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The following report(s) provides findings from an FDA-initiated query using its Mini-Sentinel pilot. While Mini-Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Mini-Sentinel, and seeking to better understand the capabilities of the Mini-Sentinel pilot.

Data obtained through Mini-Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from the Mini-Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Mini-Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request TO07_MPR_WP02
Request ID: TO07_MPR_WP02 **Request Description:** This report investigates major gastrointestinal (GI) bleeding, intracranial hemorrhage, and ischemic stroke events following new use of extended-release niacin and fenofibrates. **Modular Program Tool Used:** Cohort Identification and Descriptive Analysis (CIDA) tool Version 2.0.4 **Data Source:** Data from January 1, 2007 - August 31, 2013 from five Data Partners contributing to the Mini-Sentinel Distributed Database (MSDD) were included in this report. This request was distributed to Data Partners on September 19, 2014. This report contains data from five Data Partners. See Appendix A for dates of available data for each Data Partner. **Study Design:** This request was designed to investigate the exposures and follow-up of major GI bleeding, intracranial hemorrhage, and ischemic stroke events following new use of extended-release niacin and fenofibrates. Various scenarios were run with combinations of niacin, niacin/statin combinations, and fenofibrates as exposures. See Appendix B for the detailed specifications of this request. **Cohort Eligibility Criteria:** Patients were required to be continuously enrolled in plans with both medical and drug coverage for 183 days prior to their exposure date, during which gaps in coverage of up to 45 days were allowed. Individuals were separated into the following age groups: 20-44, 45-54, 55-64, 65-74, 75-84, 85-99 years. **Limitations:** Algorithms to define exposures are imperfect and, therefore, they may be misclassified. **Notes:** Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

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Glossary of Terms for Analyses Using
Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the black

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency Department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). The Care Setting, along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

- **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: 01: Cohort includes only the first valid treatment episode during the query period; 02: Cohort includes all valid treatment episodes during the query period; 03: Cohort includes all valid treatment

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled”

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same

Event Deduplication - specifies how events are counted by the MP algorithm: 0: Counts all occurrences of an HOI during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions days are added after any episode gaps have been bridged

Lookback Period - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Monitoring Period - used to define time periods of interest for both sequential analysis and simple cohort characterization requests.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether the exposure episode will be truncated at the occurrence of a requester-

Washout Period (drug/exposure) - number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

Table 1a. Cohort of New Initiators of Niacin and Fenofibrates (Unmatched)

	Primary Analysis		Covariate Balance	
	N (%) Niacin	N (%) Fenofibrate	Absolute Difference	Standardized Difference
Patient Characteristics				
Female	73080 (31.2%)	146363 (37.7%)	-6.5	-0.1
Mean Age (Years) (standard deviation)	56.9 (11.5)	55.3 (11.8)	1.6	0.1
20-44	40656 (17.4%)	85230 (22.0%)	-4.6	-0.1
45-54	62603 (26.7%)	111536 (28.8%)	-2.1	0.0
55-64	71398 (30.5%)	101498 (26.2%)	4.3	0.1
65-74	41586 (17.8%)	62962 (16.2%)	1.6	0.0
75-84	15475 (6.6%)	23141 (6.0%)	0.6	0.0
85-99	2524 (1.1%)	3470 (0.9%)	0.2	0.0
Recorded use of:				
Angiotensin-converting enzyme (ACE) inhibitors/ angiotensin receptor blockers (ARBs)	100815 (43.0%)	160155 (41.3%)	1.7	0.0
Antiarrhythmics	6614 (2.8%)	9391 (2.4%)	0.4	0.0
Anticoagulants	9119 (3.9%)	13037 (3.4%)	0.5	0.0
Antiplatelets	26273 (11.2%)	22010 (5.7%)	5.5	0.2
Beta blockers	70362 (30.0%)	99749 (25.7%)	4.3	0.1
Bisphosphonates	5774 (2.5%)	9079 (2.3%)	0.2	0.0
Calcium channel blockers	29857 (12.7%)	49164 (12.7%)	0.0	0.0
Corticosteroids	18806 (8.0%)	35254 (9.1%)	-1.1	0.0
Diuretic - k-sparing	9590 (4.1%)	15826 (4.1%)	0.0	0.0
Diuretic - loop	13831 (5.9%)	22429 (5.8%)	0.1	0.0
Diuretic - thiazides	18248 (7.8%)	31592 (8.1%)	-0.3	0.0
Estrogens	10006 (4.3%)	20367 (5.3%)	-1.0	0.0
H2 antagonists	4651 (2.0%)	9012 (2.3%)	-0.3	0.0
Insulin	11688 (5.0%)	25070 (6.5%)	-1.5	-0.1
Metformin	32746 (14.0%)	70061 (18.1%)	-4.1	-0.1
Nitrates	14541 (6.2%)	13015 (3.4%)	2.8	0.1
Nonsteroidal antiinflammatory drugs (NSAIDs)	31009 (13.2%)	60828 (15.7%)	-2.5	-0.1
Other antidiabetic agents	12584 (5.4%)	23301 (6.0%)	-0.6	0.0
Other antihyperlipidemics	22789 (9.7%)	25828 (6.7%)	3.0	0.1
Proton pump inhibitors	35536 (15.2%)	63007 (16.2%)	-1.0	0.0
Selective serotonin reuptake inhibitors (SSRIs) / serotonin–norepinephrine reuptake inhibitors (SNRIs)	33391 (14.3%)	68285 (17.6%)	-3.3	-0.1
Statins	103670 (44.3%)	142483 (36.7%)	7.6	0.2
Sulfonylureas	14736 (6.3%)	33788 (8.7%)	-2.4	-0.1
Thyroid hormone replacement	24313 (10.4%)	42133 (10.9%)	-0.5	0.0
Recorded history of:				
Combined Comorbidity Score	0.2 (1.4)	0.2 (1.4)	0.0	0.0
Acute kidney failure	2662 (1.1%)	4304 (1.1%)	0.0	0.0
Acute myocardial infarction	14759 (6.3%)	11331 (2.9%)	3.4	0.2
Alcohol abuse	788 (0.3%)	1965 (0.5%)	-0.2	0.0
Anemia	18682 (8.0%)	29228 (7.5%)	0.5	0.0

Asthma	9879 (4.2%)	17372 (4.5%)	-0.3	0.0
Chronic kidney failure	10515 (4.5%)	22019 (5.7%)	-1.2	-0.1
Chronic liver disease	179 (0.1%)	270 (0.1%)	0.0	0.0
Chronic obstructive pulmonary disease (COPD)	11882 (5.1%)	20695 (5.3%)	-0.2	0.0
Coronary revascularization (diagnoses)	16280 (7.0%)	12044 (3.1%)	3.9	0.2
Dementia	2253 (1.0%)	3636 (0.9%)	0.1	0.0
Diabetes	60390 (25.8%)	125014 (32.2%)	-6.4	-0.1
Falls	1825 (0.8%)	2927 (0.8%)	0.0	0.0
Fractures (diagnoses)	3640 (1.6%)	5994 (1.5%)	0.1	0.0
Gout	6672 (2.8%)	14262 (3.7%)	-0.9	0.0
Heart failure	10925 (4.7%)	13576 (3.5%)	1.2	0.1
Hyperlipidemia	183427 (78.3%)	290848 (75.0%)	3.3	0.1
Hypertension (diagnoses)	133514 (57.0%)	222827 (57.5%)	-0.5	0.0
Inflammatory arthritis	3077 (1.3%)	5635 (1.5%)	-0.2	0.0
Intracranial hemorrhage	414 (0.2%)	677 (0.2%)	0.0	0.0
Ischemic stroke	4457 (1.9%)	6205 (1.6%)	0.3	0.0
Malignancy	11122 (4.7%)	16888 (4.4%)	0.3	0.0
Microvascular disease (diagnoses)	63665 (27.2%)	129823 (33.5%)	-6.3	-0.1
Obesity	4549 (1.9%)	9323 (2.4%)	-0.5	0.0
Other cerebrovascular disease	5355 (2.3%)	7672 (2.0%)	0.3	0.0
Other ischemic heart disease (diagnoses)	62849 (26.8%)	57040 (14.7%)	12.1	0.3
Gastrointestinal bleed	15823 (6.8%)	26704 (6.9%)	-0.1	0.0
Other major bleed	7995 (3.4%)	12252 (3.2%)	0.2	0.0
Peptic ulcer disease	1008 (0.4%)	1723 (0.4%)	0.0	0.0
Peripheral vascular disease	15788 (6.7%)	19749 (5.1%)	1.6	0.1
Syncope	4513 (1.9%)	6217 (1.6%)	0.3	0.0
Transient ischemic attack (TIA)	3316 (1.4%)	4436 (1.1%)	0.3	0.0
Tobacco use (diagnoses)	16551 (7.1%)	26593 (6.9%)	0.2	0.0
Cardioablation	71 (0.0%)	65 (0.0%)	0.0	0.0
Cardioversion	452 (0.2%)	413 (0.1%)	0.1	0.0
Coronary revascularization (procedures)	13340 (5.7%)	7653 (2.0%)	3.7	0.2
Fractures (procedures)	265 (0.1%)	350 (0.1%)	0.0	0.0
Home health care	2228 (1.0%)	3703 (1.0%)	0.0	0.0
Home oxygen use	2943 (1.3%)	4902 (1.3%)	0.0	0.0
Hypertension (procedures)	1 (0.0%)	2 (0.0%)	0.0	0.0
Microvascular disease (procedures)	167 (0.1%)	243 (0.1%)	0.0	0.0
Other ischemic heart disease (procedures)	0 (0.0%)	0 (0.0%)	0.0	-
Tobacco use (procedures)	1118 (0.5%)	2015 (0.5%)	0.0	0.0
Walker use	1159 (0.5%)	1944 (0.5%)	0.0	0.0
Wheelchair use	659 (0.3%)	1250 (0.3%)	0.0	0.0
Health Service Utilization Intensity:				
Number of generics	5.5 (4.3)	5.7 (4.5)	-0.2	0.0
Number of filled prescriptions	14.2 (13.4)	14.7 (14.3)	-0.5	0.0
Number of inpatient hospital encounters (IP)	0.2 (0.4)	0.1 (0.4)	0.1	0.1
Number of non-acute institutional encounters (IS)	0.1 (0.7)	0.1 (0.8)	0.0	0.0
Number of emergency room encounters (ED)	0.2 (0.6)	0.2 (0.7)	0.0	0.0
Number of ambulatory encounters (AV)	7.2 (7.6)	6.6 (7.3)	0.6	0.1
Number of other ambulatory encounters (OA)	1.6 (2.9)	1.6 (2.9)	0.0	0.0

Table 1b. Cohort of New Initiators of Niacin and Fenofibrates (Matched Predefined Propensity Score (PS), Caliper = .05

	Primary Analysis		Covariate Balance	
	N (%) Niacin	N (%) Fenofibrate	Absolute Difference	Standardized Difference
Patient Characteristics				
Female	69653 (33.1%)	70163 (33.3%)	-0.2	0.0
Mean Age (Years) (standard deviation)	56.3 (11.5)	56.4 (11.7)	0.0	0.0
20-44	39370 (18.7%)	40038 (19.0%)	-0.3	0.0
45-54	57632 (27.4%)	59363 (28.2%)	-0.8	0.0
55-64	62489 (29.7%)	58431 (27.8%)	1.9	0.0
65-74	36086 (17.2%)	35961 (17.1%)	0.1	0.0
75-84	12869 (6.1%)	14381 (6.8%)	-0.7	0.0
85-99	1943 (0.9%)	2215 (1.1%)	-0.2	0.0
Recorded use of:				
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)	87355 (41.5%)	87750 (41.7%)	-0.2	0.0
Antiarrhythmics	5421 (2.6%)	5501 (2.6%)	0.0	0.0
Anticoagulants	7614 (3.6%)	7709 (3.7%)	-0.1	0.0
Antiplatelets	16405 (7.8%)	16927 (8.0%)	-0.2	0.0
Beta blockers	56751 (27.0%)	57318 (27.2%)	-0.2	0.0
Bisphosphonates	5201 (2.5%)	5228 (2.5%)	0.0	0.0
Calcium channel blockers	26333 (12.5%)	26341 (12.5%)	0.0	0.0
Corticosteroids	17229 (8.2%)	17336 (8.2%)	0.0	0.0
Diuretic - k-sparing	8515 (4.0%)	8485 (4.0%)	0.0	0.0
Diuretic - loop	11828 (5.6%)	11939 (5.7%)	-0.1	0.0
Diuretic - thiazides	16435 (7.8%)	16409 (7.8%)	0.0	0.0
Estrogens	9619 (4.6%)	9659 (4.6%)	0.0	0.0
H2 antagonists	4018 (1.9%)	4078 (1.9%)	0.0	0.0
Insulin	10912 (5.2%)	11054 (5.3%)	-0.1	0.0
Metformin	30912 (14.7%)	31126 (14.8%)	-0.1	0.0
Nitrates	9352 (4.4%)	9622 (4.6%)	-0.2	0.0
Nonsteroidal antiinflammatory drugs (NSAIDs)	28825 (13.7%)	28793 (13.7%)	0.0	0.0
Other antidiabetic agents	11652 (5.5%)	11760 (5.6%)	-0.1	0.0
Other antihyperlipidemics	17983 (8.5%)	18057 (8.6%)	-0.1	0.0
Proton pump inhibitors	31628 (15.0%)	31809 (15.1%)	-0.1	0.0
Selective serotonin reuptake inhibitors (SSRIs)/ serotonin–norepinephrine reuptake inhibitors (SNRIs)	31207 (14.8%)	31605 (15.0%)	-0.2	0.0
Statins	85919 (40.8%)	85959 (40.9%)	-0.1	0.0
Sulfonylureas	13937 (6.6%)	14001 (6.7%)	-0.1	0.0
Thyroid hormone replacement	22135 (10.5%)	22212 (10.6%)	-0.1	0.0
Recorded history of:				
Combined Comorbidity Score	0.2 (1.4)	0.2 (1.4)	0.0	0.0
Acute kidney failure	2174 (1.0%)	2187 (1.0%)	0.0	0.0
Acute myocardial infarction	8496 (4.0%)	8755 (4.2%)	-0.2	0.0
Alcohol abuse	710 (0.3%)	725 (0.3%)	0.0	0.0
Anemia	15979 (7.6%)	16203 (7.7%)	-0.1	0.0

Asthma	8823 (4.2%)	8860 (4.2%)	0.0	0.0
Chronic kidney failure	9504 (4.5%)	9636 (4.6%)	-0.1	0.0
Chronic liver disease	146 (0.1%)	142 (0.1%)	0.0	0.0
Chronic obstructive pulmonary disease (COPD)	10445 (5.0%)	10592 (5.0%)	0.0	0.0
Coronary revascularization (diagnoses)	9642 (4.6%)	9913 (4.7%)	-0.1	0.0
Dementia	1898 (0.9%)	1945 (0.9%)	0.0	0.0
Diabetes	56514 (26.9%)	56910 (27.0%)	-0.1	0.0
Falls	1516 (0.7%)	1521 (0.7%)	0.0	0.0
Fractures (diagnoses)	3166 (1.5%)	3192 (1.5%)	0.0	0.0
Gout	6206 (2.9%)	6211 (3.0%)	-0.1	0.0
Heart failure	8396 (4.0%)	8477 (4.0%)	0.0	0.0
Hyperlipidemia	162265 (77.1%)	162251 (77.1%)	0.0	0.0
Hypertension (diagnoses)	117882 (56.0%)	118367 (56.3%)	-0.3	0.0
Inflammatory arthritis	2752 (1.3%)	2812 (1.3%)	0.0	0.0
Intracranial hemorrhage	340 (0.2%)	358 (0.2%)	0.0	0.0
Ischemic stroke	3719 (1.8%)	3737 (1.8%)	0.0	0.0
Malignancy	9547 (4.5%)	9593 (4.6%)	-0.1	0.0
Microvascular disease (diagnoses)	59304 (28.2%)	59704 (28.4%)	-0.2	0.0
Obesity	4156 (2.0%)	4178 (2.0%)	0.0	0.0
Other cerebrovascular disease	4424 (2.1%)	4487 (2.1%)	0.0	0.0
Other ischemic heart disease (diagnoses)	43084 (20.5%)	44016 (20.9%)	-0.4	0.0
Gastrointestinal bleed	14190 (6.7%)	14243 (6.8%)	-0.1	0.0
Other major bleed	6886 (3.3%)	6990 (3.3%)	0.0	0.0
Peptic ulcer disease	892 (0.4%)	884 (0.4%)	0.0	0.0
Peripheral vascular disease	12318 (5.9%)	12421 (5.9%)	0.0	0.0
Syncope	3628 (1.7%)	3706 (1.8%)	-0.1	0.0
Transient ischemic attack (TIA)	2753 (1.3%)	2798 (1.3%)	0.0	0.0
Tobacco use (diagnoses)	13518 (6.4%)	13698 (6.5%)	-0.1	0.0
Cardioablation	43 (0.0%)	46 (0.0%)	0.0	0.0
Cardioversion	292 (0.1%)	302 (0.1%)	0.0	0.0
Coronary revascularization (procedures)	6616 (3.1%)	6982 (3.3%)	-0.2	0.0
Fractures (procedures)	203 (0.1%)	198 (0.1%)	0.0	0.0
Home health care	1795 (0.9%)	1829 (0.9%)	0.0	0.0
Home oxygen use	2552 (1.2%)	2615 (1.2%)	0.0	0.0
Hypertension (procedures)	0 (0.0%)	1 (0.0%)	0.0	-
Microvascular disease (procedures)	141 (0.1%)	135 (0.1%)	0.0	0.0
Other ischemic heart disease (procedures)	0 (0.0%)	0 (0.0%)	0.0	-
Tobacco use (procedures)	985 (0.5%)	992 (0.5%)	0.0	0.0
Walker use	986 (0.5%)	990 (0.5%)	0.0	0.0
Wheelchair use	589 (0.3%)	606 (0.3%)	0.0	0.0
Health Service Utilization Intensity:				
Number of generics	5.4 (4.3)	5.5 (4.3)	0.0	0.0
Number of filled prescriptions	13.9 (13.4)	14.0 (13.5)	-0.1	0.0
Number of inpatient hospital encounters (IP)	0.1 (0.4)	0.1 (0.4)	0.0	0.0
Number of non-acute institutional encounters (IS)	0.1 (0.6)	0.1 (0.7)	0.0	0.0
Number of emergency room encounters (ED)	0.2 (0.6)	0.2 (0.6)	0.0	0.0
Number of ambulatory encounters (AV)	6.8 (7.1)	6.9 (7.9)	0.0	0.0
Number of other ambulatory encounters (OA)	1.5 (2.7)	1.5 (3.0)	0.0	0.0

Table 2a. Primary Analysis - Niacin and Niacin/Statin Combinations and Fenofibrates as Exposures

Outcome	Match Ratio	Niacin New Users	Niacin Events	Niacin Person-Time	Fenofibrate New Users	Fenofibrate Events	Fenofibrate Person-Time	Hazard Ratio (95% CI)
Major Gastrointestinal Bleeding	Unadjusted	234,242	482	31,451,365	387,837	1,016	64,806,644	1.01 (0.91, 1.13)
	1:1 match	210,389	400	26,911,467	210,389	595	37,300,671	0.98 (0.82, 1.18)
	Variable match	210,400	397	26,952,201	387,819	1,018	64,808,116	0.98 (0.83, 1.16)
Intracranial Hemorrhage	Unadjusted	234,355	59	31,519,502	387,978	90	64,950,086	1.45 (1.04, 2.03)
	1:1 match	210,473	45	27,041,230	210,473	57	37,445,168	1.21 (0.66, 2.22)
	Variable match	210,483	46	27,044,632	387,960	90	64,951,954	1.21 (0.71, 2.06)
Ischemic Stroke	Unadjusted	233,919	171	31,435,094	387,247	417	64,773,344	0.90 (0.75, 1.07)
	1:1 match	210,048	127	27,011,795	210,048	238	37,368,133	0.82 (0.61, 1.11)
	Variable match	210,060	133	26,963,367	387,228	416	64,774,137	0.80 (0.61, 1.04)

Table 2b. Secondary Analysis #1 - Niacin/Statin Combinations Only as Exposure

Outcome	Match Ratio	Niacin New Users	Niacin Events	Niacin Person-Time	Fenofibrate New Users	Fenofibrate Events	Fenofibrate Person-Time	Hazard Ratio (95% CI)
Major Gastrointestinal Bleeding	Unadjusted	36,125	48	4,737,913	167,316	561	32,549,615	0.67 (0.50, 0.91)
	1:1 match	32,341	41	4,289,571	32,341	57	5,560,735	0.77 (0.43, 1.38)
	Variable match	32,337	41	4,290,563	113,962	295	20,643,408	0.97 (0.62, 1.51)
Intracranial Hemorrhage	Unadjusted	36,140	5	4,745,834	167,387	52	32,633,871	0.82 (0.32, 2.09)
	1:1 match	32,356	4	4,299,115	32,356	6	5,636,778	0.67 (0.11, 3.99)
	Variable match	32,352	4	4,302,212	113,988	24	20,690,576	1.29 (0.35, 4.68)
Ischemic Stroke	Unadjusted	36,116	18	4,739,859	166,891	264	32,507,243	0.58 (0.36, 0.95)
	1:1 match	32,326	16	4,287,470	32,326	23	5,642,232	1.12 (0.43, 2.92)
	Variable match	32,322	16	4,282,774	113,702	121	20,621,223	1.01 (0.54, 1.89)

Table 2c. Secondary Analysis #2 - Niacin-Only Exposures and Excluding Prior Niacin/Statin Combination Users

Outcome	Match Ratio	Niacin New Users	Niacin Events	Niacin Person-Time	Fenofibrate New Users	Fenofibrate Events	Fenofibrate Person-Time	Hazard Ratio (95% CI)
Major Gastrointestinal Bleeding	Unadjusted	199,459	429	26,536,636	388,726	1,019	64,925,784	1.05 (0.93, 1.17)
	1:1 match	181,619	369	23,140,363	181,619	541	32,917,448	1.11 (0.92, 1.35)
	Variable match	181,638	374	23,126,583	388,707	1,021	64,927,212	1.12 (0.95, 1.32)
Intracranial Hemorrhage	Unadjusted	199,558	53	26,595,893	388,867	90	65,070,034	1.51 (1.07, 2.12)
	1:1 match	181,698	44	23,185,321	181,698	53	32,899,811	1.57 (0.80, 3.07)
	Variable match	181,714	42	23,197,423	388,848	90	65,071,858	1.02 (0.58, 1.79)
Ischemic Stroke	Unadjusted	199,144	153	26,517,971	388,133	417	64,892,304	0.92 (0.77, 1.11)
	1:1 match	181,315	121	23,095,747	181,315	238	32,834,750	0.97 (0.71, 1.30)
	Variable match	181,328	118	23,113,006	388,113	416	64,893,053	0.88 (0.68, 1.15)

Table 2d. Secondary Analysis #3 - First 30 days exposed time only

Outcome	Match Ratio	Niacin New Users	Niacin Events	Niacin Person-Time	Fenofibrate New Users	Fenofibrate Events	Fenofibrate Person-Time	Hazard Ratio (95% CI)
Major Gastrointestinal Bleeding	Unadjusted	225,760	128	6,510,832	378,533	188	10,896,100	1.18 (0.94, 1.48)
	1:1 match	203,290	118	5,860,311	203,288	109	5,870,376	1.07 (0.83, 1.39)
	Variable match	203,299	116	5,860,759	378,512	188	10,895,512	1.15 (0.90, 1.46)
Intracranial Hemorrhage	Unadjusted	225,866	8	6,515,630	378,670	17	10,902,165	0.90 (0.39, 2.10)
	1:1 match	203,375	6	5,864,332	203,373	10	5,874,038	0.60 (0.22, 1.65)
	Variable match	203,381	6	5,864,470	378,649	17	10,901,577	0.67 (0.26, 1.75)
Ischemic Stroke	Unadjusted	225,447	48	6,502,882	377,975	94	10,880,980	0.94 (0.67, 1.34)
	1:1 match	202,986	34	5,852,669	202,986	48	5,862,660	0.69 (0.44, 1.07)
	Variable match	202,986	33	5,852,666	377,953	94	10,880,363	0.63 (0.42, 0.96)

Table 2d. Secondary Analysis #3 - First 30 Days Exposed Time Only

Outcome	Match Ratio	Niacin New Users	Niacin Events	Niacin Person-Time	Fenofibrate New Users	Fenofibrate Events	Fenofibrate Person-Time	Hazard Ratio (95% CI)
Major Gastrointestinal Bleeding	Unadjusted	225,760	128	6,510,832	378,533	188	10,896,100	1.18 (0.94, 1.48)
	1:1 match	203,290	118	5,860,311	203,288	109	5,870,376	1.07 (0.83, 1.39)
	Variable match	203,299	116	5,860,759	378,512	188	10,895,512	1.15 (0.90, 1.46)
Intracranial Hemorrhage	Unadjusted	225,866	8	6,515,630	378,670	17	10,902,165	0.90 (0.39, 2.10)
	1:1 match	203,375	6	5,864,332	203,373	10	5,874,038	0.60 (0.22, 1.65)
	Variable match	203,381	6	5,864,470	378,649	17	10,901,577	0.67 (0.26, 1.75)
Ischemic Stroke	Unadjusted	225,447	48	6,502,882	377,975	94	10,880,980	0.94 (0.67, 1.34)
	1:1 match	202,986	34	5,852,669	202,986	48	5,862,660	0.69 (0.44, 1.07)
	Variable match	202,986	33	5,852,666	377,953	94	10,880,363	0.63 (0.42, 0.96)

Appendix A. Available Data in the Mini-Sentinel Distributed Database (MSDD) for Each Data Partner as of Request Send Date (September 19, 2014)

Data Partner ID	Start Date	End Date
DP001	6/1/2007	8/31/2013
DP002	1/1/2008	8/31/2013
DP003	1/1/2008	8/30/2013
DP004	1/1/2007	8/31/2013
DP005	1/1/2007	8/31/2013

Appendix B. Specifications for Request TO07_MPR_WP02

The Cohort Identification and Descriptive Analysis (CIDA) tool with Propensity Score Matching will be used to investigate major GI bleeding, intracranial hemorrhage, and ischemic stroke events following new use of extended release niacin and fenofibrates.

Query level	2
Analytic adjustment method	Propensity score matching
Cohort identification strategy	Exposures and follow-up
Study start	January 1, 2007
Study end	August 31, 2013
Age groups	20-44, 45-54, 55-64, 65-74, 75-84, 85-99 years
Coverage type	Medical and Drug Coverage
Maximum enrollment gap	45 days
Continuous enrollment before exposure	183 days

		Drug/Exposure										
Run	Scenario	Incident exposure	Incident w/ respect to:	Washout (days)	Exposed Time Assessment	Defined Exposed Time	Cohort Definition	Episode Gap	Min Episode Duration	Min Days Supply	Episode Extension	Episode Truncation
Primary analysis												
1	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
1	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
2	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
2	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
3	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
3	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings

Secondary analysis #1 - niacin/statin combos only as exposure												
4	**1**	Niacin + Statin Combination only	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
4	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
5	**1**	Niacin + Statin Combination only	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
5	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
6	**1**	Niacin + Statin Combination only	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
6	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
Secondary analysis #2 - niacin only exposures and excludes prior niacin/statin combo users												
7	**1**	Niacin only, no niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
7	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
8	**1**	Niacin only, no niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
8	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings
9	**1**	Niacin only, no niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any fibrate or fenofibrate dispensings
9	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Create episodes	NA	01	10	1	1	10	Yes - truncate on any niacin or niacin/statin combo dispensings

Secondary analysis #3 - Limit exposed time to first 30 days, exclude dispensing if days supplied <30 days

10	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any fibrate or fenofibrate dispensings
10	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any niacin or niacin/statin combo dispensings
11	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any fibrate or fenofibrate dispensings
11	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any niacin or niacin/statin combo dispensings
12	**1**	Niacin and niacin/statin combos	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any fibrate or fenofibrate dispensings
12	**2**	Fenofibrate	All niacin, niacin/statin combos, fenofibrate, and fibrate products	183	Defined exposed time	30	01	NA	NA	30*	NA	Yes - truncate on any niacin or niacin/statin combo dispensings

* Minimum days supplied of 30 days was applied via the combo tool and not the "Minimum Days Supplied" parameter

National Drug Codes (NDCs) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
Healthcare Common Procedure Coding System (HCPCS) codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
Current Procedural Terminology, Fourth Revision (CPT-4) codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

Inclusion/Exclusion					Event/Outcome					Propensity Score Matching					
Condition	Include/ Exclude	Lookback Start	Lookback End	CareSetting Principal	Event/ Outcome	Incident w/ respect to:	Washout (days)	Care Setting PDx	Blackout Period	Evaulation Window	Perform HDPS Analysis	Covariate Selection Method	Matching Ratio	Matching Caliper Settings	Zero Cell Correction
none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke(stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke(stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No

none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
Statin use	Include	-40	0	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
Statin use	Include	-40	0	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
Statin use	Include	-40	0	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No

none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Major GI bleeding events (GIH)	Major GI bleeding events (GIH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Intracranial hemorrhage (ICH)	Intracranial hemorrhage (ICH)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No
none	N/A	N/A	N/A	N/A	Ischemic Stroke (stroke)	Ischemic Stroke (stroke)	30	IPP	1	183	No	Exposure-based association	1:1	.05	No