASA, thiopurines, anti-TNF, enteral budesonide) (indicates that intial diagnosis of IBD was wrong).

2. Diagnosis of HIV-infection (ICD B25, R75), cancer (ICD C00-C97), organ transplantation (ICD Y830) or congenital immunodeficiency (ICD D80-D84) (confounds the study since these are independently associated with increased risk of HZ and other OI).

The exclusion criteria are not likely to have a significant impact on the number of patients available for analysis.

9.3. Variables

See Section 9.4 for description of data sources. For inclusion, NPR will be used to identify patients with ICD codes related to diagnosis of IBD. In addition, sub-group identifiers such as age, gender and localization of disease (Table 1) will be collected.

For exclusion of patients, the study will use variables that (i) identify lack of claims for IBD medication (NorPD; Table 2) and (ii) diagnosis codes of other conditions that increase risk of HZ and OI (ie, HIV infection, malignancy, organ transplantation and congenital immunodeficiency; Table 1).

Exposure to medical treatment will either be identified in NPR (hospital administered drugs) or in NorPD (Table 2). Data will be collected that allows estimation of treatment duration, dosages, as well as combination therapy (eg, with azathioprine) and concomitant glucocorticoid use. Importantly, NorPD only captures that a certain drug has been dispensed and it will have to be an assumption that it was actually used.

Discontinuation of treatment is defined as 3 months without a new infusion or prescription of a drug after the predefined DDD period for the drug (ie, medication gap >90 days). Combination treatment is defined as at least 30 DDDs overlap of a biologic and immunomodulator. These definitions will be assessed in a sensitivity analysis.

Outcomes (Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8 will either be identified by variables in NPR (ie, cases of HZ and OI and intravenous anti-viral treatment), MSIS (notifiable communicable diseases; Table 7), KUHR (consultations for HZ; coded as S70) and NorPD (prescription of valacyklovir or acyklovir). Importantly, the exact date of occurrence may not be known (to minimize risk of deidentification), but the precision level will be sufficient to match exposure and outcome.

Table 1. Variables Used for Inclusion, Exclusion and Sub-group Identification of Patients

Variable	Role	Data Source	Operational Definition
Crohn's disease	Inclusion criterion	NPR	ICD K50
Ulcerative colitis	Inclusion criterion	NPR	ICD K51
Cancer	Exclusion criterion	NPR	ICD C00-C97
HIV infection	Exclusion criterion	NPR	ICD B20-B24
Congential immunodeficiency	Exclusion criterion	NPR	ICD D80-84
Organ transplantation	Exclusion criterion	NPR	ICD Z94*
Subclassification of Crohn's disease	Sub-group identifier	NPR	K500, K501, K508, K509
Subclassification of ulcerative colitis	Sub-group identifier	NPR	K510-K519
Sex	Sub-group identifier	NPR	Male/female
Age	Sub-group identifier	NPR	years

Table 2. Variables Collected for Individuals Meeting Inclusion Criteria

Variable	Role	Data Sources	Operational Definition
Drug exposure			
5-ASA	Exposure	NorPD	ATC A07E C
budesonide	Exposure	NorPD	ATC A07E A
prednisolone	Exposure	NorPD	ATC H02A B06
azathioprine	Exposure	NorPD	ATC L04A X01
mercaptopurine	Exposure	NorPD	ATC L01B B
methotrexate	Exposure	NorPD	ATC L04A X03
infliximab	Exposure	NPR	ATC L04 A B02
adalimumab	Exposure	NorPD	ATC L04A B04
golimumab	Exposure	NorPD	ATC L04A B06
vedolizumab	Exposure	NPR	ATC L04A A33
tofacitinib	Exposure	NorPD	ATC L04A A29
ustekinumab	Exposure	NPR/NorPD	ATC L04A C05
For each ATC code			
Dispensing month	Exposure	NorPD	-
Number of packages	Exposure	NorPD	-
Number of DDDs	Exposure	NorPD	-
Drug strength	Exposure	NorPD	-
Package size	Exposure	NorPD	-

Table 3. Outcome Variables – Viral Infections

Variable	Role	Data Source	Operational Definition
Zoster [herpes zoster]	Outcome	NPR	ICD B02
Zoster encephalitis	Outcome	NPR	ICD B02.0
Zoster meningitis	Outcome	NPR	ICD B02.1
Zoster with other nervous system involvement	Outcome	NPR	ICD B02.2
Zoster ocular disease	Outcome	NPR	ICD B02.3
Disseminated zoster	Outcome	NPR	ICD B02.7
Zoster with other complications	Outcome	NPR	ICD B02.8
Zoster without complication	Outcome	NPR	ICD B02.9
Anogenital herpesviral [herpes simplex] infection	Outcome	NPR	ICD A60.0
Progressive multifocal leukoencephalopathy	Outcome	NPR	ICD A812
Herpesviral [herpes simplex] infections	Outcome	NPR	ICD B00
Eczema herpeticum	Outcome	NPR	ICD B00.0
Herpesviral vesicular dermatitis	Outcome	NPR	ICD B00.1
Herpesviral gingivostomatitis and pharyngotonsillitis	Outcome	NPR	ICD B00.2
Herpesviral meningitis	Outcome	NPR	ICD B00.3
Herpesviral encephalitis	Outcome	NPR	ICD B00.4
Herpesviral ocular disease	Outcome	NPR	ICD B00.5
Disseminated herpesviral disease	Outcome	NPR	ICD B00.7
Other forms of herpesviral infection	Outcome	NPR	ICD B00.8
Herpesviral infection, unspecified	Outcome	NPR	ICD B00.9
Varicella [chickenpox]	Outcome	NPR	ICD B01
Varicella meningitis	Outcome	NPR	ICD B01.0
Varicella encephalitis	Outcome	NPR	ICD B01.1
Varicella pneumonia	Outcome	NPR	ICD B01.2
Varicella with other complications	Outcome	NPR	ICD B01.8
Varicella without complication	Outcome	NPR	ICD B01.9
Acute viral hepatitis unspecified	Outcome	NPR	ICD B17.9
Cytomegaloviral disease	Outcome	NPR	ICD B25
Cytomegaloviral pneumonitis	Outcome	NPR	ICD B25.0
Cytomegaloviral hepatitis	Outcome	NPR	ICD B25.1
Cytomegaloviral pancreatitis	Outcome	NPR	ICD B25.2
Other cytomegaloviral diseases	Outcome	NPR	ICD B25.8
Cytomegaloviral disease, unspecified	Outcome	NPR	ICD B25.9
Cytomegaloviral mononucleosis	Outcome	NPR	ICD B27.1
Pneumonia in viral diseases classified elsewhere	Outcome	NPR	ICD J17.1

Table 4. Outcome Variables – Bacterial and Mycobacterial Infections

Variable	Role	Data Source	Operational Definition
Salmonella enteritis	Outcome	NPR	ICD A02
Enterocolitis due to *Clostridium difficile*	Outcome	NPR	ICD A04.7
Listeriosis	Outcome	NPR	ICD A32
Sepsis due to *Streptococcus pneumoniae*	Outcome	NPR	ICD A40.3
Actinomycosis	Outcome	NPR	ICD A42
Nocardiosis	Outcome	NPR	ICD A43
Bartonellosis	Outcome	NPR	ICD A44
Legionnaires disease	Outcome	NPR	ICD A48.1
Nonpneumonic Legionnaires disease [Pontiac fever]	Outcome	NPR	ICD A48.2
Streptococcus pneumoniae as the cause of diseases classified to other chapters	Outcome	NPR	ICD B95.3
Pneumonia due to *Streptococcus pneumoniae*	Outcome	NPR	ICD J13
Tuberculosis of lung, confirmed by sputum microscopy with or without culture	Outcome	NPR	ICD A15
Tuberculosis of lung, bacteriologically and histologically negative	Outcome	NPR	ICD A16
Tuberculosis of nervous system	Outcome	NPR	ICD A17
Tuberculosis of other organs	Outcome	NPR	ICD A18
Miliary tuberculosis	Outcome	NPR	ICD A19
Infection due to other mycobacteria	Outcome	NPR	ICD A31
Tuberculous oesophagitis (A18.8†)	Outcome	NPR	ICD K23.0
Tuberculous peritonitis (A18.3†)	Outcome	NPR	ICD K67.3
Tuberculous disorders of intestines, peritoneum and mesenteric glands (A18.3†)	Outcome	NPR	ICD K93.0
Tuberculous arthritis (A18.0†)	Outcome	NPR	ICD M01.1
Tuberculosis of spine (A18.0†)	Outcome	NPR	ICD M49.0
Tuberculosis of bone (A18.0†)	Outcome	NPR	ICD M90.0
Tuberculous cystitis (A18.1†)	Outcome	NPR	ICD N33.0
Tuberculous infection of cervix uteri (A18.1†)	Outcome	NPR	ICD N74.0
Female tuberculous pelvic inflammatory disease (A18.1†)	Outcome	NPR	ICD N74.1

Table 5. Outcome Variables – Fungal Infections

Variable	Role	Data Source	Operational Definition
Candidiasis	Outcome	NPR	ICD B37
Candidal stomatitis	Outcome	NPR	ICD B37.0
Pulmonary candidiasis	Outcome	NPR	ICD B37.1
Candidiasis of skin and nail	Outcome	NPR	ICD B37.2
Candidiasis of vulva and vagina	Outcome	NPR	ICD B37.3
Candidiasis of other urogenital sites	Outcome	NPR	ICD B37.4
Candidal meningitis	Outcome	NPR	ICD B37.5
Candidal endocarditis	Outcome	NPR	ICD B37.6
Candidal sepsis	Outcome	NPR	ICD B37.7
Candidiasis of other sites	Outcome	NPR	ICD B37.8
Candidiasis, unspecified	Outcome	NPR	ICD B37.9
Coccidioidomycosis	Outcome	NPR	ICD B38
Histoplasmosis	Outcome	NPR	ICD B39
Blastomycosis	Outcome	NPR	ICD B40
Paracoccidioidomycosis	Outcome	NPR	ICD B41
Sporotrichosis	Outcome	NPR	ICD B42
Chromomycosis and phaeomycotic abscess	Outcome	NPR	ICD B43
Aspergillosis	Outcome	NPR	ICD B44
Invasive pulmonary aspergillosis	Outcome	NPR	ICD B44.0
Other pulmonary aspergillosis	Outcome	NPR	ICD B44.1
Tonsillar aspergillosis	Outcome	NPR	ICD B44.2
Disseminated aspergillosis	Outcome	NPR	ICD B44.7
Other forms of aspergillosis	Outcome	NPR	ICD B44.8
Aspergillosis, unspecified	Outcome	NPR	ICD B44.9
Cryptococcosis	Outcome	NPR	ICD B45
Zygomycosis	Outcome	NPR	ICD B46
Mycetoma	Outcome	NPR	ICD B47
Other mycoses, not elsewhere classified	Outcome	NPR	ICD B48
Opportunistic mycoses	Outcome	NPR	ICD B48.7
Other specified mycoses	Outcome	NPR	ICD B48.8
Unspecified mycosis	Outcome	NPR	ICD B49
Pneumocystosis	Outcome	NPR	ICD B59
Fungal meningitis	Outcome	NPR	ICD G02.1
Fungal pneumoniae	Outcome	NPR	ICD J17.2

Table 6. Outcome Variables – Parasitic Infections

Variable	Role	Data Source	Operational Definition
Cryptosporidium	Outcome	NPR	ICD A07.2
Isosporiasis	Outcome	NPR	ICD A07.3
Leishmaniasis	Outcome	NPR	ICD B55
Toxoplasmosis	Outcome	NPR	ICD B58
Strongyloidiasis	Outcome	NPR	ICD B78

Table 7. Outcome Variables in MSIS

Variable	Role	Data Source	Operational Definition
Cryptosporidiosis	Outcome	MSIS	Positive case
Legionellosis	Outcome	MSIS	Positive case
Listeriosis	Outcome	MSIS	Positive case
Pneumococcal systemic disease	Outcome	MSIS	Positive case
Salmonellosis	Outcome	MSIS	Positive case
Infection or carrier state of toxinproducing *Clostridium difficile*	Outcome	MSIS	Positive case
Streptococcus Group A systemic disease	Outcome	MSIS	Positive case
Streptococcus Group B systemic disease	Outcome	MSIS	Positive case
Tularaemia	Outcome	MSIS	Positive case
Viral infections in central nervous system	Outcome	MSIS	Positive case

Table 8. Additional Outcome Variables

Variable	Role	Data Source(s)	Operational Definition
valacyklovir	Outcome	NorPD	ATC J05A B11
acyklovir	Outcome	NorPD	ATC J05A B01 tabl.
acyklovir i.v.	Outcome	NPR	ATC J05A B01* inj
herpes zoster	Outcome	KUHR	ICPC S70
post-herpetic neuralgia	Outcome	NPR	ICD G53.0

9.4. Data Sources

The study will use data from 4 different sources, ie, registries with entries that cover patient interactions with specialty and primary health care, diagnoses and dispensation of drugs. Linkage of these data sources is necessary to address the study objectives.

All data sources are part of the portal helsedata.no and are validated sources for the exposures and outcomes of the current study.

NPR (Norwegian Patient Registry; https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/norsk-pasientregister-npr/innhold-og-kvalitet-i-npr) contains health information about all persons that have received treatment or are waiting for treatment in specialty health care (hospitals and out-patient clinics). It is mandatory for all Norwegian hospitals to submit data to NPR. Diagnoses and complications at discharge are coded by physicians according to the International Classification of Diseases (ICD-10 Norwegian version) for each hospital admission. NPR also contain data on use of hospital-administered drugs (ie, infusions). The completeness with regards to registration of diagnoses is not known.

MSIS (Norwegian Surveillance System for Communicable Diseases; https://www.fhi.no/en/hn/health-registries/msis/) is notified when a patient is diagnosed with an infection that is listed as a notifiable disease. The MSIS registry contains health information on these patients.

NorPD (Norwegian Prescription Database; https://www.fhi.no/en/hn/health-registries/norpd/) contains a complete listing of all prescription drugs dispensed by pharmacies since 2004 (but not hospital administered drugs, ie, infusions). All pharmacies in Norway register prescriptions electronically, and the information is sent to NorPD in pseudonymised form.

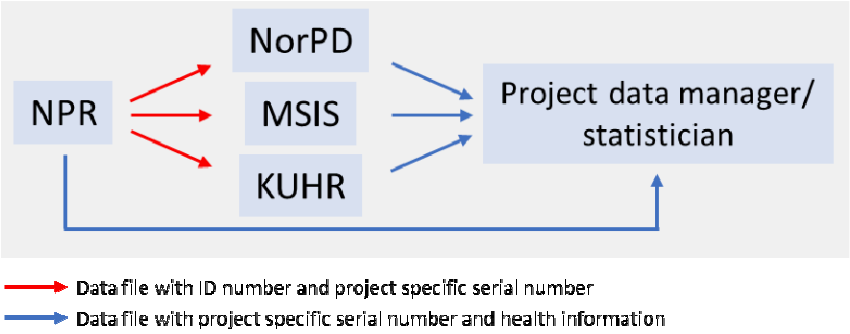
KUHR (Kontroll og utbetaling av helserefusjoner; «Norway Control and Payment of Health Reimbursement»; https://www.helsedirektoratet.no/tema/statistikk-registre-og-rapporter/helsedata-og-helseregistre/kuhr) is a national system that handles reimbursement claims from practicioners and institutions in primary health care to the government. These claims form a basis for the information in the registry.

9.4.1. Linkage Between Data Sources

Following ethical approval and approval from the registries, data from NPR using the model that NPR prefers, ie, “distributed linkage” (Figure 1) will be requested. To assure that patients are anonymized, NPR will generate a list of individuals meeting the study inclusion criteria with project specific serial numbers from the patients’ unique personal identification numbers (the key remains with NPR). This ensures that each patient can only be counted a single time. NPR will further request data (the study requested variables) from NorPD, MSIS and KUHR. The data manager/statistician will receive data files from each of the

4 registries and will use the project specific serial number to link the 4 data files and generate the full data set.

Figure 1. Overview on Deidentification of Patients and Linkage of Data Sources



9.5. Study Size

Sample size calculations are not applicable. The study will include all patients in Norway aged ≥18 years with a diagnosis code of IBD in NPR in 2008-2019, approximately 55,000 individuals (~60% UC, ~40% CD). All outcome variables will be counted in the entire included population.

9.6. Data Management

As outlined in Section 9.4.1, the data manager/statistician will receive data files from the 4 registries and will use a project specific serial number to link the 4 data files and generate the full data set. All study data exist as structured data by the time of study start. The data will be stored on an external hard disk which is password protected (256-bit AES encryption). Only the data manager/statistician will have access to the raw data. Data handling and analysis will be done using Python 3.X.

9.7. Data Analysis

9.7.1. Data Management

- The datasets will be checked for missing values and inconsistencies (eg, a patient being registered with different age in the same year of registry entry or being both male and female).

- Missing values will be imputed if possible, eg, patients with partly missing values for age or sex. Observations without patient ID will be deleted (likely to be less than 0.01%).

- New datasets merged from the involved registries will be used for analysis (eg, time to event analysis), including variables of interest such as gender, age, Charlson comorbidity index, cohort (year of diagnosis), treatment and dummies for treatment line.

- To control for bias and confounders, the analyses will be adjusted for available covariates such as gender, age, Charlson comorbidity index, year of diagnosis. The registries do not contain information about other clinically relevant variables such as disease severity, laboratory/biochemical parameters, smoking and weight.

9.7.2. Statistical Analyses

Primary objectives – Incidence rates

Events (ie, infections; categorical variables) will be described as incidence rate/1,000 PY and as number of values and percentages according to diagnosis of CD or UC. Data will also be calculated according to age categories (≥18 to 29, ≥30 to 39, ≥40 to 49, ≥50 to59 and ≥60 years). Finally, and to evaluate if changing standards of care are affecting the incidence of infections, the data will also be presented according to when infections occur (2008-2009; 2010-2011; 2012-2013; 2014-2015; 2016-2017; 2018-2019).

Secondary objectives – Association between medical treatment and incidence of HZ and OI

In addition to the descriptive statistics, methods from survival analysis will be used and Kaplan Meier curves will be calculated to describe the proportion of patients who experienced an infection after a given number of days since the patient first received the IBD diagnosis. These curves will first be calculated for the whole sample (proportion that ended up with an infection), but also for the following sub-groups:

- Plots for different cohorts (depending on the year the patient received the first IBD diagnosis);
- Separate plots for males versus females;
- Different plots for different age groups (≥18-64 years versus ≥65 years);
- Plots for different types of treatment.

To assess the association between immunosuppressive treatment (glucocorticoids, thiopurines, methotrexate, anti-TNF, anti-TNF+thiopurine, vedolizumab, ustekinumab and tofacitinib) and incidence of HZ or other OI, a Cox regression with both fixed and time-dependent covariates will be performed. This entails following the patients from their first IBD diagnosis or date of first entry in NPR (index date; first IBD registration in NPR cannot be earlier than 2008) to their first diagnosis of HZ or other OI, adjusting for other covariates (age, gender, treatment [both current and prior]). Subgroup analyses for patients ≥18-64 years and 65 years or older at cohort entry will be performed. The results will be presented as multivariable adjusted hazard ratios and survival plots, adjusted for the effects of these independent covariates.

An assessment will be performed to determine if there is an association between specific immunosuppressive treatment regimens and such infections. P-values are considered to be descriptive statistics with $p \leq 0.05$. The validity of each statistical comparison will be evaluated based on number of events in group. Specifically, in the Cox regression model, the risk of HZ and OI in IBD patients will be compared, stratified by UC and CD, with current exposure to (1) conventional therapy (ie, 5-ASA, thiopurine, methotrexate) versus advanced pharmacological treatment (ie, anti-TNF, anti-TNF+thiopurine, vedolizumab, ustekinumab and tofacitinib, (2) anti-TNF monotherapy versus anti-TNF combination with thiopurines versus thiopurine monotherapy, (3) infliximab versus adalimumab versus golimumab versus vedolizumab versus ustekinumab versus tofacitinib.

Secondary objectives - Proportions

Proportions of HZ events in IBD patients managed in general practice and in hospitals and proportion of patients that are receiving anti-viral therapy for HZ events will be described as percentages and as number of values.

9.8. Quality Control

Data manager/statistician is the current Principal Investigator in a similarly designed study and has access to the data applied for. NI Study Principal Researchers are supervising the project, so there is previous experience with similar data. The analysis will be rerun and the code will be reviewed by another statistician to ensure its quality.

9.9. Limitations of the Research Methods

Data from NPR is limited to ICD diagnoses and do not directly report on disease severity. IBD disease severity will be estimated based on treatment history and hospitalizations, but IBD disease activity (which could increase risk of opportunistic infections),[1] unless it requires hospitalization, is hard to estimate. Moreover, the registries do not contain data on other clinically relevant variables such as laboratory/biochemical parameters, smoking and weight. The lack of data on these parameters and to following inability to fully adjust for these confounding parameters, represents an important limitation of the study design. Treatment received and the use of surgery can be used as a proxy for disease severity and will be included as covariates in statistical and sensitivity analyses.

NPR started registration in 2008. This means that maximum disease duration captured in the registry is 12 years. As it is difficult to define the event “first IBD diagnosis” based on the NPR coding, this term will be used with care and focus on time from index date (first mention in NPR) to infectious event.

The study relies on the identification of IBD patients in NPR. It is a possibility that patients with a very mild history of IBD are not included in NPR, which is a hospital-based registry. This could potentially infer a selection/information bias which could potentially increase the incidence rates of HZ and OI. This will be regarded as a minor issue.

Data on drug use from NorPD will be based on retrieval of prescriptions with no verification of actual use or discontinuation of the drugs, specific time points for start and discontinuation, further the data cannot provide any explanation, association or other patient characteristics. Thus, there is a risk that actual use of some drugs (eg, glucocorticoid and thiopurines) are misestimated.

Although a strength of the study design is that all patients with IBD in Norway (given that they are included in NPR) will be included, statistical precision is not estimated as the extent of HZ and OI cases in the study population is not known. With reference to the study secondary objective on the association between immunosuppressive treatment and HZ/OI, a low number of HZ/OI cases may restrict the analyses to the most commonly used immunosuppressive drugs, such as TNF inhibitors.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves 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.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study will require approval from the Regional Ethcial Committee of South-Eastern Norway. The approval from the individual registries also assures that ethical and data privacy concerns are addressed.

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. 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 the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology and the ENCePP Code of Conduct.[13,14]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol will be registered in the EU PAS Register upon approval and results will be communicated upon study completion.

The study involves retrieval of retrospective structured data from 4 Norwegian health registries. The data will be received in 4 separate files from the registries and will be linked by the data manager as outlined in Section 9.4.1, to create the full data-set. Therefore, it is not relevant to generate interim reports on data gathering. However, there is some uncertainty related to the variables that the registries will allow the sponsor to collect. Thus, a progress report will be created with an update on which variables that will be included in the full data set. If deemed necessary, the protocol will be updated accordingly. An interim report will be generated when data extraction has been ordered.

A final study report will be made as outlined in Pfizer Standard Operational Procedures.

The study results will be disseminated in the form of abstracts submitted to major gastroenterological congresses in Europe. The sponsor will aim to publish the study results as 1 or 2 manuscripts, depending on the nature of the findings, in international peer-reviewed gastroenterological journals.

In the event of any prohibition or restriction imposed (eg, 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.

13. REFERENCES

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2. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis. 2014;8(6):443-68.

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4. Khan N, Patel D, Trivedi C, et al. Overall and Comparative Risk of Herpes Zoster With Pharmacotherapy for Inflammatory Bowel Diseases: A Nationwide Cohort Study. Clin Gastroenterol Hepatol. 2018;16(12):1919-27 e3.

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13. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 7). 2018.

14. The ENCePP Code of Conduct. For Scientific Independence and Transparency in the Conduct of Pharmacoepidemiological and Pharmacovigilance Studies. 2018.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009.

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Herpes zoster and other opportunistic infections in patients with inflammatory bowel disease in Norway – associations with immunosuppressive treatment (NOZOIBD)

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection[1]	☒	☐	☐	Section 6
	1.1.2 End of data collection[2]	☒	☐	☐	Section 6
	1.1.3 Progress report(s)	☒	☐	☐	Section 6
	1.1.4 Interim report(s)	☒	☐	☐	Section 6
	1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Section 6
	1.1.6 Final report of study results.	☒	☐	☐	Section 6

Comments:

Secondary analysis of structured registry data from 2008-2019. Availability depends on approval and turnaround time in the registries.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
	2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 7
	2.1.2 The objective(s) of the study?	☒	☐	☐	Section 8
	2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	Section 9.7.2
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	Section 9.1

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section 9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 9.1
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	Section 9.1
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	Section 9.7.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	Section 11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	Section 9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	Section 9.2
	4.2.2 Age and sex	☒	☐	☐	Section 9.2
	4.2.3 Country of origin	☒	☐	☐	Section 9.2
	4.2.4 Disease/indication	☒	☐	☐	Section 9.2
	4.2.5 Duration of follow-up	☒	☐	☐	Section 9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	Section 9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 9.3
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	Section 9.3
5.3	Is exposure categorised according to time windows?	☒	☐	☐	Section 9.3
5.4	Is intensity of exposure addressed? (eg dose, duration)	☒	☐	☐	Section 9.3
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9.3
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	Section 9.7.2

Comments:

5.6: Advanced immunosuppressive treatments regiments will be compared to conventional therapy. Different advanced immunosuppressive treatments will be compared directly.

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Section 9.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 9.3
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

6.3: Validity of the results is confirmed by the clinical experts participating in the study. Sensitivity analysis will be conducted to assess the robustness of the results. The data from NPR is generally assumed to have high accuracy and precision, but no known relevant validity study is made to confirm this claim.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

The analysis will be adjusted for available covariates, but the registries do not hold information about other clinically relevant variables such as disease severity, laboratory/biochemical parameters, smoking and weight.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	Section 9.7.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Section 9.3
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 9.7.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9.3
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 9.3
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	Section 9.3
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	Section 9.4.1

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☒	☐	Section 9.5
10.3 Are descriptive analyses included?	☒	☐	☐	Section 9.7.2
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	Section 9.7.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	Section 9.7.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	Section 9.3, Section 9.9

Comments:

Statistical precision is not estimated in this study as the extent of HZ and OI cases in the study population is not known. Outcome misclassification is possible if the wrong ICD-10/ICPC-2 code is registered in the registries. This cannot be accounted for, but the validity of the results are confirmed by the clinical experts participating in the study.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section 9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	Section 9.9
12.1.2 Information bias?	☒	☐	☐	Section 9.9
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	Section 9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Section 9.9

Comments:

Patients will be followed from first observed diagnosis in NPR to event of interest, end of follow-up or death, whichever comes first.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	Section 10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 10.1

Comments:

13.2 The protocol will be updated upon ethical approval.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	Section 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 12

Comments:

Name of the main author of the protocol: Arne Yndestad, NI PASS Study Lead, Pfizer

Date: 04/May/2020

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	A3921367_PROTOCOL and APPROVAL_V1.0_04MAY2020
Document Title:	A3921367_PROTOCOL and APPROVAL_V1.0_04MAY2020

Signed By:	Date(GMT)	Signing Capacity
Gruben, David C	08-Jun-2020 13:25:52	Final Approval
Henrohn, Dan	08-Jun-2020 14:37:28	Final Approval
De Bernardi, Barbara	10-Jun-2020 08:13:41	EUQPPV Approval