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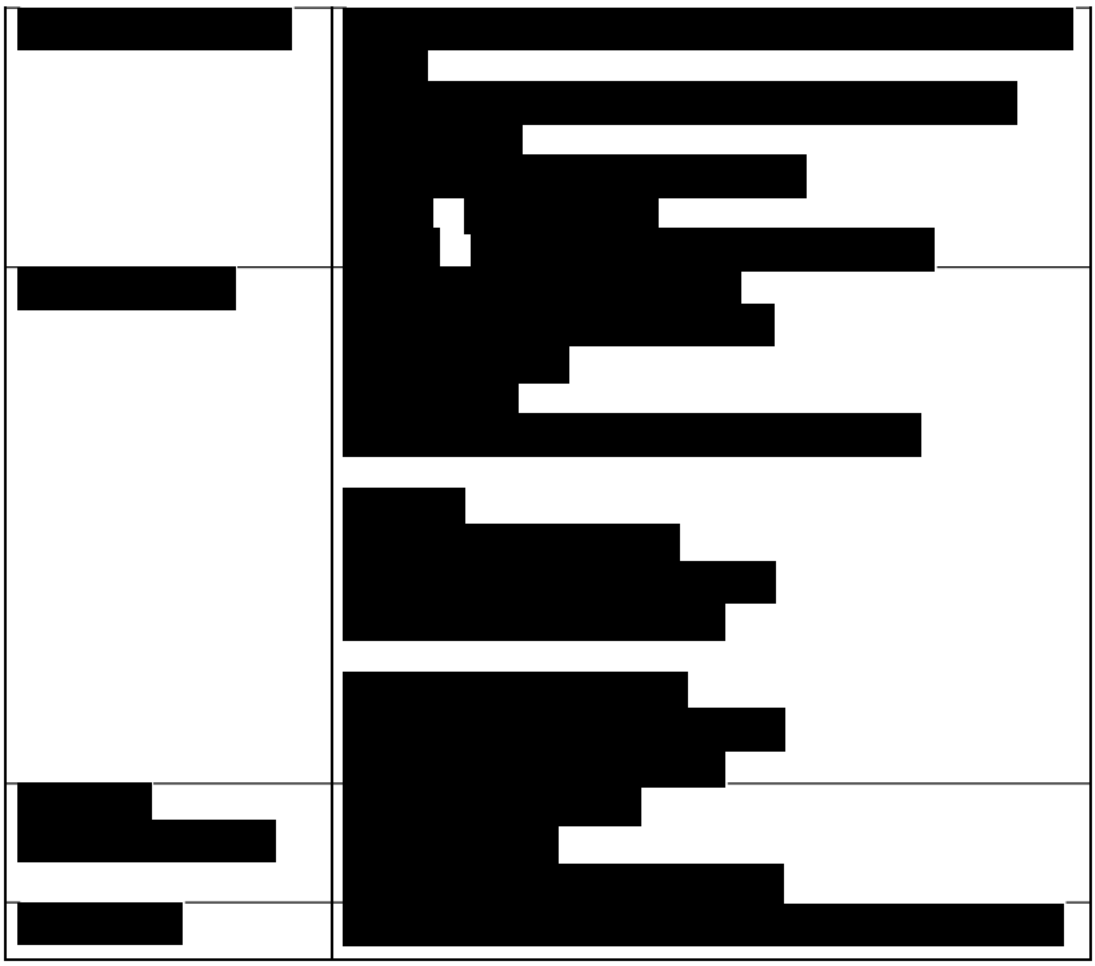

4. Abstract

Title	A Non-interventional Observational Longitudinal Post Authorization Safety Study (PASS) of SIMPONI® in Treatment of Ulcerative Colitis using Nordic National Health Registries
Protocol Number / Version	MK8259-013-00/*1*
Date	09-Jan-2015
Author	[redacted]
Rationale & Background	Simponi received European marketing authorization for treatment of moderately to severely active ulcerative colitis (UC) on 19-Sep-2013. This registry-based study is being established to provide additional information on colorectal cancer (CRC) and dysplasia,

	colectomy, and hepatosplenic T-cell lymphoma (HSTCL), as outlined in the Risk Management Plan for SIMPONI® that was approved with authorization of the UC indication. This study will use data from nationwide health registries in Denmark and Sweden. To provide a context for interpreting the long-term safety data on UC patients treated with golimumab (GLM), this study will also follow patients with UC treated with alternative therapies for UC, including non-biologic and biologic therapies. [redacted] UC is a severe, relatively frequent and life-long disease that may be associated with severe symptoms and impaired quality of life. In the case of intractable disease, colectomy may be indicated. Patients with UC are at increased risk of developing cancer of the colon and rectum compared to the general population.
Research Question(s) & Objective(s)	The study will address whether, in patients with UC, the use of GLM is associated with the risk of CRC, colorectal dysplasia, colectomy for intractable disease, and HSTCL as compared with alternative therapies for similar severity of disease. [redacted] **1. Primary objectives** 1.1. To characterize the clinical and demographic profile of first-time users of GLM in the treatment of UC, compared with the corresponding profile of first-

	time users of alternative therapies 1.2. To describe the risk of the following endpoints in patients exposed to GLM and exposed to alternative therapies 1.2a. Incident CRC or incident high grade colorectal dysplasia (HGD) as a composite endpoint 1.2b. Colectomy for intractable disease 1.3. If baseline characteristics suggest comparability of the respective cohorts, to estimate the risk of CRC/HGD and the risk of colectomy for intractable disease associated with GLM use relative to that associated with alternative therapies **2. Secondary objectives** 2.1. To describe the risk of incident CRC in patients exposed to GLM and exposed to alternative therapies 2.2. If baseline characteristics suggest comparability, to estimate the risk of CRC associated with GLM use relative to that associated with alternative therapies **3. Exploratory objectives** [redacted] 3.2. To describe the risk of incident HSTCL associated with exposures of interest
Study Design	This study is a long-term observational (non-interventional), prospective post-authorization safety study. It will use a new user cohort design with option for nested case control (NCC) analysis if the baseline characteristics of the cohorts indicate they are comparable. It will use data that were primarily collected for administrative reasons and to document clinical care. One exposed and two

	comparator cohorts will be assembled: Inception cohort of UC patients treated with GLM (GLM Cohort): this cohort will comprise all patients registered as new users of GLM. An inception comparator cohort of UC patients treated with anti-tumor necrosis factor (TNF) agents other than GLM (anti-TNF cohort): this cohort will comprise patients initiating one of the anti-TNF agents approved for the treatment of UC (currently infliximab and adalimumab). An inception cohort of UC patients treated with a thiopurine (azathioprine (AZA) or 6-mercaptopurine (6-MP)) (Thiopurine Cohort): this cohort will comprise patients initiating first time treatment with thiopurines (AZA or 6-MP), which are non-biologic immunomodulating drugs. Patients in each cohort will be followed for the outcomes of CRC, HGD, HSTCL, and colectomy through 18- Mar-2021. The pooled inception cohorts will form the basis of NCC studies. This pool will be the source for cases (patients experiencing an event of CRC, HGD, or colectomy) and controls. For each NCC analysis, four controls will be randomly selected for each case from risk sets assembled using incidence density sampling, matching on calendar time of outcome, clinical unit and age. [redacted]
Population	The study will include all patients with UC starting a cohort-defining treatment in Denmark and Sweden during the period 19-Sep-2013 (when GLM was approved for UC)

	through 18-Sep-2020.
Variables	***Exposures*** The main exposure of interest is treatment with GLM in patients with moderate-to-severe UC, compared with exposure to alternative therapies for moderate-to-severe UC for this indication: (1) other anti-TNF agents indicated for treatment of UC and (2) thiopurines (AZA or 6-MP). Over the course of time, UC patients who initiate GLM may have received or may later receive comparator treatments in various sequences. The actual patterns of treatment of UC in Denmark and Sweden are currently unknown to the Sponsor. [redacted] ***Outcomes*** *The primary outcomes* comprise: • Composite CRC /HGD • Colectomy due to intractable disease The *secondary* outcome comprises: • CRC The *exploratory* states and outcomes are specified as follows: • [redacted] • HSTCL The list of *covariates* includes: • Age • Gender • Country (Denmark or Sweden) • Time of enrolment (by calendar year) • Hospital department

	• Disease duration • Extent of disease • Disease activity (measured through proxies) • Treatments for UC not included as cohort-defining exposures • Co-morbidities • Colonoscopy
Data Sources	• Nationwide central hospital registration systems in Denmark and Sweden will be used to identify the study base population of patients with UC • Nationwide central hospital registration systems (in Denmark) and prescription registries (in Sweden) will be used to identify the GLM inception cohort and the inception comparator cohorts • Nationwide health registries (hospital activity registries, prescription registry, pathology registries, cancer registries) will be used to ascertain outcomes and changes in treatment • In the NCC studies, data on exposures and covariates will be validated and supplemented from medical records at the clinical units managing the care of the individual UC patients • Deaths will be captured from the Civil Registration Services in Denmark and Sweden. Death will be treated as a censoring event. • Data from the various sources will be linked at individual patient level using the unique Personal Identification Number (PIN) assigned to all citizens in Denmark and Sweden.
Study Size	The size of the study base (i.e., the current prevalent population of patients with UC) is estimated to be approximately 55,000 (20,000 patients in Denmark and 35,000 patients in Sweden).

	The sizes of the inception cohorts to be established and followed-up during the study are unknown. Based on the most recent sales projections, about 100 patients across both countries will initiate treatment with GLM each year leading to 2450 person-years of follow-up over the course of the study. Assuming a background incidence rate of 1/1000 PY for the composite outcome of CRC/HGD in the unexposed study population, 2450 person-years of GLM exposed person-time, α=0.05 and a 1:5 ratio of GLM to comparator group in follow-up time, this study is estimated have 80% power to exclude a relative risk of 4.0 for the CRC/HGD composite endpoint between GLM- and Thiopurine- exposed UC patients. Under the same conditions but assuming an incidence rate of 2/1000 PY for the composite outcome of CRC/HGD in the unexposed study population, this study will be able to exclude a relative risk of 2.9.
Data Analysis	• Baseline analyses will describe each cohort in terms of patient characteristics that can be ascertained from automated registry data. For each of the three inception cohorts, annual enrolment will be described, along with cumulative person-years accrued. • The risk of primary and secondary outcomes (CRC//HGD composite, colectomy due to intractable disease, CRC) will be estimated as cumulative incidence within each inception cohort in unadjusted and adjusted analyses. Censoring events will include death, emigration, and first occurrence of study outcomes. The cohort analyses will be conducted based on automated data only, using survival analysis techniques to estimate cumulative risks. • Provided that baseline characteristics indicate comparability of exposure groups, NCC studies will be performed within the pooled inception cohorts.

	Separate analyses are planned for the following outcomes: composite CRC/HGD, CRC alone, and colectomy for intractable disease. For each case of an outcome, four controls will be sampled at random from risk sets matched on calendar time of outcome, clinical unit and age. Exposure will be based on the history of treatment with GLM and its comparator treatments, ascertained from automated data and supplemented with information from chart review. The odds ratio will be used as the measure of association. In the analysis, adjustment will be made for relevant covariates. [redacted] • The incidence rate of HSTCL will be described for each inception cohort.
Milestones Start of data collection: End of data collection: Study progress report(s): Final report of study results:	 01-Dec-2015 31-Oct-2021 First report: Jun-2016, thereafter annually 31-Oct-2022

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