NOVARTIS

Global Clinical Epidemiology

Non-Interventional Study Protocol

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REDACTED PROTOCOL

Title	Angioedema among patients with hypertension treated with aliskiren or other anti-hypertensive medications in the US – a cohort Study and a nested case-control analysis using health claims data
Protocol version identifier	v0
Date of last version of protocol	15 August 2013
EU PAS register number	
Active substance	Aliskiren (C09XA/Renin-inhibitors)
Medicinal product	Rasilez®, Tekturna®
Product reference	EMEA/H/C/000780
Procedure number	Not applicable
Marketing authorization holder(s)	Novartis Europharm Limited Wimblehurst Road Horsham West Sussex RH12 5AB United Kingdom

Joint PASS	No
Research questions and objectives	[redacted]
Country (-ies) of study	United States
Author	[redacted]

[redacted]

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

ACE	Angiotensin-converting-enzyme
ARB	Angiotensin II Receptor Blocker
CCI	Charlson Comorbidity Index
CHMP	Committee for Medicinal Products for Human Use
CPT-4	Current Procedural Terminology, 4th Edition
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
HMO	Health Maintenance Organization
ICD-9-CM	The International Classification of Diseases, Ninth Revision, Clinical Modification
NDC	National Drug Code
OR	Odds Ratio
PPO	Preferred Provider Organization
POS	Point-of-Service
RAAS	Renin-angiotensin-aldosterone-system
SD	Standard Deviation

3 Responsible parties

Table 3-1 Main responsible parties

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

4 Abstract

Title	Angioedema among patients with hypertension treated with aliskiren or other anti-hypertensive medications in the US – a cohort Study and a nested case-control analysis using health claims data
Version and date	v0 15 August 2013
Name and affiliation of main author	[redacted]
Rationale and background	Angioedema is characterized by a swelling of the subcutaneous and submucosal levels of the skin. Drug-induced angioedema appears to be attributed to increased levels of bradykinin, causing the swelling of the skin. Severe cases can exhibit airway restriction, often requiring immediate emergency care. Drug-induced angioedema prevalence is unknown and problematic to establish. First, mild cases often go under-reported or unnoticed, second, only severe cases result in emergency room visits and it can be difficult to determine the cause and third, it is hard to attribute incident cases of angioedema directly to a drug. Anti-hypertensive medications, notably ACE-inhibitors and angiotensin-II antagonists, can play a role in drug-induced angioedema. One study investigated elderly hypertensive patients treated with either a calcium channel blocker, an ACE-inhibitor, an alpha-blocker or a diuretic and found the overall rate of angioedema to be 0.12%, largely driven by ACE-inhibitor use. Aliskiren is the first known representative of a new class of non-peptide orally active renin inhibitors that blocks the renin-angiotensin-aldosterone-system (RAAS) at its rate-limiting step. While rare cases of angioedema were identified in association with aliskiren use in clinical trials, no significant difference in incidence compared to placebo (0.3% vs. 0.4%) or other anti-hypertensive drugs was detected. A recent meta-analysis found that angiotensin-receptor blockers and direct renin inhibitors (i.e. aliskiren) had similar rates of angioedema, and were not statistically different from placebo. However, recent findings from a non-interventional study found that patients treated with ACE inhibitors or aliskiren each had approximately three times the risk of angioedema compared with patients treated with beta blockers. As a result, further investigation into the impact of anti-hypertensive medications on the incidence and prevalence of angioedema is valuable. In this context, the Committee for Medicinal Products for Human Use (CHMP) has requested that Novartis conduct a study to quantify the prevalence and incidence of angioedema in users of aliskiren.
Research question and objectives	The primary objective of this study is to [redacted] The secondary objective is to [redacted]
Study design	The study is a retrospective database analysis with secondary use of data from the IMS PharMetrics Plus™ claims database from the United States, stratifying prevalence and incidence of angioedema based upon the anti-hypertensive medication most recently taken. A retrospective case-control

	study will be conducted to compare patients treated with aliskiren for hypertension compared to those treated with other anti-hypertensive medications.
Population	All adult subjects with a prescription for an anti-hypertensive medication of interest between July 1, 2007 and September 30, 2012 will initially be selected for inclusion into the study derived from the IMS PharMetrics Plus™ claims database, a commercially insured population. Patients must meet the following additional criteria: • ≥1 diagnosis of hypertension (ICD-9-CM code 401.xx-405.xx) in the 6-month period (pre-index) preceding patients' first anti-hypertensive medication prescription in the window above • A second diagnosis of hypertension (ICD-9-CM code 401.xx-405.xx) at least 30 days apart from the first diagnosis identified in the pre-index period • Aged 18 years or older on January 1st of the calendar year of interest • Continuous enrollment in their health plan for a minimum of 6 months prior to, and 1 month after, January 1st of the calendar year of interest • Patients will be required to have continuous health plan enrollment for 12 months prior to January 1st of the calendar year of interest for the incidence analysis • Non-missing age and sex data For the relative risk of angioedema estimation via a nested case-control design, the angioedema event date will be set as the date of first angioedema diagnosis, and the exposure period will begin on the angioedema event date and look back one year immediately preceding the angioedema event.
Variables	The primary outcome is a [redacted] The primary exposure is evidence o [redacted] Exposures of interest include: • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] Patients will be categorized into the aforementioned exposure groups on a hierarchical, mutually exclusive basis, with the above listing representing the preferred order for assignment. Other variables used as covariates include gender, age group, type of health plan, type of payer, geographic region of the health plan, prescribing physician specialty, evidence of prior use of anti-hypertensive therapy, comorbidities of interest, specific concurrent medications, and the Charlson Comorbidity Index.

Data sources	The study will employ the IMS PharMetrics Plus™ claims database, which includes approximately 60 million active patients in 2011. Records in this database are representative of the national, commercially insured population in terms of age and gender.
Study size	Because this is an exploratory epidemiologic 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 An initial database query identified over 66,600 patients who received aliskiren during the time period of interest.
Data analysis	The demographic and clinical characteristics of study patients will be described using frequency and percentage distributions for categorical variables and descriptive statistics (mean, standard deviation [SD], and median) for continuous and count variables, measured as of the first of the calendar year or based on his/her pre-index period, unless otherwise specified. For a qualifying subset of the patient sample, prevalence of angioedema will be calculated for each of calendar years 2008, 2009, 2010 and 2011. For both prevalence and incidence estimation, patients with angioedema (numerator) will be categorized into various treatment groups referenced above based on the anti-hypertensive medication immediately preceding the date of their angioedema diagnosis. Since this study is evaluating prevalence and incidence of angioedema among patient actively treated for hypertension, medication will be required of all cases within 30 days preceding the angioedema event date. Patients treated for hypertension (denominator) will be categorized into the aforementioned treatment groups for estimation of prevalence and incidence based on the anti-hypertensive medication(s) for which the patient had days supply on each specific day of exposure. In order to evaluate the relative risk of experiencing angioedema among patients treated with aliskiren for hypertension compared to those treated with other anti-hypertensive medications, a retrospective case-control study will be conducted. Sample size permitting, patients will be matched on an up to 4:1 basis using a direct match method. Any residual differences between cohorts in baseline variables will be inserted into a regression model to adjust for remaining differences ($p>0.05$). A conditional logistic regression model will be constructed for the case-control matched sets. The dependent (outcome) variable will be the condition of experiencing an angioedema event within the study period. Results will be expressed in the form of odds ratios (ORs) with 95% confidence intervals (95% CIs). Exposure to anti-hypertensive medications in the one year preceding angioedema events will be evaluated.
Milestones	Start of data collection: 22 August 2013 End of data collection: 22 September 2013 Registration in the EU PAS register: 19 August 2013 Final report of study results: 31 January 2014

5 Amendments and updates

Not applicable.

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection	22 August 2013
End of data collection	22 September 2013
Registration in the EU PAS register	19 August 2013
Final report of study results	31 January 2014

7 Rationale and background

Angioedema is characterized by a swelling of the subcutaneous and submucosal levels of the skin. This condition can be considered hereditary, acquired or drug-induced, though clinical symptoms are identical and the former two are caused by a deficiency in C1-inhibitor (Weber and Messerli 2008, Cicardi and Zanichelli 2010). Drug-induced angioedema appears to be attributed to increased levels of bradykinin, causing the swelling of the skin (Weber and Messerli 2008). Symptoms can last 2-5 days and typically consist of swelling near the face, mouth and limbs, as well as abdominal pain (Weber and Messerli 2008, Cicardi and Zanichelli 2010). Severe cases can exhibit airway restriction, often requiring immediate emergency care (Salih and Thomas 2006). Hereditary angioedema prevalence is estimated to range between 1 in 10,000 to 1 in 50,000 (Cicardi and Zanichelli 2010). However, the prevalence of acquired angioedema is difficult to determine but is crudely estimated to be 1 in 100,000 to 1 in 500,000 (Cicardi and Zanichelli 2010). Drug-induced angioedema prevalence is unknown and problematic to establish (Salih and Thomas 2006). First, mild cases often go under-reported or unnoticed, second, only severe cases result in emergency room visits and it can be difficult to determine the cause and third, it is hard to attribute incident cases of angioedema directly to a drug (Piller et al 2006, Weber and Messerli 2008, Roberts et al 2012). African-American patients were found to be almost 3-times as likely to experience an event. Additional risk factors include prior allergic reactions, being over the age of 65, being female and having diabetes (Miller et al 2008, Weber and Messerli 2008).

Antihypertensive medications, notably ACE-inhibitors and angiotensin-II antagonists (angiotensin receptor blockers [ARBs]), can play a role in drug-induced angioedema. ACE-inhibitors, in particular, may increase the likelihood of angioedema by preventing the conversion of bradykinins to inactive entities (Salih and Thomas 2006). Most episodes of angioedema take place during the early phase of treatment, but there is evidence that events can emerge months or years after ACE-inhibitor therapy initiation. While angioedema is largely a rare occurrence, the increased rate of people treated for hypertension amplifies the quantity of episodes (Weber and Messerli 2008). The ALLHAT clinical study, which included outcomes up to 6 years post-randomization, investigated elderly hypertensive patients treated with either a calcium channel blocker, an ACE-inhibitor, an alpha-blocker or a diuretic and

found the overall rate of angioedema to be 0.12%, largely driven by ACE-inhibitor use. Approximately 0.41% of patients treated with an ACE-inhibitor developed angioedema (Piller et al 2006). ACE-inhibitor induced angioedema is estimated to occur in 0.1-2.2% of patients (Vasekar and Craig 2012).

The incidence rate of angioedema in ACE-inhibitor users is about 2 per 1,000 person-years (Miller et al 2008, Makani et al 2012), compared with 0.4-0.8 per 1,000 person-years for users of non-ACE-inhibitors, non-ARB anti-hypertensive medications (Makani et al 2012). Overall, 1-2 per 1,000 ACE-inhibitor users may develop angioedema while being treated (Piller et al 2006, Salih and Thomas 2006, Roberts et al 2012). The adjusted relative risk of angioedema for patients newly initiating ACE-inhibitor therapy compared to other anti-hypertensive medications was 3.56 (95% confidence interval of 2.82 – 4.44) (Miller et al 2008). The risk is greatest immediately following treatment initiation and gradually diminishes over time but remains higher than no use (Roberts et al 2012). Some cases manifest only after a prolonged duration of therapy, sometimes one year or more after treatment initiation (Roberts et al 2012).

Treatment options vary with the severity of the episode. Most cases of angioedema are mild, so patients often go untreated or receive antihistamines or corticosteroids. However, severe cases often require hospitalization and substantial intervention, particularly for opening up constricted airways (Weber and Messerli 2008). Adrenaline is recommended in these instances (Salih and Thomas 2006). If a prescription medication is suspected, the treatment will be discontinued and the patient will be monitored for further signs. But because many episodes remain unreported, either to medical practitioners or to manufacturers, the rate and outcomes associated with drug-induced angioedema remain unclear (Weber and Messerli 2008).

Aliskiren is the first known representative of a new class of non-peptide orally active renin inhibitors that blocks the renin-angiotensin-aldosterone-system (RAAS) at its rate-limiting step. It induces a net reduction in plasma renin activity, angiotensin II and aldosterone levels. Aliskiren is effective in reducing blood pressure and overall is well tolerated. The incidence of adverse events and the number of study discontinuations related to adverse events during treatment were relatively low and generally similar to placebo (Angeli et al 2012). Aliskiren (Rasilez®, Tekturna®) was first approved for hypertension in the United States and in the European Union in 2007 (Novartis 2012).

An *in vitro* study assessed the ability of human plasma and pulmonary vascular endothelial cells to metabolize bradykinin and compared the inhibition of bradykinin degradation seen by an ACE inhibitor (enalapril, as a positive control) with aliskiren. Aliskiren had no effect upon the rate of bradykinin degradation in plasma and a minimal effect employing vascular endothelial cells. The latter suggests inhibition of a non-renin enzyme that is a minor contributor to bradykinin degradation (Joseph et al 2013).

While rare cases of angioedema were identified in association with aliskiren use in clinical trials, no significant difference in incidence compared to placebo (0.3% vs. 0.4%) or other anti-hypertensive drugs was detected. A recent meta-analysis found that angiotensin-receptor blockers and direct renin inhibitors (i.e. aliskiren) had similar rates of angioedema, and were not statistically different from placebo. Their rates were half that of ACE-inhibitors (0.11% and 0.13% vs. 0.3%) (Makani et al 2012). Since this study used clinical trial data and not real

world evidence, it is critical to investigate the overall rate of angioedema in anti-hypertensive medications.

However, findings from a non-interventional study by Toh et al (2012) found that patients treated with ACE inhibitors and aliskiren each had approximately three times the risk of angioedema compared with patients treated with beta blockers.

As a result, further investigation into the impact of anti-hypertensive medications on the incidence and prevalence of angioedema is valuable.

In this context, the Committee for Medicinal Products for Human Use (CHMP) has requested that Novartis conduct a study to quantify the prevalence and incidence of angioedema in users of aliskiren.

8 Research question and objectives

The primary objective of this study is to [redacted] The secondary objective is to explore [redacted]

9 Research methods

9.1 Study design

We propose to employ a retrospective database cohort analysis with secondary use of data from the IMS PharMetrics Plus™ claims database from the United States (US), stratifying prevalence and incidence of angioedema based upon the anti-hypertensive medication(s) most recently taken. Patient demographic characteristics and other outcomes will be reported by specific treatment group, including a calculation of the relative risk of angioedema between aliskiren monotherapy and other treatment groups. A retrospective study of this nature allows for the direct incidence and prevalence calculation of anti-hypertensive medication-associated angioedema in a commercially insured population.

In order to evaluate the relative risk of experiencing angioedema among patients treated with aliskiren for hypertension compared to those treated with other anti-hypertensive medications, a retrospective nested case-control study will be conducted. Cases will be defined as patients treated with anti-hypertensive medication with an incident angioedema diagnosis derived from the incidence estimation analysis. Controls will be defined as patients treated with anti-hypertensive medication who have not shown any evidence of angioedema in their claims data during the study period, pulled from the eligible at-risk population.

For both prevalence and incidence estimation, patients will be categorized into various treatment groups (see Section 9.3.2 details).

Patients treated for hypertension (denominator) will be categorized into the treatment groups (detailed in Section 9.3.2) based on the anti-hypertensive medication for which the patient had days supplied for each specific day of exposure.

For the case-control analysis, medication exposure for the different treatment categories will be quantified during the one year period immediately preceding the matched pairs angioedema event (case) date.

The primary endpoint is [redacted]

9.2 Setting

All adult hypertensive subjects with a prescription for an anti-hypertensive medication of interest between July 1, 2007 and September 30, 2012 will initially be selected for inclusion into the study derived from the IMS PharMetrics Plus™ US claims database. Records in the IMS PharMetrics Plus™ claims database are generally representative of the US, commercially insured population in terms of age and gender. The data are also longitudinal, with an average duration of member enrollment of two years. Only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples (see also Section 9.4 for more details).

The angioedema event date will be defined in both the incidence and prevalence analyses as the date of first angioedema diagnosis in the given year.

Data from calendar years 2007 through 2012 (or the most recent version of data available at the time of extraction) will be available for baseline characteristics, incidence estimation, and prevalence estimation. Patients must meet the following additional criteria:

- ≥1 diagnosis of hypertension (ICD-9-CM code 401.xx-405.xx) in the 6-month period (pre-index) preceding patients' first anti-hypertensive medication prescription in the window above
- A second diagnosis of hypertension (ICD-9-CM code 401.xx-405.xx) at least 30 days apart from the first diagnosis in the pre-index period
- Aged 18 years or older on January 1st of the calendar year of interest
- Continuous enrollment in their health plan for a minimum of 6 months prior to, and 1 month after, January 1st of the calendar year of interest
- Patients will be required to have continuous health plan enrollment for 12 months prior to January 1st of the calendar year of interest for the incidence analysis
- Non-missing age and sex data

For the relative risk of angioedema estimation via a nested case-control design, the angioedema event date will be set as the date of first angioedema diagnosis during the study period, and the exposure period will begin on their angioedema event date and look back one year immediately preceding the angioedema event.

9.3 Variables

9.3.1 Outcome

[redacted]

9.3.2 Exposure of interest

[redacted]

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

Patients will be categorized into the aforementioned exposure groups on a hierarchical, mutually exclusive basis, with the above listing representing the preferred order for assignment.

Note that since this study is evaluating prevalence and incidence of angioedema among patient actively treated for hypertension, anti-hypertensive medication will be required of all cases within 30 days preceding the angioedema event date.

Patients treated for hypertension (denominator) will be categorized into the aforementioned treatment groups based on the antihypertension medication for which the patient had days supplied for each specific day of exposure.

9.3.3 Other variables

The following variables are used as covariates for the analyses in this study. They are expected to serve as either confounders or effect modifiers and will be used to adjust the models:

- Gender;
- Age group (18-34, 35-44, 45-54, 55-64, 65+) as of January 1st of the year of interest (prevalence or incidence) or angioedema event date (case-control);
- Type of health plan [Health Maintenance Organization (HMO), Preferred Provider Organization (PPO), Point of Service (POS), indemnity, consumer-directed, or other/unknown];

- Type of payer (commercial, Medicare risk, Medicare cost, self-insured, Medicaid, or unknown);
- Geographic region of the health plan (Northeast, South, Midwest, or West);
- Prescribing physician specialty for the index anti-hypertensive medication;
- Evidence of prior use of anti-hypertensive therapy;
- Specific comorbidities of interest: congestive heart failure, ischemic heart disease, myocardial infarction, diabetes, asthma, urticarial, allergic reactions (for codes, see Annex 3-Table 3-3);
- Specific concurrent medications of interest, including: estrogens, non-steroidal anti-inflammatory drugs (NSAIDs), anti-platelets, statins, antidiabetic medications;
- Charlson Comorbidity Index (CCI) score (Dartmouth-Manitoba adaptation)
- Prior history of angioedema (applies only to prevalence)

9.4 Data sources

IMS PharMetrics Plus Health Plan Claims Database

The data for this study will be retrieved from the IMS PharMetrics Plus Health Plan Claims Database. IMS will perform the analysis following their own internal standard operating procedures (SOPs).

IMS' collaboration with Health Intelligence Company, which operates as [redacted] allows IMS' bio-pharmaceutical clients sole access to one of the largest US health plan claims databases. The aggregated IMS PharMetrics Plus claims database comprises adjudicated claims for more than 150 million unique patients across the United States, or more than 1 in 3 Americans, with approximately 60 million active in calendar year 2011. Data are available from 2005 onwards; with a typical 3-4 month lag due to claims adjudication.

PharMetrics Plus 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 included, with coverage of data from 90% of US hospitals, 80% 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, PharMetrics Plus has detailed information on the pharmacy and medical benefit (copayment/ coinsurance amount, deductible, in-network vs. out-of-network), the inpatient stay (admitting vs. other diagnoses, admission type and source, discharge status) and provider details (specialty, zip code, attending, referring, rendering, prescribing, primary care provider). All 3-digit zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography.

Amounts charged by providers and amounts allowed and paid by health plans are available for all services rendered, as well as dates of service for all claims. Other data elements include 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 (approximately 1 in 3 Americans), records in the PharMetrics Plus database are representative of the national, commercially insured population in terms of age and gender. The data are also longitudinal, with approximately 40 million patients with 4 or more years of continuous enrolment. Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are HIPAA compliant to protect patient privacy.

This is a non-interventional study based on secondary use of health claims data. It does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule.

9.5 Study size

Because this is an exploratory epidemiologic 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.

An initial database query identified over 66,600 patients who received aliskiren during the time period of interest. This number is preliminary and will be reduced after applying in-/exclusion criteria.

9.6 Data management

Data will be extracted from the IMS PharMetrics Plus Health Plan Claims Database according to all aforementioned inclusion and exclusion criteria. All analyses, including data manipulation and statistical methods, will be performed using SAS version 9.1 (SAS Institute Inc., Cary, NC).

9.7 Data analysis

All analyses, including data manipulation and statistical methods, will be performed by IMS using SAS version 9.1 (SAS Institute Inc., Cary, NC).

9.7.1 Cohort analysis

Demographic characteristics

The demographic and clinical characteristics of study patients will be described using frequency and percentage distributions for categorical variables and descriptive statistics (mean, standard deviation [SD], and median) for continuous and count variables, measured as of the January 1st for the year of interest or based on his/her pre-index period, unless otherwise specified. In order to avoid repetitive measures, all baseline characteristics will be presented for all patients eligible for inclusion in the study. Baseline characteristics will be stratified based upon:

- Whether or not a patient has had an episode of angioedema in their 6-month pre-index period; and
- Whether or not a patient has one or more prescriptions for an anti-hypertensive medication in their 6-month pre-index period

The following baseline characteristics will be measured:

- Age (mean and SD)

- Gender
- Geographic region (Northeast, Midwest, South, West)
- Health plan type (consumer-directed, HMO, indemnity, point-of-service [POS], PPO, unknown)
- Payer type (commercial, Medicaid, Medicare Risk, self-insured, unknown)
- Prescribing physician specialty for the index anti-hypertensive medication (general practice, cardiology, other)
- Evidence of prior use of anti-hypertensive therapy (yes/no)
- Charlson comorbidity index (CCI) score, Dartmouth-Manitoba adaptation (continuous and by categories of 0, 1-2, 3-4, 5+)
- Specific comorbidities of interest (potential conditions include congestive heart failure, myocardial infarction, ischemic heart disease, diabetes, asthma, urticaria, allergic reactions);Specific concurrent medications of interest, including those used to treat comorbid conditions: non-steroidal anti-inflammatory drugs [NSAIDs] including aspirin, use of estrogens (Agostoni and Cicardi 2001), anti-platelets, statins, antidiabetic medications)
- Pre-index total hospitalizations (mean, SD)

To test differences in baseline characteristics between treatment groups , chi-square tests will be used for categorical data and Wilcoxon rank-sum tests will be used for continuous data. Two-sided alpha levels will be set at 0.05 for determination of statistical significance.

[redacted]

[redacted].

Figure 9-1 [redacted]

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- [redacted]

[redacted]

The denominator patient exposure, measured in days, will only include days falling within complete continuous enrollment and with treatment for hypertension based on days supply. The days of treatment exposure will be allocated based on the specific treatment for each day. Patients with angioedema (numerator cases) will only contribute those days to the denominator that preceded their angioedema event date.

For example, a patient with three months of treatment with a diuretic who then adds aliskiren as part of a fixed dose combination, followed by angioedema two weeks later, would be categorized as a fixed dose combination angioedema case based on immediate proximity to the event. Only the two weeks of fixed dose combination therapy would be counted in the denominator for aliskiren as part of a fixed dose combination, with the three months of diuretic treatment only being counted in the denominator for diuretic angioedema cases.

In addition to the overall estimates, the calculated prevalence of angioedema will be stratified by age group, gender, treatment group and type of care required at diagnosis (inpatient, outpatient or emergency room [ER] visit).

[redacted]

Figure 9-2 [redacted]

[redacted]

[redacted]:

- [redacted]
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[redacted]

Patients treated for hypertension (denominator) will be categorized into the aforementioned treatment groups based on the anti-hypertensive medication days supplied for each individual day of exposure. Only days in which patients had treatment will be included in the denominator.

The denominator patient exposure, measured in days, will only include days falling within complete continuous enrollment and with treatment for hypertension based on days supply. The days of treatment exposure will be allocated based on the specific treatment for each day. Patients with angioedema (numerator cases) will only contribute those days to the denominator that preceded their angioedema event date.

In addition to the overall estimates, the calculated incidence of angioedema will be stratified by age group, gender, treatment group and type of care required at diagnosis (inpatient, outpatient or ER visit). Incidence will also be assessed per 1,000 patient-years of follow-up.

9.7.2 Nested case control analysis

Risk of angioedema by treatment status

In order t[redacted]. All incident angioedema cases from the aforementioned analysis will be included as cases for this risk analysis, with the date of first angioedema diagnosis serving as their angioedema event date. All anti-hypertensive medication treated patients enrolled at the time of their prospective case match will be eligible for selection as a control. Both cases and prospective controls must have a minimum of one year of continuous enrollment preceding the date of the case's angioedema. Sample size permitting, patients will be matched on an up to 4:1 basis using direct matching on the basis of the following characteristics:

- Age
- Gender
- Calendar year of angioedema diagnosis

Other variables for consideration in direct matching may include Charlson comobidity index (CCI), pre-index total hospitalizations, and additional demographic and clinical characteristics as sample sizes allow. Prospective controls will be assigned a "dummy" index date based on suitable proxy for eligibility in the year of their matched case's angioedema event. All unsuccessfully matched patients will be excluded from subsequent analyses. Pre-match cohort sizes will be shared with Novartis, and IMS and Novartis will jointly decide if the cohort sizes are large enough to support matching.

Medication exposure

Exposure to anti-hypertensive medications in the one-year time period preceding angioedema events will be quantified using total days supplied from prescriptions. The following medications will be measured for total exposure on a patient level, with aggregate days supplied being calculated for both the case and control groups:

- Aliskiren monotherapy
- Aliskiren as part of a fixed-dose combination therapy
- Aliskiren as part of a free-standing combination therapy
- ACE inhibitors (monotherapy or combination therapy)
- Angiotensin II Receptor Blockers (ARBs) (monotherapy or combination therapy)
- Beta-blockers (monotherapy or combination therapy)
- Calcium channel blockers (monotherapy or combination therapy)
- Diuretics (monotherapy or combination therapy)
- All other anti-hypertensive medications

All anti-hypertensive drug users' medications exposure will be quantified for the three months immediately preceding the angioedema-related case-control index date. The medication exposure will be classified into the following exclusive categories:

- Current use (patient had coverage for the drug on the date of their angioedema diagnosis or up to 7 days prior)
- Recent use (among those without current use, patient had coverage for the drug within 30 days of their angioedema diagnosis, but no coverage for the drug within 7 days prior to the date of diagnosis)
- Past use (among those without current or recent use, patient had coverage for the drug within 90 days of their angioedema diagnosis, but no coverage for the 30 days prior to the date of diagnosis)

Multivariate model

A conditional logistic regression model will be constructed for the case-control matched sets, incorporating all aforementioned demographic and clinical characteristics available at the matched index date as independent variables, as well as all recent medication exposures as outlined above. The dependent (outcome) variable will be the condition of experiencing an angioedema event within the study period. The reference case is treatment with beta blockers. The final model will be evaluated based on significance of predictors, backwards selection of covariates based on chi-square values may be performed. The significance (p-value) threshold for variable inclusion and retention in the model will be set to 0.10. Results will be expressed in the form of odds ratios (ORs) with 95% confidence intervals (95% CIs).

9.8 Quality control

A number of procedures are implemented in the IMS PharMetrics Plus Health Plan Claims Database to ensure data integrity. The database is comprised of fully adjudicated medical and pharmaceutical claims, and only health plans that submit data for all members are included in the database, ensuring complete data capture and representative samples. Data contributions

are subjected to a series of quality checks to ensure a uniform data file format (to accommodate aggregating data from multiple sources) and to minimize error rates, and incoming data elements must conform to basic data validity norms. Data contributors are required to submit predefined data variables with standard variable definitions in a predefined file layout. Data are then standardized by cross-walking key variables to standard definitions, including provider type, specialty, type of service, reimbursement type, and payer type. Evaluation of all variables is performed and compared to expected distributions, and in the event that variances cannot be resolved, the data set, in its entirety would not be included in the database.

9.9 Limitations of the research methods

This study is limited to a US managed care population; although this is ideal for assessing cost for a US Managed Care population (the population of interest), the results are unlikely to be generalizable to either elderly populations or non-US payers.

In this study, there are limitations associated with making drug-drug comparisons based on non-random treatment assignment. Previous analyses have suggested limited confounding by indication in these populations, however this cannot be definitively ruled out.

One possible effect modifier related to the use of ACEIs which is not accounted for in this analysis is African American race. It is not known though whether this is also the case for aliskiren. However, health plan claims data do not include patient-level characteristics such as ethnicity. We will therefore not be able to take race/ethnicity into consideration in our analyses.

In addition, health plan claims data do not include other patient-level characteristics such as smoking status and weight, the extent of potential confounding due to these factors cannot be quantified in this study, as outlined above for ethnicity.

Claims data is primarily collected to facilitate provider reimbursement by health plans, thus is biased to treatment in patients with insurance. The use of fully adjudicated claims will minimize the likelihood of missing or erroneous cost data.

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.

11 Management and reporting of adverse events/adverse reactions

As this is a non-interventional study with secondary use of data form a US health claims database, 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

A final report documenting the study's methodology as well as summary findings will be provided to Novartis from IMS.

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. It is anticipated that one abstract and manuscript will be developed based on the observed results if sufficient data exists. All authors will meet the criteria for authorship, and all people who meet the criteria will be authors. Potential conflicts of interest will be disclosed. All authors will have: (1) made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) participated in drafting the article or revising it critically for important intellectual content; and (3) approved the version to be published. Each author will meet all of these conditions. Acquisition of funding, collection of data, or general supervision of the research group will not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications will comply with the International Committee of Medical Journal Editors (ICMJE).

For non-interventional PASS studies, the final manuscript 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)

Agostoni A and Cicardi M (2001) Drug-induced angioedema without urticaria. Incidence, prevention and management. Drug Saf; 24(8):599-606.

Angeli F, Reboldi G, Mazzotta G, et al (2012) Safety and efficacy of aliskiren in the treatment of hypertension: a systematic overview. Expert Opin Drug Saf; 11(4):659-70.

Cicardi M and Zanichelli A (2010) Acquired angioedema. Allergy Asthma Clin Immunol; 6(1):14 (Internet) Available from: <http://www.aacijournal.com/content/pdf/1710-1492-6-14.pdf> (Accessed 05 February 2013).

Joseph K, Tholanikunnel TE, Kaplan AP (2013) In vitro comparison of bradykinin degradation by aliskiren, a renin inhibitor, and an inhibitor of angiotensin-converting enzyme. J Renin Angiotensin Aldosterone Syst; (Internet) Available from: <http://jra.sagepub.com/content/early/2013/06/13/1470320313491997.full.pdf+html> (Accessed 16 August 2013).

Makani H, Messerli FH, Romero J, et al (2012) Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. Am J Cardiol; 110:383-91.

Miller DR, Oliveria SA, Berlowitz DR, et al (2008) Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. Hypertension; 51:1624-30.

Novartis (2012) Media release: Novartis announces Aliskiren will continue to be available to appropriate patients, as FDA interim assessment is concluded; product information updated. Basel (Switzerland): Novartis International AG, 19 April 2012 (Internet) Available from: <http://www.novartis.com/newsroom/media-releases/en/2012/1604332.shtml> (Accessed 16 August 2013).

Piller LB, Ford CE, Davis BR, et al (2006) Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: a report from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens; 8(9):649-58.

Roberts JR, Lee JJ, Marthers DA (2012) Angiotensin-converting enzyme (ACE) inhibitor angioedema: the silent epidemic. Am J Cardiol; 109(5):774-5.

Salih I and Thomas S (2006) Causes and management of drug-induced angioedema. Prescriber; 17(7):14-8.

Schneider G, Kachroo S, Jones N, et al (2012) A systematic review of validated methods for identifying anaphylaxis, including anaphylactic shock and angioneurotic edema, using administrative and claims data. Pharmacoepidemiol Drug Saf; 21 Suppl 1:240-7.

Toh S, Reichman ME, Houstoun M, et al (2012) Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. Arch Intern Med; 172(20):1582-9.

Vasekar M and Craig TJ (2012) ACE inhibitor-induced angioedema. Curr Allergy Asthma Rep; 12(1):72-8.

Weber MA and Messerli FH (2008) Angiotensin-converting enzyme inhibitors and angioedema: estimating the risk. Hypertension; 51:1465-7.

Annex 1 – List of stand-alone documents

Annex 1-Table 1-1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Not applicable	31 January 2013	Novartis Angioedema in Hypertension SAP Table Shells

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:

Angioedema among Patients with Hypertension Treated with Aliskiren or other Anti-hypertensive Medications in the US - a Cohort Study and a Nested Case-Control Analysis Using Health Claims Data

Study reference number:

CSPP100A2415

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]	☒	☐	☐	9, 10
1.1.2 End of data collection [2]	☒	☐	☐	9, 10
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	9, 10
1.1.6 Final report of study results.	☒	☐	☐	9, 10

Comments:

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Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1Does 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)	☒	☐	☐	11-12
2.1.2 The objective(s) of the study?	☒	☐	☐	12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12-13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9, 16

Comments:

There is no a priori hypothesis.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12-13
3.2Does the protocol specify the primary and secondary (if	☒	☐	☐	12

[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	Page Number(s)
applicable) endpoint(s) to be investigated?				
3.3Does 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)	☒	☐	☐	17-21

Comments:

The study investigates prevalence, incidence, and the odds ratio of experiencing an angioedema event in association with aliskiren versus other anti-hypertensive drugs

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1Is the source population described?	☒	☐	☐	13
4.2Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	14
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	13
4.2.5 Co-morbidity?	☒	☐	☐	15
4.2.6 Seasonality?	☐	☒	☐	
4.3Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12-13

Comments:

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Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	14
5.2Does 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)	☐	☒	☐	
5.3Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	21
5.4Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

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Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14
6.2Does 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)	☒	☐	☐	14

Comments:

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Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	14-15
7.2Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	14-15, 21

Comments:

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Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1Does 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.)	☒	☐	☐	15-16
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.)	☒	☐	☐	15-16
8.1.3 Covariates?	☒	☐	☐	15-16
8.2Does 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)	☒	☐	☐	15
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	14
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	16-17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15, 34
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory	☒	☐	☐	14, 33

Section 8: Data sources	Yes	No	N/A	Page Number(s)
Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	33-34
8.4Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	16

Comments:

Because this is an exploratory epidemiologic 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.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17-20
10.3 Are descriptive analyses included?	☒	☐	☐	17-19
10.4 Are stratified analyses included?	☒	☐	☐	16, 19, 20
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	20, 21
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	20, 21

Comments:

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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?	☒	☐	☐	13, 22
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	15, 16, 21, 22
11.3 Are methods of quality assurance described?	☒	☐	☐	16, 21, 22
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	15, 16, 22
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	22
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)	☒	☐	☐	22
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	22

Comments:

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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?	☒	☐	☐	16, 22

Comments:

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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?	☒	☐	☐	10

Comments:

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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)?	☒	☐	☐	23
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	23

Comments:

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Annex 3 – Additional information

Annex 3-Table 3-1 Diagnoses codes of interest

Diagnosis	ICD-9 code
Hypertension	401.xx-405.xx
Angioedema	995.1 Angioneurotic edema, not elsewhere classified; Giant urticaria; Allergic angioedema

Annex 3-Table 3-2 Medication codes of interest

Drug / Drug class	GPI code	HCPCS code
Aliskiren	36170010*	
Aliskiren fixed-dose combinations	36996002*	
Includes:	36996502*	
ALISKIREN-VALSARTAN	36996702*	
ALISKIREN-HCTZ	36996803*	
ALISKIREN-AMLODIPINE		
ALISKIREN-AMLODIPINE-HCTZ		
ACE inhibitors (includes fixed- dose combinations)	3610*	
Above + thiazide combos,	369918*	
Above + CCB combos	369915*	
Angiotensin II Receptor Blockers (ARBs) (includes fixed-dose combinations)	3615*	
	369940*	
Above + thiazide combos,	369945*	
Above + CCB combos,	369930*	
Above + CCB + thiazide combos		
Beta-blockers	33*	
(includes fixed dose combinations)	369920*	
Calcium Channel Blockers (excluding fixed dose combinations)	34*	
Alpha Blockers	56852025*	
	369955027*	
	36202030*	
	36202005*	
	36202040*	
Loop Diuretics	3720*	S0171
		J1940
		J3265
Potassium Sparing Diuretics	3750*	
	379900*	
Thiazide diuretics (excluding fixed-dose combinations already captured elsewhere)	3760*	J1205
	369990*	
Centrally Acting alpha agonists (clonidine, methyldopa)	362010*	
	369950*	
Calcium Channel Blockers (excluding fixed dose combinations)	34*	

Annex 3-Table 3-3 Comorbidity diagnosis codes of interest

Diagnosis	ICD-9 code
Congestive heart failure	428.0x
Myocardial infarction	410.xx, 412
Other ischemic heart disease	411.xx, 413.xx, 414.xx
Diabetes	250.xx, 249.xx
Asthma	493.xx
Urticaria	708.xx, 782.1
Allergic reactions (includes anaphylaxis and dermatitis)	995.0, 995.1, 995.27, 995.3, 995.6x, 995.9x, 692.xx, 693.x

Annex 3-Table 3-4 Medication codes of to treat specific comorbidities

Drug / Drug class	GPI code
Non-steroidal anti-inflammatory drugs (NSAIDs)	6610*
Estrogens (systemic and vaginal)	24*, 5535*
Anti-platelets	8515*
Statins	3940*, 399940023*
Antidiabetic medications (injectable and oral)	27*