NOVARTIS

Global Clinical Epidemiology

Redacted Non-Interventional Study Protocol

CSPP100A2418

Title	Incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data
Protocol version identifier	v0 (revised)
Date of last version of protocol	24 March 2014
EU PAS register number	Not registered yet
Active substance	Aliskiren (C09XA/Renin-inhibitors)
Medicinal product	Rasilez®, Tekturna®
Product reference	MEA 034
Procedure number	EMEA/H/C/000780
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom

Joint PASS	No
Research questions and objectives	Due to the lack of real-world data on colorectal hyperplasia in association with aliskiren exposure, this study aims to determine [redacted]. Therefore, the overall objective is to [redacted]. Additionally, Novartis proposes to assess the [redacted].
Country (-ies) of study	United States
Author	[redacted]

QPPV or delegate | Signature | Date

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom
MAH contact person	[redacted]

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2 List of abbreviations

AB	Alpha Blocker
ACEI	Angiotensin-Converting Enzyme inhibitor
ARB	Angiotensin II Receptor Blocker
BB	Beta Blocker
CCB	Calcium Channel Blocker
CCI	Charlson Comorbidity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CPT	Current Procedural Terminology
CRC	Colorectal Cancer
EMA	European Medicine Agency
FOBT	Fecal Occult Blood Test
GI	Gastrointestinal
GIST	Gastrointestinal Stromal Tumor
GPI	Generic Product Identification
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
HCPCS	Healthcare Common Procedure Coding System
HR	Hazard Ratio
IC	Ischemic Colitis
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IQR	Interquartile Range
IR	Incidence Rate
NDC	National Drug Code
PPO	Preferred Provider Organization
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-Year
RMP	Risk Management Plan
US	United States

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Main protocol author	[redacted]
Principal investigator (PI)	[redacted]
MAH contact person	[redacted]

4 Abstract

Title	Incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data
Version and date	v0 (revised) 24 March 2014
Name and affiliation of main author	[redacted]
Rationale and background	Aliskiren (Rasilez®) is the first orally active direct renin inhibitor approved for the treatment of hypertension. Aliskiren's inhibitory effect on angiotensin I generation, through renin blockade, is highly specific and long-lasting (up to 24 hours). Colorectal hyperplasia is listed as a potential risk in the aliskiren risk management plan (RMP). This is based upon findings in a rodent carcinogenicity study; however, these findings have not been confirmed in a 2-year marmoset study or in targeted clinical studies including a colonoscopy study. Information in the literature on the incidence rate data of colorectal cancer or more general of colorectal hyperplasia in hypertensive patients is very limited. In that context and in the context of the renewal procedure for Rasilez® and Riprazo®, the Committee for Medicinal Products for Human Use (CHMP) requested Novartis to perform a non-interventional study on the incidence of colorectal hyperplasia in aliskiren-treated patients, as well as in hypertensive patients not exposed to aliskiren but treated with other antihypertensive drugs, and in a general, non-hypertensive population without antihypertensive treatment
Research question and objectives	Due to the lack of real-world data on colorectal hyperplasia in association with aliskiren exposure, Novartis will determine the [redacted]. The primary objective of this study is to [redacted]s. Novartis proposes to additionally determine [redacted]. As a secondary objective, the study will assess the [redacted].
Study design	Retrospective cohort study with secondary use of data derived from a large United States (US) health claims database ([redacted]) including a large aliskiren-exposed population. CHMP has approved the use of a US data source for this study in March 2013. The study period will be from 1 July 2006 through 30 June 2013 (or the most

	recent data available at the time of extraction)
Population	Using the index window from 1 January 2007 through 31 December 2012, patients (for the treatment groups) will be selected into the study cohort if they (1) have at least 1 prescription for an antihypertensive medication (the first such prescription will be defined as a patient's index date), (2) evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) in 180-day pre-index, (3) are 18+ years of age at the time of the index date, and (4) have continuous health plan enrollment for a minimum of 180 days prior to the index date and a minimum of 180 days following the index date (**Note:** sensitivity analyses will be performed to estimate the number of patients potentially lost because of this requirement, and we may adjust the post-index continuous enrollment criteria accordingly). Individuals for the general population control group will be selected into the study cohort if they have (1) no prescriptions for an antihypertensive medication between 1 July 2006 and 30 June 2013 (2) no evidence of a hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) any time between 1 July 2006 and 30 June 2013), (3) are 18+ years of age at the time of the index date, and (4) have continuous health plan enrollment for a minimum of 180 days prior to the index date and a minimum of 180 days following the index date. Patients will be excluded if they have a gap in enrollment ≥ 30 days at any time during the post-index period, no recorded gender or age, or other incomplete data (cost or otherwise) in the database. In addition, for the assessment of incident colorectal hyperplasia, we will exclude patients with a prior history of colorectal hyperplasia (defined as one or more diagnosis code for colorectal hyperplasia during the 180 day pre-index period or within the first 30 days following the index date). For the assessment of incident GI cancer, those with prior history of GI cancer (defined as one or more diagnosis code for GI cancer during the 180 day pre-index period or within the first 30 days following the index date). The follow-up period for a patient will begin on the index date and end on the earliest of one of the following: (1) recorded diagnosis of colorectal hyperplasia (when investigating colorectal hyperplasia) or recorded diagnosis of GI cancer (when investigating GI cancer); (2) end of enrollment in the database; (3) end of the study period (30 June 2013 [or latest available update])
Variables	Endpoints of interest: [redacted] Additional variables of interest include age, gender, geographic region,

	health plan type, payer type, available days of follow-up, Charlson comorbidity index, screening procedures for colorectal cancer or GI cancer, various comorbid conditions and drug therapies
Data sources	The [redacted] Health Plan Claims Database will be used for this retrospective database analysis. [redacted]. The [redacted] database is comprised of adjudicated claims for more than 150 million unique enrollees across the US. Enrollees with both medical and pharmacy coverage in 2011 represent 42 million active lives. Data are available from 2006 onwards; with a typical 3-4 month lag due to claims adjudication. The database includes both inpatient and outpatient diagnoses (in ICD-9-CM format) and procedures (in CPT-4 and HCPCS formats) as well as both retail and mail order prescription records. Available data on prescription records include the National Drug Code (NDC) and the Generic Product Identification (GPI) code, as well as the quantity of the medication dispensed. Additional data elements include demographic variables (age, gender, and geographic region), health plan type (e.g., health maintenance organization [HMO], preferred provider organization [PPO]), payer type (e.g., commercial, self-pay), provider specialty, and start and stop dates of health-plan enrollment.
Study size	Because this is an exploratory non-interventional study and not a hypothesis testing study, power analysis for sample size estimation was not conducted. Sample size will be determined based on the number of patients available in the database, and who meet study inclusion criteria. Antihypertensive treatment (aliskiren) group: all aliskiren patients fulfilling the inclusion/exclusion criteria will be included. Antihypertensive treatment (other than aliskiren) group: all other hypertensive patients treated with antihypertensives and fulfilling the inclusion/exclusion criteria will be included. General population group: a random sample of subjects (approximately the same number as the hypertensive cohort) fulfilling the inclusion/exclusion criteria for the general population will be included.
Data analysis	All analyses will employ SAS version 9.2 (SAS Institute Inc., Cary, NC). All data will be reported for the aggregate antihypertensive treatment population, as well as stratified by the incident versus prevalent antihypertensive treatment cohorts, and finally the general population control cohort. Unless otherwise specified, results for categorical measures will be provided as the frequency and percentage of total study patients observed in each category. For continuous variables, descriptive statistics (mean, standard deviation [SD], range, median, and interquartile range [IQR]) will be presented. When necessary, continuous variables will be categorized into intervals, with the distribution of patients for each interval provided. [redacted]

	[redacted]. No statistical analyses will be performed, and all comparisons between cohorts will be descriptive in nature only. [redacted]
Milestones	Registration in the EU PAS register: Date of protocol approval by the Pharmacovigilance Risk Assessment Committee (PRAC) + 1 month Start of data collection: Date of protocol approval by PRAC + 1 month End of data collection: Date of protocol approval by PRAC + 2 months Final report of study results: Date of protocol approval by PRAC + 12 months

5 Amendments and updates

Based on the 'Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's PASS protocol Assessment Report' dated 10 October 2013, and received by Novartis on 05 November 2013, and the PRAC Rapporteur's PASS protocol Assessment Report on the MAH's responses dated 06 February 2014 and received by Novartis on 05 March 2014 the protocol was revised and updated as outlined below. Revisions of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

The below table outlines in detail the protocol revisions.

Table 5-1 Updates of the protocol

Number	Date	Section of study protocol	Amendment or update	Reason
Update 1	26 November 2013	4 Abstract	Changes throughout the abstract to reflect various revisions of the protocol	Adapt abstract to revisions in the protocol based on Rapporteur's feedback
		7 Rationale and background & 8.2 Secondary objectives & 9.7.2.1 [redacted]	[redacted]	Following the Rapporteur's request
		9.2.1 Inclusion criteria	Exposure period for an antihypertensive medication was added	To better clarify the time period for the exposure inclusion criterion
			The criterion of a hypertension diagnosis will be applied to the pre-index period only – and no longer to both pre- and post-index periods	Addressing the Rapporteur's comment of removing the criterion for a hypertension diagnosis in aliskiren exposed patients
		9.3.2.1 Patient stratification by antihypertensive drug use	The free-dose combination of aliskiren with an ACE inhibitor was added as a specific sub-group of interest for the 'dual combination initiators including aliskiren' exposure group	Following the Rapporteur's request
		9.3.3 Other variables & 9.7.1.1 [redacted]	Age stratification changed to 18-44, 45-64, ≥ 65 years to have a separate age stratum for the age group ≥ 65	Adapted to take into consideration that the age group of ≥ 65 years is under-represented in the database and to get a specific age-stratified incidence rate estimate for that age category. The previously defined age stratum of ≥ 60 years would have been affected

Number	Date	Section of study protocol	Amendment or update	Reason
				by the under-representation of the age group ≥ 65 years
		9.3.3. Other variables	Added ulcerous recto-colitis, Crohn's disease, and diabetes mellitus as additional comorbid diseases of interest	Following the Rapporteur's request
			Added information on screening procedures for colorectal or GI cancer	To assess whether there is differential use of screening procedures across different antihypertensive exposure groups
			Added information on co-medications of interest (e.g. prescription non-steroidal anti-inflammatory drugs [NSAIDs] including aspirin, statins, hormone replacement therapy, proton pump inhibitors [PPIs], anti-diabetic drugs)	Following the Rapporteur's request
		9.7.1.1 [redacted]	[redacted]	Following the Rapporteur's request
			Stratified analyses in the prevalent treatment cohort taking into account the date of the first antihypertensive drug prescription identified in the 180 days period prior to the initial index date as the 'new index date' were skipped	Following the Rapporteur's request
		9.7.1.2 [redacted]	[redacted]	Following the Rapporteur's request

Number	Date	Section of study protocol	Amendment or update	Reason
			[redacted]	
			Stratified analyses in the prevalent treatment cohort taking into account the date of the first antihypertensive drug prescription identified in the 180 days period prior to the initial index date as the 'new index date' were skipped	Following the Rapporteur's request
		9.9 Limitations of the research method	Information was added that outcomes of interest identified by ICD-9-CM codes will not be further validated by medical chart review or review of diagnostic scans or tests	Following the Rapporteur's request
			Under-representation of the age group ≥ 65 years old and its potential impact on incidence rate estimates are discussed	Following the Rapporteur's request
			Information was added that a pre-index period of 180 days may be associated with a misclassification of cases as incident which in fact may be prevalent	Following the Rapporteur's request
		Annex 3.1 - Antihypertensive drugs – single agents	Annex 3.1 was updated to include the complete list of antihypertensive drugs of interest	Following the Rapporteur's request
		Annex 3.6 - Comorbid conditions	Added ulcerous rectocolitis, Crohn's disease, and diabetes mellitus as additional comorbid diseases of interest with the corresponding ICD-9 CM diagnosis codes	Following the Rapporteur's request
Update 2	24 March 2014	9.3.1.1	Mitigating strategy was added for addressing the lack of data to confirm diagnosis of colorectal hyperplasia (i.e., test results, imaging data, etc.)	Following the Rapporteur's request
		9.3.1.2	Mitigating strategy was added for addressing the lack of data to confirm diagnosis of GI cancer (i.e.,	Following the Rapporteur's request

Number	Date	Section of study protocol	Amendment or update	Reason
			test results, imaging data, etc.)	
		9.7.1	Information was added on lifestyle factors and additional stratifications (age group, sex)	Following the Rapporteur's request
		Annex 3-Table 3-1 Antihypertensive drugs – single agents	Update of codes	--
		Annex 3-Table 3-6 Comorbid conditions	Update of codes	
		Annex 3-Table 3-7 Screening procedures	Additional codes for screening procedures	

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	Date of Protocol approval by PRAC + 1 month
End of data collection	Date of Protocol approval by PRAC + 2 months
Registration in the EU PAS register	Date of Protocol approval by PRAC + 1 month
Final report of study results	Date of Protocol approval by PRAC + 12 months

PRAC = Pharmacovigilance Risk Assessment Committee

7 Rationale and background

Aliskiren (Rasilez®) is the first orally active direct renin inhibitor approved for the treatment of hypertension. Aliskiren's inhibitory effect on angiotensin I generation, through renin blockade, is highly specific and long-lasting (24 hours) (Frampton and Curran 2007).

Colorectal hyperplasia is listed as a potential risk in the aliskiren risk management plan (RMP). This is based upon findings in a rodent carcinogenicity study. However, these findings have not been confirmed in a 2-year marmoset study or in targeted clinical studies including a colonoscopy study. Therefore, the increased risk of colorectal hyperplasia observed in the rodent study may reflect high intraluminal drug concentrations in rats or could be a species-specific difference between rats and humans in response to aliskiren exposure [Rasilez/Riprazo/RasilezHCT/Rasilamlo/Rasitrio Safety Risk Management Plan 13-Sep-2012].

Epidemiologic studies examining a potential association of hypertension with the development of colorectal cancer (CRC) have reported inconsistent findings. Basically, the literature suggests that hypertension is not a risk factor for the development of CRC. Most published epidemiologic studies did not find an increased CRC risk in patients with hypertension compared to normotensive patients (e.g. Negri et al 1999, Lindgren et al 2005, Stürmer et al 2006, Kim et al 2007, Aleksandrova et al 2011). However, there is also some evidence from observational studies that hypertension might be associated with an increased CRC risk (Othman and Zin 2008, Stocks et al 2008, Pelucchi et al 2010), especially in hypertensive patients with type 2 diabetes mellitus and obesity (Stocks et al 2008). Additionally, there is some evidence that the mortality of CRC may be higher in hypertensive compared to normotensive patients (Batty et al 2003, Watanabe et al 2005).

Information in the literature on the incidence rate data of colorectal cancer or more general of colorectal hyperplasia in hypertensive patients is very limited though. Bhaskaran et al (2012) assessed the overall risk of cancer and risk of major site specific cancers (breast, lung, colon, prostate) in adult hypertensive patients who were exposed to angiotensin receptor blockers (ARBs) for at least one year using data from the United Kingdom (UK) General Practice Research Database (GPRD). They estimated an incidence rate of colon cancer in ‘ever users’ of ARBs of 1.0 per 1,000 patient-years (95% confidence interval [CI]: 0.9-1.1). In a similar retrospective analysis of adult hypertensive patients in the GPRD (Azoulay et al 2012), the

use of ARBs was associated with a modest decreased risk of colorectal cancer (adjusted risk ratio: 0.88; 95% CI: 0.81–0.96).

In the context of the renewal procedure for Rasilez® and Riprazo®, the Committee for Medicinal Products for Human Use (CHMP) requested from Novartis a "description and timelines for the new observational study on incidence of colorectal hyperplasia in aliskiren-treated patients". In addition, in October 2012, Novartis was asked "to compare the incidence of any safety endpoint among patients exposed to aliskiren with a population of hypertensive patients with similar characteristics (i.e. age, gender, time since first antihypertensive prescription of doctor diagnosis of hypertension, co-morbidity, multidrug therapy) not exposed to aliskiren but treated with other antihypertensive drugs. Furthermore, CHMP asked Novartis that "… incidence estimates from the general population ... not treated with any antihypertensive drug should be also provided".

Based on the CHMP request, Novartis committed to do a study to assess the incidence rates and relative risk of colorectal hyperplasia in a treated hypertensive population stratified by exposure to aliskiren. Furthermore, Novartis proposed to additionally assess the incidence rates and relative risk of gastrointestinal (GI) cancer in a treated hypertensive population stratified by exposure to aliskiren. This is because CHMP is also interested in the GI cancer risk in association with aliskiren and because Novartis was asked to add GI cancer as a pre-specified endpoint in all new aliskiren clinical trials.

In response to the Rapporteur's request from November 2013, Novartis will also assess the relative risk of colorectal hyperplasia and GI cancer in hypertensive patients exposed to aliskiren versus a general population sample of patients without a diagnosis of hypertension and without antihypertensive drug use.

8 Research question and objectives

Due to the lack of real-world data on colorectal hyperplasia in association with aliskiren exposure, Novartis will determine the [redacted]. Therefore, the overall objective of this non-interventional study is to [redacted].

8.1 Primary objective

[redacted]:

- [redacted]
- [redacted]
- [redacted])

As outlined above, Novartis proposes to additionally determine [redacted]

[redacted].

8.2 Secondary objective

As a secondary objective, the study will assess the [redacted].

9 Research methods

9.1 Study design

The planned study is a retrospective cohort study with use of secondary data derived from a large United States (US) health claims database ([redacted]).

[redacted]

Novartis acknowledges that the external validity (generalizability) of data derived from a US data source to a European population may be limited (see also Section 9.9), e.g. due to different distribution of risk factors for colorectal hyperplasia (such as ethnicity, life style habits [smoking, alcohol, diet, physical activity] etc.). Despite this limitation, Novartis still believes that a study based on US data would currently provide more valuable information than data from any European data source as the number of aliskiren-exposed patients in European data sources is low and therefore limits any conclusions. A feasibility assessment of the total number of patients with at least one recorded prescription for any aliskiren-containing drug (i.e. both single agent and fixed-dose combinations) identified in [redacted] (data from 1 July 2007 through 30 September 2012) within 180 days after a hypertension diagnosis showed that this population would encompass over 78,400 patients of which almost 64,900 patients have at least 6-month of continuous enrollment in their health plan before the indexed aliskiren claim. Of note: these counts are preliminary and would be lower once all inclusion/exclusion criteria were to be applied.

Such a large aliskiren-exposed population is currently not available in any European data source, and would be challenging or impossible to accrue even when using a European multi-database approach.

CHMP approved the use of a US data source for this study in March 2013.

9.2 Setting

This will be a retrospective cohort study with secondary use of data derived from the [redacted] database with a study period from 1 July 2006 through 30 June 2013 (or the most recent data available at the time of data extraction).

Using the index window from 1 January 2007 through 31 December 2012, patients will be selected into the study cohort if they meet the below criteria.

9.2.1 Inclusion criteria

Treated cohorts (exposed to/not exposed to aliskiren)

- At least 1 prescription for an antihypertensive medication (Annex 3.1, Annex 3.2, Annex 3.3) between 1 July 2006 and 30 June 2013;
- Evidence of at least 1 hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) in the 180-day pre-index period
- 18 years of age or older at the time of the index date (see Section 9.2.3 for details);
- Continuous health plan enrollment for a minimum of 180 days prior to the index date (pre-index period) and a minimum of 180 days following the index date (post-index period). (**Note:** sensitivity analysis will be performed to determine the number of patients potentially lost because of this requirement [i.e. 180 days post-index period]).

Controls (no diagnosed hypertension, no antihypertensive drug use)

- No prescriptions for an antihypertensive medication (Annex 3.1, Annex 3.2, Annex 3.3) between 1 July 2006 and 30 June 2013;
- No evidence of a hypertension diagnosis (ICD-9-CM codes 401.xx-405.xx) any time between 1 July 2006 and 30 June 2013;
- 18 years of age or older at the time of the index date (see Section 9.2.3 for details);
- Continuous health plan enrollment for a minimum of 180 days prior to the index date (pre-index period) and a minimum of 180 days following the index date (post-index period).

9.2.2 Exclusion criteria

Treated cohorts (exposed to/not exposed to aliskiren)

- For the assessment of incident colorectal hyperplasia: prior history of colorectal hyperplasia (for definition of colorectal hyperplasia, see Annex 3.4 for related ICD-9-CM diagnosis codes) in the 180 days prior to the index date or within the first 30 days following drug initiation;
- For the assessment of incident GI cancer: prior history of GI cancer (see Annex 3.5 for related ICD-9-CM diagnosis codes) in the 180 days prior to the index date or within the first 30 days following drug initiation;
- A gap in enrollment $\geq$ 30 days at any time during the post-index period;
- Invalid or missing data (including cost data);
- No recorded gender or age.

Controls

- For the assessment of incident colorectal hyperplasia: prior history of colorectal hyperplasia (defined as one or more diagnosis code for colorectal hyperplasia during the 180 day pre-index period or within the first 30 days following the index date);
- For the assessment of incident GI cancer: prior history of GI cancer (defined as one or more diagnosis code for GI cancer during the 180 day pre-index period or within the first 30 days following the index date);
- A gap in enrollment ≥ 30 days at any time during the post-index period;
- Invalid or missing data (including cost data);
- No recorded gender or age.

9.2.3 Patient index date selection

Treated cohorts (exposed to/not exposed to aliskiren)

Pharmacy claims for all hypertensive patients will be examined starting on 1 January 2007 and continuing through the end of the index window (31 December 2012) to identify any claims for aliskiren (Annex 3.1). Patients with at least 1 prescription for aliskiren **at any time** during the index window, regardless of evidence of any other antihypertensive medication use prior to the aliskiren claim, will be considered index aliskiren patients, and the first aliskiren claim identified during the index window will be considered the index date.

For all other hypertensive patients with no evidence of any aliskiren claims during the index window, the date of the first prescription for an antihypertensive medication other than aliskiren (Annex 3.1, Annex 3.2, Annex 3.3) will be considered the index date.

Controls

A random date within the index window (1 January 2007 and 31 December 2012) will be chosen to represent the index date for the general population patients; general population patients will be followed for the same period as individuals in the hypertensive cohort.

The table below further outlines the time periods for 'index window' and 'index date'.

Table 9-1 Definitions 'index window', 'selection window, and 'index date'

Term	Definition, timing
Index window	1 January 2007 – 31 December 2012
Index date (aliskiren)	Date of first aliskiren claim within the index window
Index date (all other antihypertensive medications)	Date of first prescription for antihypertensive medication (other than aliskiren) within the index window
New index date for prevalent hypertension cohort	The date created for the prevalent hypertension cohort to reflect the date of the first antihypertensive drug prescription identified in the 180 days prior to the initial index date (see Section 9.7)

9.2.4 Follow-up period

The follow-up period for a patient will begin on the index date and end on the earliest of one of the following:

1. Recorded diagnosis of colorectal hyperplasia (when investigating colorectal hyperplasia) or recorded diagnosis of GI cancer (when investigating GI cancer);
2. End of enrollment in the database;
3. End of the study period (30 June 2013 [or latest available update]).

9.3 Variables

9.3.1 Endpoints of interest

9.3.1.1 [redacted]

[redacted]

9.3.1.2 [redacted]

[redacted]

9.3.2 Exposure of interest –

[redacted]

9.3.2.1 [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
  - [redacted]
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  - [redacted]

[redacted]

[redacted]

[redacted]

[redacted].

9.3.2.2 [redacted]

[redacted]

[redacted].

9.3.3 Other variables

Demographic characteristics will be based on data from the index date and include the following:

- Age and age group (18-44, 45-64, ≥ 65 years)
- Gender (male, female)
- Geographic region (Northeast, Midwest, South, West)
- Health plan type (consumer-directed healthcare product, HMO, indemnity, point-of-service [POS], PPO, unknown)
- Payer type (commercial, Medicaid, Medicare Risk, self-insured, unknown)

Baseline clinical characteristics also will be evaluated from the index date or during the defined pre-index period, unless otherwise noted:

- Available days of follow-up (post-index)
- Charlson Comorbidity Index (CCI) score, Dartmouth-Manitoba adaptation (pre-index); **Note:** the Dartmouth-Manitoba adaptation of the CCI is the recommended approach for longitudinal claims database analyses where DRG and ICD procedure codes are not consistently available
- Comorbid conditions (history of helicobacter pylori infection, history of stomach lymphoma, history of stomach surgery, irritable bowel syndrome, ischemic bowel disease, chronic diarrhea, chronic constipation, peripheral vascular disease, vascular insufficiency of intestine, acute coronary syndrome, coronary heart disease or angina [including acute coronary syndrome], heart failure, stroke or transient ischemic attack), ulcerous rectocolitis, Crohn's disease, diabetes mellitus, pre- and post-index (Annex 3.6)
- Screening procedures for colorectal cancer or GI cancer (for colorectal cancer: fecal occult blood test (FOBT), sigmoidoscopy, and colonoscopy; for GI cancer: endoscopy, gastroscopy, H. pylori testing), pre- and post-index) (Annex 3.7)
- Co-medication (e.g. prescription non-steroidal anti-inflammatory drugs [NSAIDs] including aspirin, statins, hormone replacement therapy, proton pump inhibitors [PPIs], anti-diabetic drugs)

9.4 Data source

The data for this study will be retrieved from the [redacted] Health Plan Claims Database. [redacted] will be the designated contract research organization (CRO) performing the analyses following their own internal standard operating procedures (SOPs).

[redacted]

The aggregated [redacted] database is comprised of adjudicated claims for more than 150 million unique enrollees across the United States. Enrollees with both medical and pharmacy coverage in 2011 represent 42 million active lives. Data are available from 2006 onwards; with a typical 3-4 month lag due to claims adjudication.

[redacted] data has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each 3-digit zip code and every Metropolitan Statistical Area of the US are represented, with coverage of data from 96% of US hospitals, 91% of all US doctors, and representation from 85% of the Fortune 100 companies.

In addition to standard fields such as inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, [redacted] has detailed information on the pharmacy and medical benefit (copayment, deductible), the inpatient stay (admission type and source, discharge status) and provider details (specialty, provider ID). All 3-digit zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography.

Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, gender, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-pay), and start and stop dates of health-plan enrolment.

Due to the broad reach of the data, records in the [redacted] database are representative of the national, commercially insured population in terms of age and gender for individuals aged 65 and under. The data are also longitudinal, with more than 30 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are Health Insurance Portability and Accountability Act (HIPAA) compliant to protect patient privacy.

This is a non-interventional study based on secondary use of [redacted] data and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule.

9.5 Study size

Because this is an exploratory, non-interventional study and not a hypothesis testing study, power analysis for sample size estimation was not conducted. Sample size will be determined based on the number of patients available in the database, and who meet the study inclusion criteria.

Antihypertensive treatment (aliskiren) group: all hypertensive aliskiren treated patients fulfilling the eligibility criteria will be included.

Antihypertensive treatment (other than aliskiren) group: all hypertensive patients treated with other (non-aliskiren) antihypertensive agents and fulfilling eligibility will be included.

General population group: a random sample of subjects (approximately the same number as the hypertensive cohort) fulfilling the eligibility criteria will be included.

9.6 Data management

All analyses will employ SAS version 9.2 (SAS Institute Inc., Cary, NC).

9.7 Data analysis

All analyses will be performed by [redacted].

All data will be reported for the aggregate antihypertensive treatment population, as well as stratified by the incident versus prevalent antihypertensive treatment cohorts, and finally the general population control cohort. Unless otherwise specified, results for categorical measures

will be provided as the frequency and percentage of total study patients observed in each category. For continuous variables, descriptive statistics (mean, standard deviation [SD], range, median, and interquartile range [IQR]) will be presented. When necessary, continuous variables will be categorized into intervals, with the distribution of patients for each interval provided. No statistical analyses will be performed, and all comparisons between cohorts will be descriptive in nature only.

9.7.1 Primary analysis

9.7.1.1 [redacted]

[redacted]. Patients' exposure time to the drug regimen will be defined by the total number of days a patient is on therapy for each drug. For combination therapy, therapy days will be defined as the total number of days that the antihypertensive drug is on-hand for all drugs in the regimen. A treatment gap of 60 days will be allowed, so as to capture those patients who may be on combination therapy but may experience a gap in days supply of one or more drugs in the regimen. Thus, a patient will be considered on therapy if they have days supply of all of the drugs in the regimen within 60 days of the end of supply of the previous fill. [redacted].

Additional stratifications will be performed in patients with the following comorbidities: diabetes, irritable bowel syndrome, ischemic bowel disease, ulcerative colitis, ulcerous rectocolitis, Crohn's disease, familial adenomatous polyps, hereditary nonpolyposis.

Note: based on ICD-9-CM code, familial adenomatous polyps cannot be distinguished from other types of benign or malignant neoplasms of the rectum/colon, including hereditary nonpolyposis (Annex 3.6). [redacted]

Furthermore, stratifications will be performed in patients with exposure at the index date and post-index with the following drug classes: prescription non-steroidal anti-inflammatory drugs (NSAIDs), statins. [redacted]

[redacted]; however, there are some challenges with this approach that must be recognized. First, this will be limited only to severe cases of the condition(s) in question,

thus precluding a large proportion of individuals with the actual conditions(s). Secondly, these diagnosis codes may likely be under-reported in the database due to the reporting structure in the US (for example, diabetes and cardiovascular diseases are highly comorbid with obesity, and are much more likely to be presented as the diagnosis rather than obesity).

[redacted]

As previously noted, it is unlikely that we will be able to differentiate between cysts, polyps and neoplasms within the claims data. Therefore, rates will be reported for overall colorectal hyperplasia.

9.7.1.2 [redacted]

[redacted]. Patients' exposure time to the drug regimen will be defined by the total number of days a patient is on therapy for each drug. For combination therapy, therapy days will be defined as the total number of days that the antihypertensive drug is on-hand for all drugs in the regimen. A treatment gap of 60 days will be allowed, so as to capture those patients who may be on combination therapy but may experience a gap in days supply of one or more drugs in the regimen. Thus, a patient will be considered on therapy if they have days supply of all of the drugs in the regimen within 60 days of the end of supply of the previous fill. [redacted]

Additional stratifications will be performed in patients with the following comorbidities: helicobacter pylori infection, diabetes, chronic stomach inflammation, stomach polyps (Annex 3.6). [redacted].

Furthermore, stratifications will be performed in patients with exposure at the index date with the following drug classes: proton pump inhibitors (PPIs), statins, hormone replacement therapy (HRT). [redacted].

[redacted]; however, there are some challenges with this approach that must be recognized. First, this will be limited only to severe cases of the condition(s) in question, thus precluding a large proportion of individuals with the actual conditions(s). Secondly, these diagnosis codes may likely be under-reported in the database due to the reporting structure in

the US (for example, diabetes and cardiovascular diseases are highly comorbid with obesity, and are much more likely to be presented as the diagnosis rather than obesity).

[redacted]

9.7.2 Secondary analysis

9.7.2.1 [redacted]

[redacted]

To control for confounding by indication we will use propensity score methods (e.g. by matching on propensity score) taking into consideration the following covariates:

- Age (at index date)
- Sex
- Antihypertensive therapy (monotherapy, dual, or triple plus therapy; number of prescriptions/duration of therapy)
- Comorbid conditions (e.g. hyperlipidemia, diabetes, ischemic heart disease, history of inflammatory bowel disease, CCI)
- Co-medication (e.g. NSAIDs including aspirin, statins, proton pump inhibitors, hormone replacement therapy, anti-diabetic drugs)
- Others (e.g. geographic region, health plan type, payer type, prescriber specialty, presence of screening procedures for colorectal cancer or GI cancer)

[redacted].

9.8 Quality control

Data contributions from the [redacted] claims database are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. All statistical codes will be quality checked by a separate programmer prior to closing out the study. At the end of each project, all project related programming code, tables, and documents are archived and stored on a server where they can

be retrieved when needed in the future. A password is required to log into the system where all data are stored.

9.9 Limitations of the research methods

As a non-interventional study, there are inherent limitations with respect to potential for alternate explanations for any observed association. The source claims data include limitations with respect to certainty of capture of exposure, covariates, and outcomes.

Health claims databases such as [redacted] do not systematically capture information on potentially relevant potential confounders or effect modifiers such as lifestyle factors (including e.g. smoking, alcohol use, diet, physical activity), body mass index (BMI), socio-economic status, race/ethnicity, etc.

If an incorrect diagnosis was listed in the medical record, or the medical record was incomplete, then patients might have been misclassified, resulting in selection bias. Furthermore, outcomes of interest identified by ICD-9-CM codes will not be further validated by medical chart review or review of diagnostic scans or tests. This is not possible given the fact that the data use agreement prohibits the behavior to track individual patients back in the claims database for the sake of patient privacy protection.

The claims dataset does not include uninsured patients and those covered only by Medicare (Part D, mainly for patients aged 65+ years old), and the source population consists primarily of commercially insured patients in the US; therefore, the results are most generalizable to similar commercially insured patients and may not be generalizable to other populations if they differ in their accessibility to physician services or prescriptions. The under-representation of the age group 65+ years may lead to an underestimate of the overall incidence rate estimates for colorectal and GI cancer, while the age-stratified estimates would not be affected (especially in the age category 65+ years).

The database does not provide information on systemic factors that could affect care, including plan limits on medication use. Due to the large and diverse nature of the plans in the database, however, these factors are not expected to have a major impact on the study results.

Given the lack of earlier diagnosis/prescription data values in a health plan claims database and the 180-day pre-index period applied in this study (to balance look-back duration vs. study sample size), it may not be possible for researchers to determine the time of a “true” first hypertension diagnosis.

The chosen 180-day time window prior to the index date to identify those patients with a prior history of colorectal hyperplasia or GI cancer (as an exclusion criterion) has its limitations, namely that those patients with a colorectal hyperplasia or GI cancer diagnosis recorded prior to this 180-day pre-index period will be missed. The consequence is that these patients would not be excluded as patients with prevalent disease but – in case they are fulfilling all other inclusion criteria – would be included and misclassified as incident cases. However, it is assumed that this potential misclassification will not be differential across the different antihypertensive treatment cohorts.

The date of diagnosis in a health plan claims database may not correspond with the real onset of cancer but is often linked to initial clinical signs of cancer (e.g. fecal blood in the case of

colorectal cancer) but the initiation and progression of cancer may have been many years earlier. A detection bias may occur under the assumption that patients with aliskiren exposure (or patients with exposure to non-aliskiren antihypertensive drug exposure) have differential use of screening procedures to identify colorectal cancer or GI cancer at an earlier stage. For that reason, Novartis proposes to include the assessment of screening procedures for colorectal cancer and GI cancer pre- and post-index.

The external validity (generalizability) of data derived from a US data source to a European population may be limited, e.g. due to different distribution of risk factors for colorectal hyperplasia or GI cancer (such as ethnicity, life style habits [smoking, alcohol, diet, physical activity], family history, conditions that irritate or compromise the gastrointestinal tract or organs, etc.), or due to different health services delivery and/or payment systems.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

As a non-interventional study, by definition no interventions will be made to patients under study.

In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data included in the analysis are de-identified; therefore, this study will be exempt from Institutional Review Board (IRB) review.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

11 Management and reporting of adverse events/adverse reactions

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011) there is no requirement for reporting of adverse drug reactions from secondary use of data (such as electronic health care databases). As this is a study based on secondary use of US health claims data, safety monitoring and safety reporting on an individual case level is not applicable. In studies based on secondary data sources with a safety relevant result, only aggregated safety results, i.e. the overall association between an exposure and an outcome, should be reported and be included in the periodic aggregated regulatory reports submitted to Health Authorities.

12 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly

accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

In order to allow EMA to review in advance the results and interpretations to be published, a final (accepted) manuscript of this study will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

13 References (available upon request)

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Annex 1 – List of stand-alone documents

Not applicable

Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP)

Study title:
Incidence of colorectal hyperplasia and gastrointestinal cancer in treated adult hypertensive patients in the United States – a cohort study based on secondary use of health claims data

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	17
1.1.2 End of data collection[2]	☒	☐	☐	17
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	17
1.1.6 Final report of study results.	☒	☐	☐	17

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	17, 18
2.1.2 The objective(s) of the study?	☒	☐	☐	18, 19
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20-22

[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 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.4 Which formal hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	
	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	19
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	23
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	28-30

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	20-22
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	20
4.2.2 Age and sex?	☒	☐	☐	20
4.2.3 Country of origin?	☒	☐	☐	20
4.2.4 Disease/indication?	☒	☐	☐	20
4.2.5 Co-morbidity?	☒	☐	☐	26
4.2.6 Seasonality?	☐	☒	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	20-22

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	23-25
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	23-25
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	23-25
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	23-25
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	23
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	25, 26, 28, 29
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	28, 29

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	26, 27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	26, 27
8.1.3 Covariates?	☒	☐	☐	25, 26
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	26, 27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	23, 24
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	25, 26
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	20
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	47-50

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	44-46
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	28-30
10.2 Is the choice of statistical techniques described?	☒	☐	☐	28-30
10.3 Are descriptive analyses included?	☒	☐	☐	27-30
10.4 Are stratified analyses included?	☒	☐	☐	24, 25, 28-30
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	30
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	30

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	21

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	30
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	20, 31, 32
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	31, 32
12.1.2 Information biases?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20, 27
12.3 Does the protocol address other limitations?	☒	☐	☐	31, 32

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee / Institutional Review Board approval been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	32

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12-16

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	33
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	33

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature: _____

Annex 3 – Additional information

Annex 3.1 - Antihypertensive drugs – single agents

Annex 3-Table 3-1 Antihypertensive drugs – single agents

Drug class	Generic names	GPI codes/HCPC codes
Direct renin inhibitor	aliskiren	3617*
Angiotensin-converting enzyme inhibitors (ACEI)	captopril, enalapril, lisinopril, benazepril, fosinopril, perindopril, quinapril, ramipril, trandolapril, moexipril	3610*, 369985*, 36991*
Angiotensin II receptor blockers (ARB)	valsartan, candesartan, losartan, eprosartan, irbesartan, olmesartan, telmisartan, azilsartan	3615*, 36994*
Alpha blockers (AB)	prazosin, terazosin, doxazosin, alfuzosin, tamsulosin, silodosin	362020*, (excluding 36202010*, 36202020*), 568520*, 568599022*
Beta blockers (BB)	atenolol, metoprolol, carvedilol, acebutolol, bisoprolol, nadolol, nebivolol, propranolol, pindolol, betaxolol, timolol, penbutolol	33*, 3699*
Calcium channel blockers (CCB)	amlodipine, diltiazem, verapamil, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, clevidipine	34*, 409925* / C9248
Diuretics	thiazides (hydrochlorothiazide, chlorthiazide, chlorthalidone, indapamide, methylclothiazide, metolazone);	2699100220*, 369910023*, 3699500260*, 3699700260*, 369980022*, 3720*, 3750*, 3760*, 379900* /
	loop diuretics (furosemide, torasemide, bumetanide, ethacrynic acid); or	S0171, J1940, J3265, J1205
	potassium-sparing diuretics (amiloride, spironolactone, triamterene)	
Vasodilators	hydralazine, diazoxide, minoxidil	3640*
Selective aldosterone receptor antagonists	eplerenone	36250030*
Centrally acting alpha agonists	clonidine, guanabenz, guanfacine, methyldopa, alseroxylon, deserpidine, rauwolfia (serpentina), reserpine, guanadrel, guanethidine, rescinnamine	362010*, 362030*, 36202010*, 36202020*

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Annex 3.2 - Antihypertensive drugs – dual fixed combinations

Annex 3-Table 3-2 Antihypertensive drugs - dual fixed combinations

Drug classes	GPI codes
AB + Diuretic	369955027*
ACEI + CCB	369915*
ACEI + Diuretic	369918*
ARB + CCB	369930*
ARB + Diuretic	369940*
BB + Diuretic	369920*
Centrally acting alpha agonist + Diuretic	369910*, 369950*, 369955023* (excluding 369910022*, 36991003*)
Centrally acting alpha agonist + Vasodilator	369910022*
Direct renin inhibitor + ARB	369965*
Direct renin inhibitor + CCB	369967*
Direct renin inhibitor + Diuretic	369960*
Vasodilator + Diuretic	369990*

AB = Alpha Blocker; ACEI = Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin II Receptor Blocker; BB = Beta Blocker; CCB = Calcium Channel Blocker.

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Annex 3.3 - Antihypertensive drugs - triple-plus fixed combinations

Annex 3-Table 3-3 Antihypertensive drugs - triple-plus fixed combinations

Drug classes	GPI codes
ARB + CCB + Diuretic	369945*
Centrally acting alpha agonist + Vasodilator + Thiazide diuretic	36991003*

ARB = Angiotensin II Receptor Blocker; CCB = Calcium Channel Blocker.

* Includes all lower level hierarchical Generic Product Identifier (GPI) identifiers providing increasingly more specific information about the drug.

Annex 3.4 - Proposed diagnosis codes for colorectal hyperplasia

Annex 3-Table 3-4 Diagnosis codes for colorectal hyperplasia

ICD-9-CM code	Description	Type
153	Malignant neoplasm of colon	Malignant neoplasm
153.0	Malignant neoplasm of hepatic flexure	Malignant Neoplasm
153.1	Malignant neoplasm of transverse colon	Malignant neoplasm
153.2	Malignant neoplasm of descending colon. Left colon	Malignant neoplasm
153.3	Malignant neoplasm of sigmoid colon. Sigmoid (flexure)	Malignant neoplasm
153.4	Malignant neoplasm of cecum. Ileocecal valve	Malignant neoplasm
153.6	Malignant neoplasm of ascending colon. Right colon	Malignant neoplasm
153.7	Malignant neoplasm of splenic flexure	Malignant neoplasm
153.8	Malignant neoplasm of other specified sites of large intestine. Malignant neoplasm of contiguous or overlapping sites of colon whose point of origin cannot be determined	Malignant neoplasm
153.9	Malignant neoplasm of colon, unspecified. Large intestine NOS	Malignant neoplasm
154	Malignant neoplasm of rectum, rectosigmoid junction, and anus	Malignant neoplasm
154.0	Malignant neoplasm of rectosigmoid junction. Colon with rectum; Rectosigmoid (colon)	Malignant neoplasm
154.1	Malignant neoplasm of rectum. Rectal ampulla	Malignant neoplasm
154.8	Malignant neoplasm of other sites of rectum, rectosigmoid junction, and anus. Anorectum; Cloacogenic zone; Malignant neoplasm of contiguous or overlapping sites of rectum, rectosigmoid junction, and anus whose point of origin cannot be determined	Malignant neoplasm
230.3	Carcinoma in situ of colon	Malignant neoplasm
230.4	Carcinoma in situ of rectum	Malignant neoplasm
211.3	Benign neoplasm of colon. Appendix; Cecum; Ileocecal valve; Large intestine NOS	Benign neoplasm
211.4	Benign neoplasm of rectum and anal canal. Anal canal or sphincter; Anus NOS; Rectosigmoid junction	Benign neoplasm
V12.72	Personal history of colonic polyps	Personal history of colonic polyps
569.0	Anal and rectal polyp. Anal and rectal polyp NOS	Anal and rectal polyps

Note: We are unable to clearly distinguish between colorectal polyps, cysts and neoplasms within the data. Colorectal polyps can be benign or malignant neoplasms as indicated in the far right column of the above table. There are no specific ICD-9-CM diagnosis codes for colorectal cysts; if they are benign they would be assigned to the benign neoplasm codes. There is a separate code for rectal polyps (569.0)

Annex 3.5 - Proposed diagnosis codes for GI cancer

Annex 3-Table 3-5 Diagnosis codes for GI cancer

ICD-9-CM code	Description	Type
144	Malignant neoplasm of floor of mouth	Malignant neoplasm of mouth
144.0	Malignant neoplasm of anterior portion of floor of mouth	Malignant neoplasm of mouth
144.1	Malignant neoplasm of lateral portion of floor of mouth	Malignant neoplasm of mouth
144.8	Malignant neoplasm of other sites of floor of mouth	Malignant neoplasm of mouth
144.9	Malignant neoplasm of floor of mouth, part unspecified	Malignant neoplasm of mouth
145	Malignant neoplasm of other and unspecified parts of mouth	Malignant neoplasm of mouth
145.0	Malignant neoplasm of cheek mucosa	Malignant neoplasm of mouth
145.1	Malignant neoplasm of vestibule of mouth	Malignant neoplasm of mouth
145.2	Malignant neoplasm of hard palate	Malignant neoplasm of mouth
145.3	Malignant neoplasm of soft palate	Malignant neoplasm of mouth
145.4	Malignant neoplasm of uvula	Malignant neoplasm of mouth
145.5	Malignant neoplasm of palate, unspecified	Malignant neoplasm of mouth
145.6	Malignant neoplasm of retromolar area	Malignant neoplasm of mouth
145.8	Malignant neoplasm of other specified parts of mouth	Malignant neoplasm of mouth
145.9	Malignant neoplasm of mouth, unspecified	Malignant neoplasm of mouth
150	Malignant neoplasm of esophagus	Malignant neoplasm of esophagus
150.0	Malignant neoplasm of cervical esophagus	Malignant neoplasm of esophagus
150.1	Malignant neoplasm of thoracic esophagus	Malignant neoplasm of esophagus
150.2	Malignant neoplasm of abdominal esophagus	Malignant neoplasm of esophagus
150.3	Malignant neoplasm of upper third of esophagus	Malignant neoplasm of esophagus
150.4	Malignant neoplasm of middle third of esophagus	Malignant neoplasm of esophagus
150.5	Malignant neoplasm of lower third of esophagus	Malignant neoplasm of esophagus
150.8	Malignant neoplasm of other specified part of esophagus	Malignant neoplasm of esophagus
150.9	Malignant neoplasm of esophagus, unspecified	Malignant neoplasm of esophagus
151	Malignant neoplasm of stomach	Malignant neoplasm of stomach
151.0	Malignant neoplasm of cardia	Malignant neoplasm of stomach
151.1	Malignant neoplasm of pylorus	Malignant neoplasm of stomach
151.2	Malignant neoplasm of pyloric antrum	Malignant neoplasm of stomach
151.3	Malignant neoplasm of fundus of stomach	Malignant neoplasm of stomach

ICD-9-CM code	Description	Type
151.4	Malignant neoplasm of body of stomach	Malignant neoplasm of stomach
151.5	Malignant neoplasm of lesser curvature of stomach, unspecified	Malignant neoplasm of stomach
151.6	Malignant neoplasm of greater curvature of stomach, unspecified	Malignant neoplasm of stomach
151.8	Malignant neoplasm of other specified sites of stomach	Malignant neoplasm of stomach
151.9	Malignant neoplasm of stomach, unspecified	Malignant neoplasm of stomach
152	Malignant neoplasm of small intestine, including duodenum	Malignant neoplasm of small intestine
152.0	Malignant neoplasm of duodenum	Malignant neoplasm of small intestine
152.1	Malignant neoplasm of jejunum	Malignant neoplasm of small intestine
152.2	Malignant neoplasm of ileum	Malignant neoplasm of small intestine
152.3	Malignant neoplasm of Meckel's diverticulum	Malignant neoplasm of small intestine
152.8	Malignant neoplasm of other specified sites of small intestine	Malignant neoplasm of small intestine
152.9	Malignant neoplasm of small intestine, unspecified	Malignant neoplasm of small intestine
153.5	Malignant neoplasm of appendix vermiformis	Malignant neoplasm of appendix
154.2	Malignant neoplasm of anal canal. Anal sphincter	Malignant neoplasm of anus
154.3	Malignant neoplasm of anus, unspecified	Malignant neoplasm of anus
230.0	Carcinoma in situ of lip, oral cavity, and pharynx. Gingiva; Hypopharynx	Malignant neoplasm of mouth
230.1	Carcinoma in situ of esophagus	Malignant neoplasm of esophagus
230.2	Carcinoma in situ of stomach	Malignant neoplasm of stomach
230.5	Carcinoma in situ of anal canal	Malignant neoplasm of anus
230.6	Carcinoma in situ of anus, unspecified	Malignant neoplasm of anus
230.7	Carcinoma in situ of other and unspecified parts of intestine	Malignant neoplasm of small intestine
159.0	Malignant neoplasm of intestinal tract, part unspecified. Intestine NOS	Gastrointestinal stromal tumor (GIST)*
159.8	Malignant neoplasm of other sites of digestive system and intra-abdominal organs. Malignant neoplasm of digestive organs and peritoneum whose point	GIST*
159.9	Malignant neoplasm of ill-defined sites within the digestive organs and peritoneum. Alimentary canal or tract NOS; Gastrointestinal tract NOS	GIST*
238.1	Neoplasm of uncertain behavior of connective and other soft tissue. Peripheral,	GIST*

ICD-9-CM code	Description	Type
	sympathetic, and parasympathetic nerves and ganglia; Stromal tumors	
171.5	Malignant neoplasm of connective and other soft tissue of abdomen	GIST*
V10.00	Personal history of malignant neoplasm of unspecified site in gastrointestinal tract	Personal history codes
V10.01	Personal history of malignant neoplasm of tongue	Personal history codes
V10.02	Personal history of malignant neoplasm of other and unspecified parts of oral cavity	Personal history codes
V10.03	Personal history of malignant neoplasm of esophagus	Personal history codes
V10.04	Personal history of malignant neoplasm of stomach	Personal history codes

* **Note:** There are no specific ICD-9-CM diagnosis codes for GIST. Some possible codes for GIST are listed

Annex 3.6 - Comorbid conditions

Annex 3-Table 3-6 Comorbid conditions

Condition	ICD-9-CM diagnosis codes
Helicobacter pylori infection	041.86
Stomach lymphoma	To be specified
Stomach surgery	43500-43999, S2085, S2082
Irritable bowel syndrome	564.1
Peripheral vascular disease	440, 440.0–440.2, 440.20–440.24, 440.29, 440.3, 440.30–440.32, 440.8, 440.9, 443, 443.0–443.2, 443.21–443.24, 443.29, 443.8, 443.81, 443.89, 443.9, 445.0, 445.01, 445.02, 445.81, 445.89, 447.8, 447.9, 459.30–459.33, 459.39, 459.8, 459.81
Vascular insufficiency of intestine (including ischemic bowel disease)	557.x
Chronic constipation	564.0x
Chronic diarrhea	564.5
Acute coronary syndrome	411.1, 411.8, 411.81, 411.89
Coronary heart disease and angina (Including acute coronary syndrome)	410–410.92, 411–411.89, 412, 413–413.9, 414–414.9
Heart failure	428.xx, 402.x1, 404.x1, 404.x3
Stroke or transient ischemic attack	325, 430–432, 432.0, 432.1, 432.9, 433, 433.0, 433.00, 433.01, 433.1, 433.10, 433.11, 433.2, 433.20, 433.21, 433.3, 433.30, 433.31, 433.8, 433.80, 433.81, 433.9, 433.90, 433.91, 434, 434.0, 434.00, 434.01, 434.1, 434.10, 434.11, 434.9, 434.90, 434.91, 435, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 436, 437, 437.0, 437.1, 437.3–437.9, 438, 438.0, 438.1, 438.10–438.12, 438.19, 438.2, 438.20–438.22, 438.3, 438.30–438.32, 438.4, 438.40, 438.41, 438.42, 438.5, 438.50–438.53, 438.6–438.8, 438.81–438.85, 438.89, 438.9, 852.01, 852.02, 852.03, 852.04, 852.05, 852.06, 852.1, 852.10
Ulcerative colitis/Ulcerous rectocolitis	556.xx
Crohn’s disease	555.xx
Diabetes mellitus	250.xx
Familial adenomatous polyps	153.xx, 154.xx, 197.5, 211.3x, 211.4x
Hereditary nonpolyposis	153.xx, 154.xx, 197.5, 211.3x, 211.4x
Chronic stomach inflammation	535.1x, 535.5x
Stomach polyps	211.1x

Annex 3.7 – Screening procedures

Annex 3-Table 3-7 Screening procedures

Procedure	Procedure codes
Endoscopy including gastroscopy	0057T, S2215, 0133T, 0008T, 42.21-42.23, 44.11-44.13, 45.16, 43200-43206, 43215-43217, 43219-43220,43226-43228, 43231, 43232, 43234-43252,43255-43259, 44360, 44361, 44363-44366, 44370, 44372, 44373, 44376-44380, 44382, 44383, 991110, 91111
H. Pylori testing	83009, 83013, 83014, 87338, 87339, 86677
FOBT	82270-82274, G0107, G0394, G0328
Sigmoidoscopy	45.24, 45300, 45303, 45305, 45307-45309, 45315, 45317, 45320, 45321, 45327, 45330-45335, 45337-45342, 45345, 48.21, 48.22, 48.23, G0104, G0106
Colonoscopy	0066T, 0067T, 0529F, 3018F, 74261-74263, 44388-44394, 44397, 45.23, 45355, 45378-45387, 45391, G0105, G0120, G0121