MINI-SENTINEL PROSPECTIVE SURVEILLANCE PLAN

PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING OF MIRABEGRON – Report 1 of 4

Version 1.0

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Overview	
Request Description	FDA has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) and Propensity Score Matching (PSM) tools to investigate diagnoses of acute myocardial infarction (AMI) and stroke events following use of mirabegron or oxybutynin in the Mini-Sentinel Distributed Database (MSDD). This request involved two runs of the program package. The package was distributed to four Data Partners on October 20, 2014. The query start date for this request was November 1, 2012. The query end date varied by data partner and reflected the most current available date at the time the package was sent out. This request is the first of at least two requests to perform sequential analysis. This report presents results for "nonsecondary" AMI diagnoses, which include all diagnoses of AMI except those coded "S" for "secondary" diagnoses in the MSDD. The other analyses are presented in three separate reports. Results provide counts of new mirabegron and oxybutynin users, dispensings, total days supplied, eligible members, member-years for patients, and number of AMI events ("nonsecondary" diagnoses only). Please see Appendix A for a list of National Drug Codes (NDCs) used to define mirabegron and oxybutynin use, Appendix B for a list of codes used to define AMI diagnoses, and Appendix C for a list of codes to define incident use.
Request ID	to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 1 of 4
Requester	FDA
Specifications	Program parameter inputs and analysis
CIDA Glossary	List of Terms found in this Report and their Definitions
PSM Glossary	List of PSM Terms found in this Report and their Definitions
Monitoring Periods	Table of Monitoring Dates for Data Partners by Monitoring Period
Table 1	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Unmatched)
Table 2	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Matched Predefined PS, Caliper = .025)
Table 3	Table displaying Sequential Estimates for AMI Events (nonsecondary diagnoses only) by Analysis Type and Drug Pair
Appendix A	Table of Generic Names and Brand Names used to Define Exposures in this Request
Appendix B	Table of Diagnosis Codes used to Define Outcomes in this Request
Appendix C	Table of Generic Names and Brand Names used to Define Incidence in this Request
Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Specifications for to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 1 of 4

The Cohort Identification and Analysis (CIDA) tool with propensity score matching (PSM) was used to investigate acute myocardial infarction (AMI, "nonsecondary*" diagnoses only) following incident treatment of mirabegron or oxybutynin. In total, one analysis was examined in this report with differing exposures of interest. See below for a description of this analysis.

Enrollment Gap	45 days
Age Groups	20-<45, 45-<65, 65+
Query Period	November 1, 2012 - Data Partner Data End Date
Coverage Requirement	Medical and Drug Coverage
Propensity Score Matching Ratio	1:1
Propensity Score Matching Caliper	0.025
Enrollment Requirement	183 days

		Exposure of Interest Mirabegron	**Comparator of Interest** Oxybutynin
Drug/Exposure:	Incident w/ respect to:	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin
	Washout (days)	183	183
	Allowed Episodes	1	1
	Episode Gap	7	7
	Exposure Extension Period	7	7
	Minimum Episode Duration	0	0
	Minimum Days Supplied	0	0
	Episode Truncation by Incident Exposure	No	No
Event/Outcome:	Event/ Outcome	AMI	AMI
	Care Setting/PDX	Inpatient, Non-secondary (IPP, IPX, IP.)	Inpatient, Non-secondary (IPP, IPX, IP.)
	Incident w/ respect to:	AMI	AMI
	Washout (days)	30	30
	Blackout Period	0	0

NDCs checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

*"Nonsecondary" diagnoses include any diagnosis that are not coded as secondary diagnoses (PDX=S) in the Mini-Sentinel Distributed Database

Glossary of Terms in CIDA*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

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

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).

Cohort Definition (drug/exposure)- Indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

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

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

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

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

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

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

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

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

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

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.

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

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

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.

*all terms may not be used in this report
**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest. Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous enrollment before exposure" field.

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and 0.05.

Matching Ratio - patients in exposed and comparator groups are matched to their nearest neighbor by a 1:1 or 1:100 (up to 100) matching ratio.

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

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the outcome. This is most suitable for disease risk scores.

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed (during requester-defined lookback).

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate differences, the number needed to treat/harm, the attributable risk, and the population attributable risk.

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Monitoring Period Key

Monitoring Period #		Available Time frames
	1	November 1, 2012- May 30, 2014
1	2	November 1, 2012- December 31, 2013
	1	November 1, 2012- January 31, 2014

Table 1. Cohort of New Initiators of Mirabegron and Oxybutynin, AMI Nonsecondary Diagnoses (Unmatched)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	4,471	100%	48,766	100%	---	---
Events while on therapy	11	0.2%	141	0.3%	-0.1	0.0
Mean person-days at risk	71.8	68.3	68.8	71.9	3.0	0.0
Patient Characteristics						
Gender (F)	2,875	64.3%	33,063	67.8%	-3.5	-0.1
Mean age	67.8	14.4	67.5	14.0	0.2	0.0
20-44	366	8.2%	4,267	8.7%	-0.5	0.0
45-64	1,411	31.6%	13,586	27.9%	3.7	0.1
65-99	2,694	60.3%	30,913	63.4%	-3.1	-0.1
Recorded use of:						
Anti-asthma and COPD2 medications	694	15.5%	6,676	13.7%	1.8	0.1
Antidementia medications	284	6.4%	1,994	4.1%	2.3	0.1
Anti-obesity medications	6	0.1%	82	0.2%	-0.1	0.0
Anti-osteoporosis medications	289	6.5%	2,710	5.6%	0.9	0.0
Antidepressant medications	1,405	31.4%	13,783	28.3%	3.1	0.1
Antidiabetic agents	748	16.7%	9,456	19.4%	-2.7	-0.1
Antihyperlipidemic medications	1,933	43.2%	21,008	43.1%	0.1	0.0
Antihypertensive medications	2,579	57.7%	30,200	61.9%	-4.2	-0.1
Antiretroviral medications	9	0.2%	72	0.1%	0.1	0.0
Smoking cessation medications	17	0.4%	174	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	1.00	1.9	1.10	2.2	-0.2	-0.1
Asthma	309	6.9%	3,162	6.5%	0.4	0.0
History of coronary artery bypass graft (CABG)	79	1.8%	951	2.0%	-0.2	0.0
Cancer	687	15.4%	6,919	14.2%	1.2	0.0
Chronic kidney disease	348	7.8%	4,702	9.6%	-1.8	-0.1
COPD	422	9.4%	5,878	12.1%	-2.7	-0.1
Dementia	298	6.7%	2,449	5.0%	1.7	0.1
Depression	639	14.3%	7,646	15.7%	-1.4	0.0
Diabetes	1,012	22.6%	13,069	26.8%	-4.2	-0.1
End stage renal disease (ESRD)	12	0.3%	266	0.5%	-0.2	0.0
Fracture	231	5.2%	2,338	4.8%	0.4	0.0
HIV/AIDS[3]	10	0.2%	79	0.2%	0.0	0.0
Hyperlipidemia	2,177	48.7%	23,849	48.9%	-0.2	0.0
Hypertension	2,428	54.3%	28,482	58.4%	-4.1	-0.1
Obesity or weight gain	451	10.1%	6,756	13.9%	-3.8	-0.1
Osteoporosis	401	9.0%	4,045	8.3%	0.7	0.0
Other heart disease	1,111	24.8%	12,998	26.7%	-1.9	0.0
Other ischemic heart disease	706	15.8%	7,858	16.1%	-0.3	0.0
History of pecutaneous coronary intervention (PCI)	61	1.4%	858	1.8%	-0.4	0.0
Peripheral artery disease	178	4.0%	2,635	5.4%	-1.4	-0.1
Prior acute myocardial infarction (AMI)	23	0.5%	434	0.9%	-0.4	0.0
Stroke, broad definition	290	6.5%	3,233	6.6%	-0.1	0.0

Stroke, narrow definition	157	3.5%	1,747	3.6%	-0.1	0.0
Tobacco use diagnosis	248	5.5%	4,416	9.1%	-3.6	-0.1
CABG	3	0.1%	64	0.1%	0.0	0.0
Carotid bypass	0	0.0%	1	0.0%	0.0	---
Carotid revascularization	3	0.1%	43	0.1%	0.0	0.0
Chronic kidney disease procedure	0	0.0%	5	0.0%	0.0	---
ESRD procedure	3	0.1%	159	0.3%	-0.2	-0.1
Fracture procedure	14	0.3%	247	0.5%	-0.2	0.0
Lower extremity amputation	2	0.0%	47	0.1%	-0.1	0.0
Lower extremity bypass	1	0.0%	27	0.1%	-0.1	0.0
Lower extremity revascularization	7	0.2%	70	0.1%	0.1	0.0
PCI	20	0.4%	270	0.6%	-0.2	0.0
Health Service Utilization Intensity:						
Number of generics	8.6	5.3	7.6	5.0	1.0	0.2
Number of Filled Rx	21.1	17.2	18.3	15.8	2.7	0.2
Number of inpatient hospital encounters (IP)	0.1	0.4	0.2	0.6	-0.1	-0.1
Number of non-acute institutional encounters (IS)	0.2	1.0	0.4	1.9	-0.2	-0.1
Number of emergency room encounters (ED)	0.3	0.8	0.4	0.9	-0.1	-0.1
Number of ambulatory encounters (AV)	13.3	10.7	10.2	9.9	3.1	0.3
Number of other ambulatory encounters (OA)	1.9	3.8	2.3	4.6	-0.4	-0.1

Table 2. Cohort of New Initiators of Mirabegron and Oxybutynin, AMI Nonsecondary Diagnoses (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	4,465	99.9%	4,465	9.2%	0.0	1.8
Events while on therapy	11	0.2%	14	0.3%	-0.1	0.0
Mean person-days at risk	71.8	68.3	67.0	71.3	4.8	0.1
Patient Characteristics						
Gender (F)	2,872	64.3%	2,837	63.5%	0.8	0.0
Mean age	67.8	14.4	67.9	14.0	-0.1	0.0
20-44	366	8.2%	325	7.3%	0.9	0.0
45-64	1,411	31.6%	1,415	31.7%	-0.1	0.0
65-99	2,688	60.2%	2,725	61.0%	-0.8	0.0
Recorded use of:						
Anti-asthma and COPD2 medications	694	15.5%	686	15.4%	0.1	0.0
Antidementia medications	284	6.4%	248	5.6%	0.8	0.0
Anti-obesity medications	6	0.1%	4	0.1%	0.0	0.0
Anti-osteoporosis medications	288	6.5%	294	6.6%	-0.1	0.0
Antidepressant medications	1,404	31.4%	1,372	30.7%	0.7	0.0
Antidiabetic agents	748	16.8%	722	16.2%	0.6	0.0
Antihyperlipidemic medications	1,931	43.2%	1,935	43.3%	-0.1	0.0
Antihypertensive medications	2,578	57.7%	2,561	57.4%	0.3	0.0
Antiretroviral medications	9	0.2%	10	0.2%	0.0	0.0
Smoking cessation medications	17	0.4%	16	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	1.0	1.9	1.0	1.9	0.0	0.0
Asthma	309	6.9%	339	7.6%	-0.7	0.0
History of coronary artery bypass graft (CABG)	79	1.8%	85	1.9%	-0.1	0.0
Cancer	686	15.4%	695	15.6%	-0.2	0.0
Chronic kidney disease	348	7.8%	346	7.7%	0.1	0.0
COPD	421	9.4%	391	8.8%	0.6	0.0
Dementia	298	6.7%	268	6.0%	0.7	0.0
Depression	639	14.3%	605	13.5%	0.8	0.0
Diabetes	1,012	22.7%	995	22.3%	0.4	0.0
End stage renal disease (ESRD)	12	0.3%	15	0.3%	0.0	0.0
Fracture	230	5.2%	241	5.4%	-0.2	0.0
HIV/AIDS[3]	10	0.2%	12	0.3%	-0.1	0.0
Hyperlipidemia	2,175	48.7%	2,167	48.5%	0.2	0.0
Hypertension	2,427	54.4%	2,400	53.8%	0.6	0.0
Obesity or weight gain	450	10.1%	444	9.9%	0.2	0.0
Osteoporosis	401	9.0%	389	8.7%	0.3	0.0
Other heart disease	1,110	24.9%	1,075	24.1%	0.8	0.0
Other ischemic heart disease	705	15.8%	715	16.0%	-0.2	0.0
History of pecutaneous coronary intervention (PCI)	61	1.4%	66	1.5%	-0.1	0.0
Peripheral artery disease	177	4.0%	175	3.9%	0.1	0.0
Prior acute myocardial infarction (AMI)	23	0.5%	25	0.6%	-0.1	0.0
Stroke, broad definition	288	6.5%	275	6.2%	0.3	0.0
Stroke, narrow definition	156	3.5%	157	3.5%	0.0	0.0

Tobacco use diagnosis	248	5.6%	263	5.9%	-0.3	0.0
CABG	3	0.1%	3	0.1%	0.0	0.0
Carotid bypass	0	0.0%	0	0.0%	0.0	---
Carotid revascularization	3	0.1%	4	0.1%	0.0	0.0
Chronic kidney disease procedure	0	0.0%	0	0.0%	0.0	---
ESRD procedure	3	0.1%	5	0.1%	0.0	0.0
Fracture procedure	14	0.3%	13	0.3%	0.0	0.0
Lower extremity amputation	2	0.0%	1	0.0%	0.0	0.0
Lower extremity bypass	1	0.0%	1	0.0%	0.0	0.0
Lower extremity revascularization	7	0.2%	7	0.2%	0.0	0.0
PCI	20	0.4%	29	0.6%	-0.2	0.0
Health Service Utilization Intensity:						
Number of generics	8.6	5.3	8.5	5.5	0.1	0.0
Number of Filled Rx	21.1	17.2	20.6	17.4	0.5	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)	0.2	1.0	0.2	1.0	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8	0.3	0.7	0.0	0.0
Number of ambulatory encounters (AV)	13.3	10.7	13.1	12.6	0.2	0.0
Number of other ambulatory encounters (OA)	1.9	3.8	1.8	3.8	0.1	0.0

Table 3: Sequential Estimates for AMI Events by Analysis Type and Drug Pair

Exposure Definition	Monitoring Period	New Users*	Person-Days at Risk	Average Person-Days at Risk	Number of Events	Incidence Rate per 1000 Person-Years at Risk	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person-Years at Risk	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)**	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Mirabegron	1	4,471	320,875	71.77	11	12.52	2.46	-2.82	-0.43	0.92 (0.49, 1.73)	0.800
Oxybutynin		48,762	3,356,558	68.84	141	15.34	2.89				
1:1 Matched Analysis; Caliper = 0.025											
Mirabegron	1	4,465	320,567	71.80	11	12.53	2.46	-4.56	-0.67	0.63 (0.20, 1.91)	0.410
Oxybutynin		4,464	299,233	67.03	14	17.09	3.14				

Appendix A. Generic Names and Brand Names used to Define Exposures in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL

Appendix B. Codes used to Define AMI in this Request

Code	Description	Code Type
410.*0	Acute myocardial infarction, episode of care unspecified	ICD-9-CM Diagnosis Code
410.*1	Acute myocardial infarction, initial episode of care	ICD-9-CM Diagnosis Code

Appendix C. Generic Names and Brand Names used to Define Incidence in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL
TOLTERODINE TARTRATE	DETROL
TOLTERODINE TARTRATE	DETROL LA
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE ER
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE
TROSPIUM CHLORIDE	SANCTURA
TROSPIUM CHLORIDE	SANCTURA XR
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE ER
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE
FESOTERODINE FUMARATE	TOVIAZ
DARIFENACIN HYDROBROMIDE	ENABLEX
SOLIFENACIN SUCCINATE	VESICARE

MINI-SENTINEL PROSPECTIVE SURVEILLANCE PLAN

PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING OF MIRABEGRON – Report 2 of 4

Version 1.0

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September 19, 2016

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I

Overview

Request Description	FDA has requested execution of the Cohort Identification and Descriptive Analysis tool (CIDA) and Propensity Score Matching (PSM) tools to investigate diagnoses of acute myocardial infarction (AMI) and stroke events following use of mirabegron or oxybutynin in the Mini-Sentinel Distributed Database (MSDD). This request involved two runs of the program package. The package was distributed to four Data Partners on October 20, 2014. The query start date for this request was November 1, 2012. The query end date varied by data partner and reflected the most current available date at the time the package was sent out. This request is the first of at least two requests to perform sequential analysis. This report presents results for primary diagnoses of AMI only. The other analyses are presented in three separate reports.
	Results provide counts of new mirabegron and oxybutynin users, dispensings, total days supplied, eligible members, member-years for patients, and number of AMI events (primary diagnoses only). Please see Appendix A for a list of National Drug Codes (NDCs) used to define mirabegron and oxybutynin use, Appendix B for a list of codes used to define AMI diagnoses, and Appendix C for a list of codes to define incident use.
Request ID	to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 2 of 4
Requester	FDA
Specifications	Program parameter inputs and analysis
CIDA Glossary	List of Terms found in this Report and their Definitions
PSM Glossary	List of PSM Terms found in this Report and their Definitions
Monitoring Periods	Table of Monitoring Dates for Data Partners by Monitoring Period
Table 1	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Unmatched)
Table 2	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Matched Predefined PS, Caliper = .025)
Table 3	Table displaying Sequential Estimates for AMI (primary diagnoses only) Events by Analysis Type and Drug Pair
Appendix A	Table of Generic Names and Brand Names used to Define Exposures in this Request
Appendix B	Table of Codes used to Define AMI in this Request
Appendix C	Table of Generic Names and Brand Names used to Define Incidence in this Request
Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Specifications for to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 2 of 4

The Cohort Identification and Analysis (CIDA) tool with propensity score matching (PSM) was used to investigate acute myocardial infarction (AMI, primary diagnoses only) following treatment with mirabegron or oxybutynin. These specifications represent analysis for primary diagnoses of stroke only. The other analyses are presented in three separate reports.

Enrollment Gap	45 days
Age Groups	20-<45, 45-<65, 65+
Query Period	November 1, 2012 - Data Partner Data End Date
Coverage Requirement	Medical and Drug Coverage
Propensity Score Matching Ratio	1:1
Propensity Score Matching Caliper	0.025
Enrollment Requirement	183 days

		Exposure of Interest Mirabegron	**Comparator of Interest** Oxybutynin
Drug/Exposure:	Incident w/ respect to:	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin
	Washout (days)	183	183
	Allowed Episodes	1	1
	Episode Gap	7	7
	Exposure Extension Period	7	7
	Minimum Episode Duration	0	0
	Minimum Days Supplied	0	0
	Episode Truncation by Incident Exposure	No	No
Event/Outcome:	Event/ Outcome	AMI	AMI
	Care Setting/PDX	Inpatient, Primary (IPP)	Inpatient, Primary (IPP)
	Incident w/ respect to:	AMI	AMI
	Washout (days)	30	30
	Blackout Period	0	0

NDC codes checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

Glossary of Terms in CIDA*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

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

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).

Cohort Definition (drug/exposure)- Indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

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

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

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

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

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

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

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

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

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

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.

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

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

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.

*all terms may not be used in this report
**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest. Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous enrollment before exposure" field.

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and 0.05.

Matching Ratio - patients in exposed and comparator groups are matched to their nearest neighbor by a 1:1 or 1:100 (up to 100) matching ratio.

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

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the outcome. This is most suitable for disease risk scores.

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed (during requester-defined lookback).

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate differences, the number needed to treat/harm, the attributable risk, and the population attributable risk.

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Monitoring Period Key

Monitoring Period #	Number of DPs	Available Timeframes
1	1	November 1, 2012- May 30, 2014
	2	November 1, 2012- December 31, 2013
	1	November 1, 2012- January 31, 2014

Table 1. Cohort of New Initiators of Mirabegron and Oxybutynin, AMI Primary Diagnoses (Unmatched)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	4,472	100%	48,835	100%	---	---
Events while on therapy	5	0.1%	55	0.1%	0.0	0.0
Mean person-days at risk	71.8	68.3	68.9	72	2.9	0.0
Patient Characteristics						
Gender (F)	2,875	64.3%	33,099	67.8%	-3.5	-0.1
Mean age	67.8	14.4	67.6	14.0	0.2	0.0
20-44	366	8.2%	4,267	8.7%	-0.5	0.0
45-64	1,411	31.6%	13,597	27.8%	3.8	0.1
65-99	2,695	60.3%	30,971	63.4%	-3.1	-0.1
Recorded use of:						
Anti-asthma and COPD2 medications	695	15.5%	6,692	13.7%	1.8	0.1
Antidementia medications	285	6.4%	1,996	4.1%	2.3	0.1
Anti-obesity medications	6	0.1%	82	0.2%	-0.1	0.0
Anti-osteoporosis medications	289	6.5%	2,711	5.6%	0.9	0.0
Antidepressant medications	1,406	31.4%	13,802	28.3%	3.1	0.1
Antidiabetic agents	748	16.7%	9,482	19.4%	-2.7	-0.1
Antihyperlipidemic medications	1,934	43.2%	21,051	43.1%	0.1	0.0
Antihypertensive medications	2,580	57.7%	30,257	62.0%	-4.3	-0.1
Antiretroviral medications	9	0.2%	72	0.1%	0.1	0.0
Smoking cessation medications	17	0.4%	174	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	1.0	1.9	1.1	2.2	-0.2	-0.1
Asthma	309	6.9%	3,174	6.5%	0.4	0.0
History of coronary artery bypass graft (CABG)	79	1.8%	959	2.0%	-0.2	0.0
Cancer	687	15.4%	6,941	14.2%	1.2	0.0
Chronic kidney disease	348	7.8%	4,723	9.7%	-1.9	-0.1
COPD	423	9.5%	5,903	12.1%	-2.6	-0.1
Dementia	299	6.7%	2,462	5.0%	1.7	0.1
Depression	640	14.3%	7,659	15.7%	-1.4	0.0
Diabetes	1,013	22.7%	13,106	26.8%	-4.1	-0.1
End stage renal disease (ESRD)	12	0.3%	269	0.6%	-0.3	0.0
Fracture	231	5.2%	2,347	4.8%	0.4	0.0
HIV/AIDS[3]	10	0.2%	79	0.2%	0.0	0.0
Hyperlipidemia	2,178	48.7%	23,895	48.9%	-0.2	0.0
Hypertension	2,429	54.3%	28,544	58.4%	-4.1	-0.1
Obesity or weight gain	451	10.1%	6,767	13.9%	-3.8	-0.1
Osteoporosis	401	9.0%	4,050	8.3%	0.7	0.0
Other heart disease	1,112	24.9%	13,059	26.7%	-1.8	0.0
Other ischemic heart disease	707	15.8%	7,911	16.2%	-0.4	0.0
History of pecutaneous coronary intervention (PCI)	61	1.4%	861	1.8%	-0.4	0.0
Peripheral artery disease	178	4.0%	2,645	5.4%	-1.4	-0.1

Prior acute myocardial infarction (AMI)	24	0.5%	503	1.0%	-0.5	-0.1
Stroke, broad definition	291	6.5%	3,250	6.7%	-0.2	0.0
Stroke, narrow definition	158	3.5%	1,756	3.6%	-0.1	0.0
Tobacco use diagnosis	248	5.5%	4,432	9.1%	-3.6	-0.1
CABG	3	0.1%	69	0.1%	0.0	0.0
Carotid bypass	0	0.0%	1	0.0%	0.0	---
Carotid revascularization	3	0.1%	43	0.1%	0.0	0.0
Chronic kidney disease procedure	0	0.0%	5	0.0%	0.0	---
ESRD procedure	3	0.1%	160	0.3%	-0.2	-0.1
Fracture procedure	14	0.3%	247	0.5%	-0.2	0.0
Lower extremity amputation	2	0.0%	47	0.1%	-0.1	0.0
Lower extremity bypass	1	0.0%	28	0.1%	-0.1	0.0
Lower extremity revascularization	7	0.2%	73	0.1%	0.1	0.0
PCI	21	0.5%	291	0.6%	-0.1	0.0
Health Service Utilization Intensity:						
Number of generics	8.6	5.3	7.6	5.0	1.0	0.2
Number of Filled Rx	21.1	17.2	18.3	15.8	2.7	0.2
Number of inpatient hospital encounters (IP)	0.1	0.4	0.2	0.7	-0.1	-0.1
Number of non-acute institutional encounters (IS)	0.2	1.0	0.4	1.9	-0.2	-0.1
Number of emergency room encounters (ED)	0.3	0.8	0.4	0.9	-0.1	-0.1
Number of ambulatory encounters (AV)	13.3	10.7	10.2	10.0	3.1	0.3
Number of other ambulatory encounters (OA)	1.9	3.8	2.3	4.6	-0.4	-0.1

[1]standard deviation where no % follows the value

[2]COPD - chronic obstructive pulmonary disease

[3]HIV/AIDS - human imunnodeficiency virus/acquired immune deficiency syndrome

Table 2. Cohort of New Initiators of Mirabegron and Oxybutynin, AMI Primary Diagnoses (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	4,466	99.9%	4,466	9.1%	0.0	1.8
Events while on therapy	5	0.1%	3	0.1%	0.0	0.0
Mean person-days at risk	71.8	68.3	66.2	70	5.6	0.1
Patient Characteristics						
Gender (F)	2,872	64.3%	2,844	63.7%	0.6	0.0
Mean age	67.8	14.4	68.1	14.2	-0.3	0.0
20-44	366	8.2%	327	7.3%	0.9	0.0
45-64	1,411	31.6%	1,375	30.8%	0.8	0.0
65-99	2,689	60.2%	2,764	61.9%	-1.7	0.0
Recorded use of:						
Anti-asthma and COPD2 medications	695	15.6%	703	15.7%	-0.1	0.0
Antidementia medications	284	6.4%	249	5.6%	0.8	0.0
Anti-obesity medications	6	0.1%	9	0.2%	-0.1	0.0
Anti-osteoporosis medications	288	6.4%	261	5.8%	0.6	0.0
Antidepressant medications	1,404	31.4%	1,411	31.6%	-0.2	0.0
Antidiabetic agents	747	16.7%	764	17.1%	-0.4	0.0
Antihyperlipidemic medications	1,932	43.3%	1,957	43.8%	-0.5	0.0
Antihypertensive medications	2,578	57.7%	2,637	59.0%	-1.3	0.0
Antiretroviral medications	9	0.2%	7	0.2%	0.0	0.0
Smoking cessation medications	17	0.4%	14	0.3%	0.1	0.0
Recorded history of:						
Combined comorbidity score	1.0	1.9	1.0	1.9	0.0	0.0
Asthma	309	6.9%	334	7.5%	-0.6	0.0
History of coronary artery bypass graft (CABG)	79	1.8%	76	1.7%	0.1	0.0
Cancer	686	15.4%	711	15.9%	-0.5	0.0
Chronic kidney disease	348	7.8%	373	8.4%	-0.6	0.0
COPD	422	9.4%	406	9.1%	0.3	0.0
Dementia	299	6.7%	270	6.0%	0.7	0.0
Depression	640	14.3%	631	14.1%	0.2	0.0
Diabetes	1,011	22.6%	1,017	22.8%	-0.2	0.0
End stage renal disease (ESRD)	12	0.3%	14	0.3%	0.0	0.0
Fracture	230	5.2%	237	5.3%	-0.1	0.0
HIV/AIDS[3]	10	0.2%	7	0.2%	0.0	0.0
Hyperlipidemia	2,174	48.7%	2,178	48.8%	-0.1	0.0
Hypertension	2,426	54.3%	2,462	55.1%	-0.8	0.0
Obesity or weight gain	451	10.1%	454	10.2%	-0.1	0.0
Osteoporosis	400	9.0%	399	8.9%	0.1	0.0
Other heart disease	1,109	24.8%	1,094	24.5%	0.3	0.0
Other ischemic heart disease	706	15.8%	674	15.1%	0.7	0.0
History of pecutaneous coronary intervention (PCI)	61	1.4%	61	1.4%	0.0	0.0
Peripheral artery disease	177	4.0%	171	3.8%	0.2	0.0

Prior acute myocardial infarction (AMI)	24	0.5%	33	0.7%	-0.2	0.0
Stroke, broad definition	290	6.5%	273	6.1%	0.4	0.0
Stroke, narrow definition	158	3.5%	156	3.5%	0.0	0.0
Tobacco use diagnosis	248	5.6%	244	5.5%	0.1	0.0
CABG	3	0.1%	1	0.0%	0.1	0.0
Carotid bypass	0	0.0%	0	0.0%	0.0	---
Carotid revascularization	3	0.1%	2	0.0%	0.1	0.0
Chronic kidney disease procedure	0	0.0%	0	0.0%	0.0	---
ESRD procedure	3	0.1%	4	0.1%	0.0	0.0
Fracture procedure	14	0.3%	11	0.2%	0.1	0.0
Lower extremity amputation	2	0.0%	1	0.0%	0.0	0.0
Lower extremity bypass	1	0.0%	0	0.0%	0.0	---
Lower extremity revascularization	7	0.2%	7	0.2%	0.0	0.0
PCI	21	0.5%	25	0.6%	-0.1	0.0
Health Service Utilization Intensity:						
Number of generics	8.6	5.3	8.7	5.5	-0.1	0.0
Number of Filled Rx	21.1	17.2	21.3	18.0	-0.3	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)	0.2	1.0	0.2	1.0	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8	0.3	0.7	0.0	0.0
Number of ambulatory encounters (AV)	13.3	10.7	13.3	13.0	0.0	0.0
Number of other ambulatory encounters (OA)	1.9	3.8	1.9	3.9	0.0	0.0

[1]standard deviation where no % follows the value

[2]COPD - chronic obstructive pulmonary disease

[3]HIV/AIDS - human imunnodeficiency virus/acquired immune deficiency syndrome

Table 3: Sequential Estimates for AMI (Primary Diagnoses) Events by Analysis Type and Drug Pair

Exposure Definition	Monitoring Period	New Users*	Person-Days at Risk	Average Person-Days at Risk	Number of Events	Incidence Rate per 1000 Person-Years at Risk	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person-Years at Risk	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)**	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Mirabegron	1	4,472	321,118	71.81	5	5.69	1.12	-0.28	-0.01	1.23 (0.48, 3.13)	0.670
Oxybutynin		48,831	3,363,905	68.89	55	5.97	1.13				
Mirabegron	2	To be completed after look 2									
Oxybutynin											
1:1 Matched Analysis											
Mirabegron	1	4,466	320,888	71.85	5	5.69	1.12	1.99	0.45	1.00 (0.14, 7.10)	1.000
Oxybutynin		4,465	295,789	66.25	3	3.70	0.67				
Mirabegron	2	To be completed after look 2									
Oxybutynin											

*One patient was removed from the matched analysis due to Data Partner compliance reasons

**For sequential analysis that the confidence intervals do not account for repeated looks or correlation in the data across looks, but are provided for descriptive purposes

Appendix A. Generic Names and Brand Names used to Define Exposures in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL

Appendix B. Codes used to Define AMI in this Request

Code	Description	Code Type
410.*0	Acute myocardial infarction, episode of care unspecified	ICD-9-CM Diagnosis Code
410.*1	Acute myocardial infarction, initial episode of care	ICD-9-CM Diagnosis Code

Appendix C. Generic Names and Brand Names used to Define Incidence in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL
TOLTERODINE TARTRATE	DETROL
TOLTERODINE TARTRATE	DETROL LA
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE ER
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE
TROSPIUM CHLORIDE	SANCTURA
TROSPIUM CHLORIDE	SANCTURA XR
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE ER
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE
FESOTERODINE FUMARATE	TOVIAZ
DARIFENACIN HYDROBROMIDE	ENABLEX
SOLIFENACIN SUCCINATE	VESICARE

MINI-SENTINEL PROSPECTIVE SURVEILLANCE PLAN

PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING OF MIRABEGRON – Report 3 of 4

Version 1.0

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September 19, 2016

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Overview	
Request Description	FDA has requested execution of the Cohort Identification and Descriptive Analysis tool (CIDA) with propensity score matching (PSM) to investigate diagnoses of acute myocardial infarction (AMI) and stroke events following use of mirabegron or oxybutynin in the Mini-Sentinel Distributed Database (MSDD). This request involved two runs of the program package. The package was distributed to four Data Partners on October 20, 2014. The query start date for this request was November 1, 2012. The query end date varied by data partner and reflected the most current available date at the time the package was sent out. This request is the first of at least two requests to perform sequential analysis. This report presents results for "nonsecondary" stroke diagnoses, which include all diagnoses of stroke except those coded "S" for "secondary" diagnoses in the MSDD. The other analyses are presented in three separate reports.
	Results provide counts of new mirabegron and oxybutynin users, dispensings, total days supplied, eligible members, member-years for patients, and number of stroke events (nonsecondary diagnoses only). Please see Appendix A for a list of National Drug Codes (NDCs) used to define mirabegron and oxybutynin use, Appendix B for a list of codes used to define stroke diagnoses, and Appendix C for a list of codes to define incident use.
Request ID	to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 3 of 4
Requester	FDA
Specifications	Program parameter inputs and analysis
CIDA Glossary	List of Terms found in this Report and their Definitions
PSM Glossary	List of PSM Terms found in this Report and their Definitions
Monitoring Periods	Table of Monitoring Dates for Data Partners by Monitoring Period
Table 1	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Unmatched)
Table 2	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Matched Predefined PS, Caliper = .025)
Table 3	Table displaying Sequential Estimates for Stroke Events (nonsecondary diagnoses only) by Analysis Type and Drug Pair
Appendix A	Table of Generic Names and Brand Names used to Define Exposures in this Request
Appendix B	Table of Diagnosis Codes used to Define Outcomes in this Request
Appendix C	Table of Generic Names and Brand Names used to Define Incidence in this Request
Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Specifications for to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 3 of 4

The Cohort Identification and Analysis (CIDA) tool with propensity score matching (PSM) was used to investigate stroke ("nonsecondary" diagnoses only) following treatment with mirabegron or oxybutynin. These specifications represent analysis for "nonsecondary" diagnoses of stroke only. The other analyses are presented in three separate reports.

Enrollment Gap	45 days
Age Groups	20-<45, 45-<65, 65+
Query Period	November 1, 2012 - Data Partner Data End Date
Coverage Requirement	Medical and Drug Coverage
Propensity Score Matching Ratio	1:1
Propensity Score Matching Caliper	0.025
Enrollment Requirement	183 days

		Exposure of Interest Mirabegron	**Comparator of Interest** Oxybutynin
Drug/Exposure:	Incident w/ respect to:	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin
	Washout (days)	183	183
	Allowed Episodes	1	1
	Episode Gap	7	7
	Exposure Extension Period	7	7
	Minimum Episode Duration	0	0
	Minimum Days Supplied	0	0
	Episode Truncation by Incident Exposure	No	No
Event/Outcome:	Event/ Outcome	Stroke	Stroke
	Care Setting/PDX	Inpatient, Nonsecondary (IPP, IPX, IP.)	Inpatient, Nonsecondary (IPP, IPX, IP.)
	Incident w/ respect to:	Stroke	Stroke
	Washout (days)	30	30
	Blackout Period	0	0

NDC codes checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

Glossary of Terms in CIDA*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

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

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).

Cohort Definition (drug/exposure)- Indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

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

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

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

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

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

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

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

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

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

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.

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

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

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.

*all terms may not be used in this report
**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest.Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous enrollment before exposure" field.

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and 0.05.

Matching Ratio - patients in exposed and comparator groups are matched to their nearest neighbor by a 1:1 or 1:100 (up to 100) matching ratio.

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

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the outcome. This is most suitable for disease risk scores.

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed (during requester-defined lookback).

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate differences, the number needed to treat/harm, the attributable risk, and the population attributable risk.

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Monitoring Period Key

Monitoring Period #	Number of DPs	Available Timeframes
1	1	November 1, 2012- May 30, 2014
	2	November 1, 2012- December 31, 2013
	1	November 1, 2012- January 31, 2014

Table 1. Cohort of New Initiators of Mirabegron and Oxybutynin, Stroke Nonsecondary Diagnoses (Unmatched)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	5,947	100%	60,457	100%	---	---
Events while on therapy	16	0.3%	318	0.5%	-0.2	0.0
Mean person-days at risk	69.5	65.8	65.1	68.6	4.4	0.1
Patient Characteristics						
Gender (F)	3,915	65.8%	41,132	68.0%	-2.2	0.0
Mean age	65.1	14.1	64.8	13.9	0.3	0.0
20-44	623	10.5%	7,205	11.9%	-1.4	0.0
45-64	2,328	39.1%	20,841	34.5%	4.6	0.1
65-99	2,996	50.4%	32,411	53.6%	-3.2	-0.1
Recorded use of:						
Anti-alcohol abuse medications	10	0.2%	46	0.1%	0.1	0.0
Antimigraine medications	152	2.6%	1,061	1.8%	0.8	0.1
Anti-obesity medications	7	0.1%	92	0.2%	-0.1	0.0
Antiarrhythmic medications	128	2.2%	1,074	1.8%	0.4	0.0
Anticoagulant medications	402	6.8%	3,806	6.3%	0.5	0.0
Antidepressant medications	1,848	31.1%	16,887	27.9%	3.2	0.1
Antidiabetic agents	947	15.9%	10,852	17.9%	-2.0	-0.1
Antihyperlipidemic medications	2,430	40.9%	23,957	39.6%	1.3	0.0
Antihypertensive medications	3,220	54.1%	34,643	57.3%	-3.2	-0.1
Antiplatelet medications	322	5.4%	3,161	5.2%	0.2	0.0
Antiretroviral medications	10	0.2%	93	0.2%	0.0	0.0
Aspirin	11	0.2%	76	0.1%	0.1	0.0
Contraceptive or HRT[2]	932	15.7%	4,701	7.8%	7.9	0.2
Smoking cessation medications	26	0.4%	213	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	0.80	1.8	1.00	2.0	-0.2	-0.1
Atrial fibrilliation, flutter	496	8.3%	4,911	8.1%	0.2	0.0
Alcohol use	40	0.7%	710	1.2%	-0.5	-0.1
Chronic kidney disease	383	6.4%	4,927	8.1%	-1.7	-0.1
Depression	845	14.2%	9,166	15.2%	-1.0	0.0
Diabetes	1,262	21.2%	14,801	24.5%	-3.3	-0.1
HIV/AIDS[3]	13	0.2%	102	0.2%	0.0	0.0
Hyperlipidemia	2,754	46.3%	27,492	45.5%	0.8	0.0
Hypertension	3,014	50.7%	32,655	54.0%	-3.3	-0.1
Ischemic heart disease	830	14.0%	8,674	14.3%	-0.3	0.0
Migraine	211	3.5%	1,620	2.7%	0.8	0.0
Obesity or weight gain	604	10.2%	8,146	13.5%	-3.3	-0.1
Other heart disease	1,126	18.9%	12,683	21.0%	-2.1	-0.1
Peripheral artery disease	195	3.3%	2,755	4.6%	-1.3	-0.1
Pulmonary circulation disease	115	1.9%	1,492	2.5%	-0.6	0.0
Rheumatic heart disease, chronic	76	1.3%	944	1.6%	-0.3	0.0
Sickle cell disease	1	0.0%	14	0.0%	0.0	0.0

Stroke, broad definition	335	5.6%	3,330	5.5%	0.1	0.0
Stroke, narrow definition	170	2.9%	1,721	2.8%	0.1	0.0
Tobacco use	328	5.5%	5,507	9.1%	-3.6	-0.1
Transient ischemic attack	87	1.5%	910	1.5%	0.0	0.0
Chronic kidney disease, procedure	0	0.0%	5	0.0%	0.0	---
Health Service Utilization Intensity:						
Number of generics	8.4	5.4	7.3	5.0	1.0	0.2
Number of Filled Rx	20.6	17.3	17.5	15.6	3.0	0.2
Number of inpatient hospital encounters (IP)	0.1	0.4	0.2	0.6	-0.1	-0.2
Number of non-acute institutional encounters (IS)	0.1	0.9	0.3	1.7	-0.2	-0.1
Number of emergency room encounters (ED)	0.3	0.8	0.4	1.0	-0.1	-0.1
Number of ambulatory encounters (AV)	12.9	10.6	9.9	9.7	3.0	0.3
Number of other ambulatory encounters (OA)	2.1	3.9	2.2	4.4	-0.1	0.0

[1]standard deviation where no % follows the value

[2]HRT - Hormone replacement therapy

[3]HIV/AIDS - human imunnodeficiency virus/acquired immune deficiency syndrome

Table 2. Cohort of New Initiators of Mirabegron and Oxybutynin, Stroke Nonsecondary Diagnoses (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	5,931	99.7%	5,931	9.8%	0.0	1.8
Events while on therapy	16	0.3%	35	0.6%	-0.3	0.0
Mean person-days at risk	69.5	65.8	62.7	66.4	6.7	0.1
Patient Characteristics						
Gender (F)	3,899	65.7%	3,872	63.5%	0.4	0.0
Mean age	65.1	14.2	65.5	13.6	-0.4	0.0
20-44	622	10.5%	543	9.2%	1.3	0.0
45-64	2,316	39.0%	2,344	39.5%	-0.5	0.0
65-99	2,993	50.5%	3,044	51.3%	-0.8	0.0
Recorded use of:						
Anti-alcohol abuse medications	9	0.2%	9	0.2%	0.0	0.0
Antimigraine medications	148	2.5%	129	2.2%	0.3	0.0
Anti-obesity medications	7	0.1%	11	0.2%	-0.1	0.0
Antiarrhythmic medications	128	2.2%	116	2.0%	0.2	0.0
Anticoagulant medications	400	6.7%	390	6.6%	0.1	0.0
Antidepressant medications	1,837	31.0%	1,849	31.2%	-0.2	0.0
Antidiabetic agents	944	15.9%	987	16.6%	-0.7	0.0
Antihyperlipidemic medications	2,421	40.8%	2,396	40.4%	0.4	0.0
Antihypertensive medications	3,209	54.1%	3,195	53.9%	0.2	0.0
Antiplatelet medications	322	5.4%	329	5.5%	-0.1	0.0
Antiretroviral medications	10	0.2%	7	0.1%	0.1	0.0
Aspirin	11	0.2%	9	0.2%	0.0	0.0
Contraceptive or HRT[2]	920	15.5%	907	15.3%	0.2	0.0
Smoking cessation medications	26	0.4%	26	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	0.80	1.8	0.90	1.8	0.0	0.0
Atrial fibrilliation, flutter	495	8.3%	500	8.4%	-0.1	0.0
Alcohol use	40	0.7%	34	0.6%	0.1	0.0
Chronic kidney disease	383	6.5%	388	6.5%	0.0	0.0
Depression	840	14.2%	814	13.7%	0.5	0.0
Diabetes	1,259	21.2%	1,282	21.6%	-0.4	0.0
HIV/AIDS[3]	13	0.2%	8	0.1%	0.1	0.0
Hyperlipidemia	2,742	46.2%	2,741	46.2%	0.0	0.0
Hypertension	3,002	50.6%	2,992	50.4%	0.2	0.0
Ischemic heart disease	829	14.0%	796	13.4%	0.6	0.0
Migraine	206	3.5%	193	3.3%	0.2	0.0
Obesity or weight gain	601	10.1%	576	9.7%	0.4	0.0
Other heart disease	1,123	18.9%	1,121	18.9%	0.0	0.0
Peripheral artery disease	195	3.3%	178	3.0%	0.3	0.0
Pulmonary circulation disease	115	1.9%	112	1.9%	0.0	0.0
Rheumatic heart disease, chronic	76	1.3%	74	1.2%	0.1	0.0

Sickle cell disease	1	0.0%	1	0.0%	0.0	0.0
Stroke, broad definition	331	5.6%	321	5.4%	0.2	0.0
Stroke, narrow definition	169	2.8%	169	2.8%	0.0	0.0
Tobacco use	327	5.5%	302	5.1%	0.4	0.0
Transient ischemic attack	87	1.5%	94	1.6%	-0.1	0.0
Chronic kidney disease, procedure	0	0.0%	0	0.0%	0.0	---
Health Service Utilization Intensity:						
Number of generics	8.3	5.3	8.3	5.4	0.1	0.0
Number of Filled Rx	20.4	17.0	20.1	17.3	0.3	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	0.9	0.1	1.0	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8	0.3	0.7	0.0	0.0
Number of ambulatory encounters (AV)	12.8	10.5	12.5	12.3	0.3	0.0
Number of other ambulatory encounters (OA)	2.0	3.7	2.0	4.4	0.0	0.0

[1]standard deviation where no % follows the value

[2]HRT - Hormone replacement therapy

Table 3: Sequential Estimates for Stroke Events by Analysis Type and Drug Pair

Exposure Definition	Monitoring Period	New Users*	Person-Days at Risk	Average Person-Days at Risk	Number of Events	Incidence Rate per 1000 Person-Years at Risk	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person-Years at Risk	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)**	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Mirabegron	1	5,947	413,203	69.48	16	14.14	2.69	-15.39	-2.57	0.60 (0.36, 1.00)	0.049
Oxybutynin		60,453	3,932,706	65.05	318	29.53	5.26				
Mirabegron	2	To be completed after look 2									
Oxybutynin											
1:1 Matched Analysis											
Mirabegron	1	5,931	412,193	69.50	16	14.18	2.70	-20.16	-3.20	0.48 (0.24, 0.96)	0.037
Oxybutynin		5,930	372,316	62.79	35	34.34	5.90				
Mirabegron	2	To be completed after look 2									
Oxybutynin											

*One patient was removed from the matched analysis due to Data Partner compliance reasons

**For sequential analysis that the confidence intervals do not account for repeated looks or correlation in the data across looks, but are provided for descriptive purposes

Appendix A. Generic Names and Brand Names used to Define Exposures in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL

Appendix B. Codes used to Define Stroke in this Request

Code	Description	Code Type
430*	Subarachnoid hemorrhage	ICD-9-CM Diagnosis Code
431*	Intracerebral hemorrhage	ICD-9-CM Diagnosis Code
433.*1	Occlusion and stenosis of precerebral arteries with cerebral infarction	ICD-9-CM Diagnosis Code
434.*1	Occlusion of cerebral arteries with cerebral infarction	ICD-9-CM Diagnosis Code
436*	Acute, but ill-defined, cerebrovascular disease	ICD-9-CM Diagnosis Code

Appendix C. Generic Names and Brand Names used to Define Incidence in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL
TOLTERODINE TARTRATE	DETROL
TOLTERODINE TARTRATE	DETROL LA
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE ER
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE
TROSPIUM CHLORIDE	SANCTURA
TROSPIUM CHLORIDE	SANCTURA XR
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE ER
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE
FESOTERODINE FUMARATE	TOVIAZ
DARIFENACIN HYDROBROMIDE	ENABLEX
SOLIFENACIN SUCCINATE	VESICARE

MINI-SENTINEL PROSPECTIVE SURVEILLANCE PLAN

PROSPECTIVE ROUTINE OBSERVATIONAL MONITORING OF MIRABEGRON – Report 4 of 4

Version 1.0

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September 19, 2016

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Overview	
Request Description	FDA has requested execution of the Cohort Identification and Descriptive Analysis (CIDA) tool and Propensity Score Matching (PSM) tools to investigate diagnoses of acute myocardial infarction (AMI) and stroke events following use of mirabegron or oxybutynin in the Mini-Sentinel Distributed Database (MSDD). This request involved two runs of the program package. The package was distributed to four Data Partners on October 20, 2014. The query start date for this request was November 1, 2012. The query end date varied by data partner and reflected the most current available date at the time the package was sent out. This request is the first of at least two requests to perform sequential analysis. This report presents results for primary diagnoses of stroke only. The other analyses are presented in three separate reports.
	Results provide counts of new mirabegron and oxybutynin users, dispensings, total days supplied, eligible members, member-years for patients, and number of stroke events (primary diagnoses only). Please see Appendix A for a list of National Drug Codes (NDCs) used to define mirabegron and oxybutynin use, Appendix B for a list of codes used to define stroke diagnoses, and Appendix C for a list of codes to define incident use.
Request ID	to12_prompt_mira_mpl3r_wp01_nsdp_v01 - Report 4 of 4
Requester	FDA
Specifications	Program parameter inputs and analysis
CIDA Glossary	List of Terms found in this Report and their Definitions
PSM Glossary	List of PSM Terms found in this Report and their Definitions
Monitoring Periods	Table of Monitoring Dates for Data Partners by Monitoring Period
Table 1	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Unmatched)
Table 2	Table displaying Cohort of New Initiators of Mirabegron and Oxybutynin (Matched Predefined PS, Caliper = .025)
Table 3	Table displaying Sequential Estimates for Stroke Events (primary diagnoses only) by Analysis Type and Drug Pair
Appendix A	Table of Generic Names and Brand Names used to Define Exposures in this Request
Appendix B	Table of Diagnosis Codes used to Define Outcomes in this Request
Appendix C	Table of Generic Names and Brand Names used to Define Incidence in this Request
Notes:	Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document.

Specifications for to12_prompt_mira_mpl3r_wp01_dpid_v01 - Report 4 of 4

The Cohort Identification and Analysis (CIDA) tool with propensity score matching (PSM) was used to investigate stroke (primary diagnoses only) following treatment with mirabegron or oxybutynin. These specifications represent analysis for primary diagnoses of stroke only. The other analyses are presented in three separate reports.

Enrollment Gap	45 days	
Age Groups	20-<45, 45-<65, 65+	
Query Period	November 1, 2012 - Data Partner Data End Date	
Coverage Requirement	Medical and Drug Coverage	
Propensity Score Matching Ratio	1:1	
Propensity Score Matching Caliper	0.025	
Enrollment Requirement	183 days	

		Exposure of Interest Mirabegron	**Comparator of Interest** Oxybutynin
Drug/Exposure:	Incident w/ respect to:	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin	Mirabegron, Oxybutynin, Tolterodine, Trospium, Fesoterodine, Darifenacin, Solifenacin
	Washout (days)	183	183
	Allowed Episodes	1	1
	Episode Gap	7	7
	Exposure Extension Period	7	7
	Minimum Episode Duration	0	0
	Minimum Days Supplied	0	0
	Episode Truncation by Incident Exposure	No	No
Event/Outcome:	Event/ Outcome	Stroke	Stroke
	Care Setting/PDX	Inpatient, Primary (IPP)	Inpatient, Primary (IPP)
	Incident w/ respect to:	Stroke	Stroke
	Washout (days)	30	30
	Blackout Period	0	0

NDC codes checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
HCPCS codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
CPT codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

Glossary of Terms in CIDA*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the MSCDM.

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

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).

Cohort Definition (drug/exposure)- Indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid incident treatment episode during the query period; (2) 02: Cohort includes all valid incident treatment episodes during the query period; (3) 03: Cohort includes all valid incident treatment episodes during the query period until an event occurs.

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

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

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

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

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

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

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode.

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

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

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.

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

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure (s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

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.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Glossary of Terms for Analyses Using Propensity Score Match (PSM) Tool*

Bias Ranking - method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which variables are selected as ranked by the Bross bias formula.

Covariate Evaluation Window - number of days before the index date to evaluate the occurrence of covariates of interest.Note: members are required to have continuous enrollment during the covariate evaluation window, regardless of the value included in the "Continuous enrollment before exposure" field.

Covariate Grouping Indicator - a requester-defined name used to indicate how codes should be grouped to identify a single covariate.

Exposure association ranking- default method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the exposure. This is most suitable for cases where there are fewer than 150 exposed outcomes.

High dimensional Propensity Score (hdPS) - allows for selection of empirically identified covariates in addition to and/or without predefined covariates based on the potential for confounding the exposure/outcome association under investigation.

Mahalanobis Distance- provides a measure of balance across all variables while accounting for their correlation.

Matching Caliper- maximum allowed difference in propensity scores between treatment and control patients. Options are 0.01, 0.025, and 0.05.

Matching Ratio - patients in exposed and comparator groups are matched to their nearest neighbor by a 1:1 or 1:100 (up to 100) matching ratio.

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

Number of covariates from pool of considered covariates to keep in hdPS model - The total number of covariates to keep in the hdPS model. Default value is the fewest of 1) 200; or 2) the number of initiators of the exposure of interest.

Number of covariates to consider for each claim type for inclusion in hdPS model - The number of covariates that are considered for inclusion in the hdPS model for each claim type (NDC, ICD9 diagnosis, ICD9 procedure, HCPCS, and CPT). If a value of 100 is specified in this field, then 500 covariates will be considered for inclusion (100 for each of the 5 claim types), Default value is 100.

Outcome Association Ranking- method for ranking/prioritizing covariates for inclusion in the hdPS model. This method yields a variable list in which the variables are selected as ranked by the strength of their relationship to the outcome. This is most suitable for disease risk scores.

Predefined Propensity Score Matched Analysis - performed by default using the Propensity Score Match Tool. Requester-defined covariates are included along with 12 other covariates: 1. Age (continuous) 2. Sex 3. Time (monitoring period) 4. Year of Exposure 5. Comorbidity Score (calculated during requester-defined lookback) 6. Medical Utilization- number of inpatient stays (during requester-defined lookback) 7. Medical Utilization- number of institutional stays (during requester-defined lookback) 8. Medical utilization- number of emergency department visits (during requester-defined lookback) 9. Medical utilization- number of outpatient visits (during requester-defined lookback) 10. Health care utilization- number of other ambulatory encounters (e.g telemedicine, email consults during requester-defined lookback) 11. Drug utilization- number of dispensings (during requester-defined lookback) 12. Drug utilization- number of unique generics dispensed (during requester-defined lookback).

Propensity Score Match Tool - performs effect estimation by comparing exposure propensity-score matched parallel new user cohorts. The Propensity Score Match Tool generates tables of patient characteristics, stratified by exposure group, for the unmatched cohort and for the 1:1 matched cohort. Tables include measures of covariate balance and the Mahalanobis distance. The program also generates histograms depicting the propensity score distributions for each exposure group, separately for each Data Partner and each monitoring period, before and after matching. Figures include c-statistics. This program provides hazard ratios and 95% confidence intervals, Mantel-Haenszel rate differences, the number needed to treat/harm, the attributable risk, and the population attributable risk.

Query Level - Mini-Sentinel routine data queries are grouped into three distinct "levels," indicative of the level of complexity, extent of analytic adjustment, and need for repeated execution and alerting tools (i.e., prospective surveillance).

Zero Cell Correction - An indicator for whether to screen variables with a zero correction added to each cell in the confounder/outcome 2x2 table. Recommended when the number of exposed outcomes is fewer than 150.

*all terms may not be used in this report

Monitoring Period Key

Monitoring Period #	Number of DPs	Available Timeframes
1	1	November 1, 2012- May 30, 2014
	2	November 1, 2012- December 31, 2013
	1	November 1, 2012- January 31, 2014

Table 1. Cohort of New Initiators of Mirabegron and Oxybutynin, Stroke Primary Diagnoses (Unmatched)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	5,952	100%	60,588	100%	---	---
Events while on therapy	6	0.1%	95	0.2%	-0.1	0.0
Mean person-days at risk	69.5	65.8	65.2	68.7	4.3	0.1
Patient Characteristics						
Gender (F)	3,917	65.8%	41,205	68.0%	-2.2	0.0
Mean age	65.1	14.1	64.8	13.9	0.3	0.0
20-44	623	10.5%	7,207	11.9%	-1.4	0.0
45-64	2,328	39.1%	20,863	34.4%	4.7	0.1
65-99	3,001	50.4%	32,518	53.7%	-3.3	-0.1
Recorded use of:						
Anti-alcohol abuse medications	10	0.2%	46	0.1%	0.1	0.0
Antimigraine medications	152	2.6%	1,063	1.8%	0.8	0.1
Anti-obesity medications	7	0.1%	92	0.2%	-0.1	0.0
Antiarrhythmic medications	129	2.2%	1,076	1.8%	0.4	0.0
Anticoagulant medications	404	6.8%	3,831	6.3%	0.5	0.0
Antidepressant medications	1,852	31.1%	16,929	27.9%	3.2	0.1
Antidiabetic agents	948	15.9%	10,882	18.0%	-2.1	-0.1
Antihyperlipidemic medications	2,433	40.9%	24,034	39.7%	1.2	0.0
Antihypertensive medications	3,224	54.2%	34,752	57.4%	-3.2	-0.1
Antiplatelet medications	324	5.4%	3,189	5.3%	0.1	0.0
Antiretroviral medications	10	0.2%	93	0.2%	0.0	0.0
Aspirin	11	0.2%	80	0.1%	0.1	0.0
Contraceptive or HRT[2]	933	15.7%	4,704	7.8%	7.9	0.2
Smoking cessation medications	26	0.4%	216	0.4%	0.0	0.0
Recorded history of:						
Combined comorbidity score	0.80	1.8	1.0	2.0	-0.2	-0.1
Atrial fibrilliation, flutter	498	8.4%	4,950	8.2%	0.2	0.0
Alcohol use	40	0.7%	718	1.2%	-0.5	-0.1
Chronic kidney disease	385	6.5%	4,953	8.2%	-1.7	-0.1
Depression	848	14.2%	9,205	15.2%	-1.0	0.0
Diabetes	1,264	21.2%	14,857	24.5%	-3.3	-0.1
HIV/AIDS[3]	13	0.2%	102	0.2%	0.0	0.0
Hyperlipidemia	2,758	46.3%	27,579	45.5%	0.8	0.0
Hypertension	3,019	50.7%	32,774	54.1%	-3.4	-0.1
Ischemic heart disease	832	14.0%	8,736	14.4%	-0.4	0.0
Migraine	211	3.5%	1,627	2.7%	0.8	0.0
Obesity or weight gain	604	10.1%	8,168	13.5%	-3.4	-0.1
Other heart disease	1,130	19.0%	12,776	21.1%	-2.1	-0.1
Peripheral artery disease	196	3.3%	2,776	4.6%	-1.3	-0.1
Pulmonary circulation disease	115	1.9%	1,511	2.5%	-0.6	0.0
Rheumatic heart disease, chronic	77	1.3%	958	1.6%	-0.3	0.0
Sickle cell disease	1	0.0%	14	0.0%	0.0	0.0

Stroke, broad definition	340	5.7%	3,463	5.7%	0.0	0.0
Stroke, narrow definition	175	2.9%	1,854	3.1%	-0.2	0.0
Tobacco use	329	5.5%	5,537	9.1%	-3.6	-0.1
Transient ischemic attack	89	1.5%	957	1.6%	-0.1	0.0
Chronic kidney disease, procedure	0	0.0%	5	0.0%	0.0	---
Health Service Utilization Intensity:						
Number of generics	8.4	5.4	7.3	5.0	1.0	0.2
Number of Filled Rx	20.6	17.3	17.5	15.6	3.0	0.2
Number of inpatient hospital encounters (IP)	0.1	0.4	0.2	0.6	-0.1	-0.2
Number of non-acute institutional encounters (IS)	0.1	0.9	0.3	1.7	-0.2	-0.1
Number of emergency room encounters (ED)	0.3	0.8	0.4	1.0	-0.1	-0.1
Number of ambulatory encounters (AV)	12.9	10.6	9.9	9.8	3.0	0.3
Number of other ambulatory encounters (OA)	2.1	3.9	2.2	4.5	-0.1	0.0

[1]standard deviation where no % follows the value

[2]HRT - Hormone replacement therapy

[3]HIV/AIDS - human imunnodeficiency virus/acquired immune deficiency syndrome

Table 2. Cohort of New Initiators of Mirabegron and Oxybutynin, Stroke Primary Diagnoses (Matched Predefined PS, Caliper = .025)

	Primary Analysis				Covariate Balance	
Characteristic	Mirabegron		Oxybutynin			
	N	%/Std Dev[1]	N	%/Std Dev[1]	Absolute Difference	Standardized Difference
Patients	5,937	99.7%	5,937	9.8%	0.0	1.8
Events while on therapy	6	0.1%	7	0.1%	0.0	0.0
Mean person-days at risk	69.5	65.8	64.3	69.5	5.2	0.1
Patient Characteristics						
Gender (F)	3,902	65.7%	3,917	66.0%	-0.3	0.0
Mean age	65.1	14.2	65.3	13.9	-0.2	0.0
20-44	622	10.5%	612	10.3%	0.2	0.0
45-64	2,317	39.0%	2,285	38.5%	0.5	0.0
65-99	2,998	50.5%	3,040	51.2%	-0.7	0.0
Recorded use of:						
Anti-alcohol abuse medications	9	0.2%	7	0.1%	0.1	0.0
Antimigraine medications	148	2.5%	153	2.6%	-0.1	0.0
Anti-obesity medications	7	0.1%	11	0.2%	-0.1	0.0
Antiarrhythmic medications	129	2.2%	119	2.0%	0.2	0.0
Anticoagulant medications	401	6.8%	408	6.9%	-0.1	0.0
Antidepressant medications	1,842	31.0%	1,809	30.5%	0.5	0.0
Antidiabetic agents	945	15.9%	970	16.3%	-0.4	0.0
Antihyperlipidemic medications	2,423	40.8%	2,391	40.3%	0.5	0.0
Antihypertensive medications	3,214	54.1%	3,279	55.2%	-1.1	0.0
Antiplatelet medications	324	5.5%	321	5.4%	0.1	0.0
Antiretroviral medications	10	0.2%	9	0.2%	0.0	0.0
Aspirin	11	0.2%	9	0.2%	0.0	0.0
Contraceptive or HRT[2]	923	15.5%	919	15.5%	0.0	0.0
Smoking cessation medications	26	0.4%	19	0.3%	0.1	0.0
Recorded history of:						
Combined comorbidity score	0.80	1.8	0.9	1.9	0.0	0.0
Atrial fibrilliation, flutter	497	8.4%	502	8.5%	-0.1	0.0
Alcohol use	40	0.7%	33	0.6%	0.1	0.0
Chronic kidney disease	385	6.5%	367	6.2%	0.3	0.0
Depression	843	14.2%	823	13.9%	0.3	0.0
Diabetes	1,261	21.2%	1,279	21.5%	-0.3	0.0
HIV/AIDS[3]	13	0.2%	11	0.2%	0.0	0.0
Hyperlipidemia	2,748	46.3%	2,762	46.5%	-0.2	0.0
Hypertension	3,009	50.7%	3,059	51.5%	-0.8	0.0
Ischemic heart disease	830	14.0%	800	13.5%	0.5	0.0
Migraine	205	3.5%	205	3.5%	0.0	0.0
Obesity or weight gain	601	10.1%	600	10.1%	0.0	0.0
Other heart disease	1,127	19.0%	1,165	19.6%	-0.6	0.0
Peripheral artery disease	195	3.3%	190	3.2%	0.1	0.0
Pulmonary circulation disease	115	1.9%	121	2.0%	-0.1	0.0
Rheumatic heart disease, chronic	77	1.3%	73	1.2%	0.1	0.0
Sickle cell disease	1	0.0%	2	0.0%	0.0	0.0

Stroke, broad definition	336	5.7%	330	5.6%	0.1	0.0
Stroke, narrow definition	174	2.9%	181	3.0%	-0.1	0.0
Tobacco use	328	5.5%	329	5.5%	0.0	0.0
Transient ischemic attack	89	1.5%	99	1.7%	-0.2	0.0
Chronic kidney disease, procedure	0	0.0%	0	0.0%	0.0	---
Health Service Utilization Intensity:						
Number of generics	8.3	5.3	8.4	5.4	0.0	0.0
Number of Filled Rx	20.4	17.0	20.5	17.6	-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	0.9	0.1	0.9	0.0	0.0
Number of emergency room encounters (ED)	0.3	0.8	0.3	0.7	0.0	0.0
Number of ambulatory encounters (AV)	12.9	10.5	12.7	12.5	0.1	0.0
Number of other ambulatory encounters (OA)	2.0	3.7	1.9	4.9	0.1	0.0

[1]standard deviation where no % follows the value

[2]HRT - Hormone replacement therapy

[3]HIV/AIDS - human imunnodeficiency virus/acquired immune deficiency syndrome

Table 3: Sequential Estimates for Stroke (primary diagnoses) Events by Analysis Type and Drug Pair

Exposure Definition	Monitoring Period	New Users*	Person-Days at Risk	Average Person-Days at Risk	Number of Events	Incidence Rate per 1000 Person-Years at Risk	Risk per 1000 New Users	Incidence Rate Difference per 1000 Person-Years at Risk	Difference in Risk per 1000 New Users	Hazard Ratio (95% CI)**	Wald P-Value
Unmatched Analysis (Site-adjusted only)											
Mirabegron	1	5,952	413,669	69.50	6	5.30	1.01	-3.48	-0.56	0.77 (0.33, 1.77)	0.533
Oxybutynin		60,584	3,951,675	65.23	95	8.78	1.57				
Mirabegron	2	To be completed after look 2									
Oxybutynin											
1:1 Matched Analysis											
Mirabegron	1	5,937	412,617	69.50	6	5.31	1.01	-1.39	-0.17	0.80 (0.21, 2.98)	0.739
Oxybutynin		5,937	381,773	64.30	7	6.70	1.18				
Mirabegron	2	To be completed after look 2									
Oxybutynin											

*One patient was removed from the matched analysis due to Data Partner compliance reasons

**For sequential analysis that the confidence intervals do not account for repeated looks or correlation in the data across looks, but are provided for descriptive purposes

Appendix A. Generic Names and Brand Names used to Define Exposures in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL

Appendix B. Codes used to Define Stroke in this Request

Code	Description	Code Type
430*	Subarachnoid hemorrhage	ICD-9-CM Diagnosis Code
431*	Intracerebral hemorrhage	ICD-9-CM Diagnosis Code
433.*1	Occlusion and stenosis of precerebral arteries with cerebral infarction	ICD-9-CM Diagnosis Code
434.*1	Occlusion of cerebral arteries with cerebral infarction	ICD-9-CM Diagnosis Code
436*	Acute, but ill-defined, cerebrovascular disease	ICD-9-CM Diagnosis Code

Appendix C. Generic Names and Brand Names used to Define Incidence in this Request

Generic Name	Brand Name
MIRABEGRON	MYRBETRIQ
OXYBUTYNIN CHLORIDE	DITROPAN
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE
OXYBUTYNIN CHLORIDE	UROTROL
OXYBUTYNIN CHLORIDE	OXYBUTYNIN CHLORIDE ER
OXYBUTYNIN CHLORIDE	DITROPAN XL
TOLTERODINE TARTRATE	DETROL
TOLTERODINE TARTRATE	DETROL LA
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE ER
TOLTERODINE TARTRATE	TOLTERODINE TARTRATE
TROSPIUM CHLORIDE	SANCTURA
TROSPIUM CHLORIDE	SANCTURA XR
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE ER
TROSPIUM CHLORIDE	TROSPIUM CHLORIDE
FESOTERODINE FUMARATE	TOVIAZ
DARIFENACIN HYDROBROMIDE	ENABLEX
SOLIFENACIN SUCCINATE	VESICARE