Disclaimer

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

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

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

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

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Overview for Request: cder_mpl2p_wp058

Request ID: cder_mpl2p_wp058

Request Description: This report contains the estimates of prevalent utilization of hydrochlorothiazide (HCTZ)-containing diuretics, non HCTZ-containing diuretics, and antihypertensives in the Sentinel Distributed Database (SDD) to understand the impact of labeling changes that were made on August 8, 2020.

Sentinel Routine Querying Module: Cohort Identification and Descriptive Analysis (CIDA) module, version 12.1.0

Data Source: We distributed this query to Merative MarketScan Research Databases on January 10, 2024. The study period included data from January 1, 2017 through December 31, 2022.

Study Design: This query assessed the prevalence of outpatient exposure to HCTZ-containing diuretics, non HCTZ-containing diuretics, and antihypertensives among individuals within the SDD, overall and by calendar year-month. Results were reported overall and stratified by age group; sex; race; and both age group and race. This query is part one of a two-part analysis, where part two contains inclusion or exclusion criteria for history of skin cancer. This report presents the results from the Interrupted time series (ITS) analyses performed using data from cder_mpl2p_wp058_nsdp1_v01. Please refer to the main report for the Appendices. This was a Type 2 analysis in the Query Request Package (QRP) documentation.

Exposure(s) of Interest: The exposures of interest were any HCTZ-containing product (including HCTZ monotherapy, any HCTZ combination product, HCTZ-angiotensin converting enzyme inhibitor [ACEi] combination product, HCTZ-angiotensin receptor blocker [ARB] combination product, HCTZ-potassium sparing diuretic combination product, HCTZ-beta blocker combination product, HCTZ-ARB-calcium channel blocker [CCB] combination product, HCTZ-direct renin inhibitor combination product, and HCTZ-central alpha 2 agonist combination product), any HCTZ containing product with HCTZ strength < 25 mg, any HCTZ containing product with HCTZ strength ≥ 25 mg, any HCTZ combination product with HCTZ strength < 25 mg, any HCTZ combination product with HCTZ strength ≥ 25 mg, any non HCTZ-containing diuretic (including chlorothiazide, bendroflumethiazide, and thiazide-like diuretics), ACEi, CCB, ARB, beta-blocker, potassium sparing diuretic, and loop diuretic. Additionally, two groups of exposures were defined as denominators for calculating proportions by calendar year-month: limited denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide, or thiazide-like diuretic) and full denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide, thiazide-like diuretic, or any antihypertensive). All qualifying exposures during the study period were evaluated. The exposures of interest were defined using National Drug Code (NDCs). See Appendix B for generic and brand names of medical products.

Cohort Eligibility Criteria: We identified cohorts which included patients of all ages. The following age groups were defined: 0-40, 41-54, 55-64, 65-74, 75-84, and 85 years of age or greater. No pre-index enrollment requirement was applied.

Follow-Up Time: We determined follow-up time based on the length of exposure episodes, which was defined using days supply information recorded in the outpatient pharmacy dispensings to create any period of continuous exposure. No exposure episode gaps or extensions were considered in the creation of the episode. Dispensings in each cohort were stockpiled with all other exposure-defining dispensings within the cohort, regardless of the original drug class. Follow-up began on the index date and continued until the last day of supply of the last dispensing, or until the first occurrence of any of the following: 1) disenrollment; 2) death; 3) the end date of the data provided by the Data Partner; or 4) the end of the query period (December 31, 2022).

Analysis: We fitted an autoregression piecewise linear model describing the change of an observed rate over exposure time in months with an autoregression lag of 12 months and an intervention date on August 8, 2020, which is the date of the HCTZ drug safety communication (DSC)[1] issued by the US Food and Drug Administration (FDA). Numerator and denominator counts used to calculate observed rates were taken to be the number of patients with any duration of the exposure episode during the corresponding month interval. The rate modeled is described below:

Overview for Request: cder_mpl2p_wp058
Cohort 1) The rate used for the interrupted time series (ITS) regression model is the number of patients with use of any HCTZ-containing product among users in the limited denominator cohort. Cohort 2) The rate used for the ITS regression model is the number of patients with use of HCTZ single ingredient among users in the limited denominator cohort. Cohort 3) The rate used for the ITS regression model is the number of patients with use of ACEI + HCTZ combo product among users in the limited denominator cohort. Cohort 4) The rate used for the ITS regression model is the number of patients with use of ARB + HCTZ combo product among users in the limited denominator cohort. Cohort 5) The rate used for the ITS regression model is the number of patients with use of potassium-sparing diuretic + HCTZ combo product among users in the limited denominator cohort. Cohort 6) The rate used for the ITS regression model is the number of patients with use of beta blocker + HCTZ combo product among users in the limited denominator cohort. Cohort 7) The rate used for the ITS regression model is the number of patients with use of ARB + CCB + HCTZ combo product among users in the limited denominator cohort. Cohort 8) The rate used for the ITS regression model is the number of patients with use of direct renin inhibitor + HCTZ combo product among users in the limited denominator cohort. Cohort 9) The rate used for the ITS regression model is the number of patients with use of central alpha 2 agonist + HCTZ combo product among users in the limited denominator cohort. Cohort 10) The rate used for the ITS regression model is the number of patients with use of any HCTZ-containing products among users in the full denominator cohort. Cohort 11) The rate used for the ITS regression model is the number of patients with use of chlorothiazide, bendroflumethiazide or thiazide-like diuretic product among users in the full denominator cohort. Cohort 12) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination ACEI product among users in the full denominator cohort. Cohort 13) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination CCB product among users in the full denominator cohort. Cohort 14) The rate used for the ITS regression model is the number of patients with use of non-HCTZ combination potassium-sparing diuretic product among users in the full denominator cohort. Cohort 15) The rate used for the ITS regression model is the number of patients with use of loop diuretic product among users in the full denominator cohort. ITS regression was performed for overall population. We also fitted these same models using an anticipatory and lag period from June 1, 2020 to October 1, 2020 during which observations were not included in the autoregression model. **Please see the Appendices C.1-C.2 for the specifications of parameters used in the analyses for this request.** **Limitations:** Algorithms to define exposures, inclusion, and exclusion criteria are imperfect and may result in misclassification. Therefore, data should be interpreted with this limitation in mind. **Notes:** Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document. For more information on Sentinel's routine querying modules, ~~please~~ refer to the documentation (https://dev.sentinelsystem.org/projects/SENTINEL/repos/sentinel-routine-querying-tool-documentation/browse). [1]Drug Safety-related Labeling Changes (SrLC). Fda.gov. Published 2020. https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/index.cfm?event=searchdetail.page&DrugNameID=2310

Sentinel

Table of Contents

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

Table 1 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ACEI Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 2 Absolute and Relative Changes in Proportion of HCTZ/ACEI Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 3 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ARB/CCB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 4 Absolute and Relative Changes in Proportion of HCTZ/ARB/CCB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 5 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ARB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 6 Absolute and Relative Changes in Proportion of HCTZ/ARB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 7 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/BB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 8 Absolute and Relative Changes in Proportion of HCTZ/BB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 9 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Central Alpha-2 Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 10 Absolute and Relative Changes in Proportion of HCTZ/Central Alpha-2 Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 11 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 12 Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 13 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 14 Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 15 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Direct Renin Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table of Contents

Table 16 Absolute and Relative Changes in Proportion of HCTZ/Direct Renin Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 17 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ Single Ingredient Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 18 Absolute and Relative Changes in Proportion of HCTZ Single Ingredient Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 19 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Potassium-Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020

Table 20 Absolute and Relative Changes in Proportion of HCTZ/Potassium-Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 21 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of ACEI Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 22 Absolute and Relative Changes in Proportion of ACEI Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 23 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of ARB Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 24 Absolute and Relative Changes in Proportion of ARB Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 25 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Beta Blocker Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 26 Absolute and Relative Changes in Proportion of Beta Blocker Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 27 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of CCB Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 28 Absolute and Relative Changes in Proportion of CCB Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 29 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 30 Absolute and Relative Changes in Proportion of Loop Diuretics Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table of Contents

Table 31 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 32 Absolute and Relative Changes in Proportion of Potassium Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Table 33 Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020

Table 34 Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020 Compared with Expected Rates Derived from Baseline Trend

Figure 1 Proportion of HCTZ/ACEI Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 2 Proportion of HCTZ/ARB/CCB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 3 Proportion of HCTZ/ARB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 4 Proportion of HCTZ/BB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 5 Proportion of HCTZ/Central Alpha-2 Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 6 Proportion of HCTZ-Containing Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 7 Proportion of HCTZ-Containing Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 8 Proportion of HCTZ/Direct Renin Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 9 Proportion of HCTZ Single Ingredient Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 10 Proportion of HCTZ/Potassium-Sparing Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020

Figure 11 Proportion of ACEI Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 12 Proportion of ARB Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 13 Proportion of Beta Blocker Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 14 Proportion of CCB Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 15 Proportion of Loop Diuretics Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 16 Proportion of Potassium Sparing Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Figure 17 Proportion of Thiazide-like Diuretics Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020

Appendix A Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (August 30, 2023)

Table of Contents
Appendix B Generic and Brand Names of Medical Products Used to Define Exposures in this Request **Appendix C** Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

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

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

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the 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). The Care Setting, along with the Principal Diagnosis Indicator (PDX), forms the Care Setting/PDX parameter.

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

Charlson/Elixhauser Combined Comorbidity Score - calculated based on comorbidities observed during a requester-defined window around the exposure episode start date (e.g., in the 183 days prior to index).

Code Days - the minimum number of times the diagnosis must be found during the evaluation period in order to fulfill the algorithm to identify the corresponding patient characteristic.

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

Computed Start Marketing Date - represents the first observed dispensing date among all valid users within a GROUP (scenario) within each Data Partner site.

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

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

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

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

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 Modular Program (MP) algorithm: 0: Counts all occurrences of a health outcome of interest (HOI) during an exposure episode; 1: de-duplicates occurrences of the same HOI code and code type on the same day; 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

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

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

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

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

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

Member-Years - sum of all days of enrollment with medical and drug coverage in the query period preceded by an exposure washout period all divided by 365.25.

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

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

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

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

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

Switch Evaluation Step Value - value used to differentiate evaluation step. Each switch pattern can support up to 2 evaluation steps (0 = switch pattern evaluation start; 1 = first evaluation; 2 = second evaluation).

Switch Gap Inclusion Indicator - indicator for whether gaps in treatment episodes that are included in a switch episode will be counted as part of the switch episode duration.

Switch Pattern Cohort Inclusion Date - indicates which date to use for inclusion into the switch pattern cohort of interest as well as optionally as the index date of the treatment episode initiating the switch pattern. Valid options are the product approval date, product marketing date, other requester defined date, or computed start marketing date.

Switch Pattern Cohort Inclusion Strategy - indicates how the switch pattern cohort inclusion date will be used: 01: used only as a switch cohort entry date. First treatment episode dispensing date is used as index for computing time to first switch; 02: used as switch cohort entry date and as initial switch step index date for computing time to first switch.

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

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

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

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

*all terms may not be used in this report

Table 1. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ACEI Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.228144	(0.225661, 0.230628)	<.001
Baseline trend	-0.000320	(-0.000410, -0.000230)	<.001
Level Change (After Intervention 1)	-0.001834	(-0.004043, 0.000375)	0.102
Trend Change (After Intervention 1)	-0.000438	(-0.000658, -0.000217)	<.001
Most Parsimonious Final Model Parameters (df = 69)[2,3]			
Intercept	0.228144	(0.225661, 0.230628)	<.001
Baseline trend	-0.000320	(-0.000410, -0.000230)	<.001
Level Change (After Intervention 1)	-0.001834	(-0.004043, 0.000375)	0.102
Trend Change (After Intervention 1)	-0.000438	(-0.000658, -0.000217)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 2. Absolute and Relative Changes in Proportion of HCTZ/ACEI Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	-0.002272	(-0.004583, 0.000039)	0.211493	0.213764
Relative Change (%) at 1 Months after Intervention 1	-1.06	(-2.14, 0.01)	0.211493	0.213764
Absolute Change at 2 Months after Intervention 1	-0.002710	(-0.004997, -0.000422)	0.210735	0.213445
Relative Change (%) at 2 Months after Intervention 1	-1.27	(-2.33, -0.20)	0.210735	0.213445
Absolute Change at 3 Months after Intervention 1	-0.003147	(-0.005432, -0.000862)	0.209978	0.213125
Relative Change (%) at 3 Months after Intervention 1	-1.48	(-2.54, -0.41)	0.209978	0.213125
Absolute Change at 4 Months after Intervention 1	-0.003585	(-0.005888, -0.001282)	0.209221	0.212806
Relative Change (%) at 4 Months after Intervention 1	-1.68	(-2.75, -0.62)	0.209221	0.212806
Absolute Change at 5 Months after Intervention 1	-0.004023	(-0.006364, -0.001681)	0.208463	0.212486
Relative Change (%) at 5 Months after Intervention 1	-1.89	(-2.98, -0.81)	0.208463	0.212486
Absolute Change at 6 Months after Intervention 1	-0.004460	(-0.006860, -0.002061)	0.207706	0.212167
Relative Change (%) at 6 Months after Intervention 1	-2.10	(-3.21, -0.99)	0.207706	0.212167
Absolute Change at 7 Months after Intervention 1	-0.004898	(-0.007373, -0.002424)	0.206949	0.211847
Relative Change (%) at 7 Months after Intervention 1	-2.31	(-3.46, -1.17)	0.206949	0.211847
Absolute Change at 8 Months after Intervention 1	-0.005336	(-0.007903, -0.002769)	0.206192	0.211527
Relative Change (%) at 8 Months after Intervention 1	-2.52	(-3.71, -1.34)	0.206192	0.211527
Absolute Change at 9 Months after Intervention 1	-0.005774	(-0.008447, -0.003100)	0.205434	0.211208
Relative Change (%) at 9 Months after Intervention 1	-2.73	(-3.97, -1.50)	0.205434	0.211208
Absolute Change at 10 Months after Intervention 1	-0.006211	(-0.009004, -0.003419)	0.204677	0.210888
Relative Change (%) at 10 Months after Intervention 1	-2.95	(-4.23, -1.66)	0.204677	0.210888
Absolute Change at 11 Months after Intervention 1	-0.006649	(-0.009573, -0.003725)	0.203920	0.210569
Relative Change (%) at 11 Months after Intervention 1	-3.16	(-4.51, -1.81)	0.203920	0.210569
Absolute Change at 12 Months after Intervention 1	-0.007087	(-0.010152, -0.004022)	0.203162	0.210249
Relative Change (%) at 12 Months after Intervention 1	-3.37	(-4.78, -1.96)	0.203162	0.210249
Absolute Change at 13 Months after Intervention 1	-0.007525	(-0.010739, -0.004310)	0.202405	0.209930
Relative Change (%) at 13 Months after Intervention 1	-3.58	(-5.07, -2.10)	0.202405	0.209930
Absolute Change at 14 Months after Intervention 1	-0.007962	(-0.011334, -0.004591)	0.201648	0.209610
Relative Change (%) at 14 Months after Intervention 1	-3.80	(-5.35, -2.24)	0.201648	0.209610
Absolute Change at 15 Months after Intervention 1	-0.008400	(-0.011935, -0.004865)	0.200891	0.209291
Relative Change (%) at 15 Months after Intervention 1	-4.01	(-5.64, -2.38)	0.200891	0.209291
Absolute Change at 16 Months after Intervention 1	-0.008838	(-0.012542, -0.005134)	0.200133	0.208971
Relative Change (%) at 16 Months after Intervention 1	-4.23	(-5.94, -2.52)	0.200133	0.208971
Absolute Change at 17 Months after Intervention 1	-0.009275	(-0.013153, -0.005397)	0.199376	0.208652
Relative Change (%) at 17 Months after Intervention 1	-4.45	(-6.24, -2.66)	0.199376	0.208652

Table 2. Absolute and Relative Changes in Proportion of HCTZ/ACEI Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	-0.009713	(-0.013769, -0.005657)	0.198619	0.208332
Relative Change (%) at 18 Months after Intervention 1	-4.66	(-6.54, -2.79)	0.198619	0.208332
Absolute Change at 19 Months after Intervention 1	-0.010151	(-0.014389, -0.005913)	0.197861	0.208012
Relative Change (%) at 19 Months after Intervention 1	-4.88	(-6.84, -2.92)	0.197861	0.208012
Absolute Change at 20 Months after Intervention 1	-0.010589	(-0.015012, -0.006165)	0.197104	0.207693
Relative Change (%) at 20 Months after Intervention 1	-5.10	(-7.14, -3.05)	0.197104	0.207693
Absolute Change at 21 Months after Intervention 1	-0.011026	(-0.015638, -0.006415)	0.196347	0.207373
Relative Change (%) at 21 Months after Intervention 1	-5.32	(-7.45, -3.18)	0.196347	0.207373
Absolute Change at 22 Months after Intervention 1	-0.011464	(-0.016266, -0.006662)	0.195590	0.207054
Relative Change (%) at 22 Months after Intervention 1	-5.54	(-7.76, -3.31)	0.195590	0.207054
Absolute Change at 23 Months after Intervention 1	-0.011902	(-0.016897, -0.006907)	0.194832	0.206734
Relative Change (%) at 23 Months after Intervention 1	-5.76	(-8.07, -3.44)	0.194832	0.206734
Absolute Change at 24 Months after Intervention 1	-0.012340	(-0.017530, -0.007149)	0.194075	0.206415
Relative Change (%) at 24 Months after Intervention 1	-5.98	(-8.39, -3.57)	0.194075	0.206415
Absolute Change at 25 Months after Intervention 1	-0.012777	(-0.018164, -0.007390)	0.193318	0.206095
Relative Change (%) at 25 Months after Intervention 1	-6.20	(-8.70, -3.70)	0.193318	0.206095
Absolute Change at 26 Months after Intervention 1	-0.013215	(-0.018800, -0.007630)	0.192561	0.205776
Relative Change (%) at 26 Months after Intervention 1	-6.42	(-9.02, -3.83)	0.192561	0.205776
Absolute Change at 27 Months after Intervention 1	-0.013653	(-0.019438, -0.007868)	0.191803	0.205456
Absolute Change at 27 Months after Intervention 1	-0.013653	(-0.019438, -0.007868)	0.191803	0.205456
Relative Change (%) at 27 Months after Intervention 1	-6.65	(-9.34, -3.95)	0.191803	0.205456
Relative Change (%) at 27 Months after Intervention 1	-6.65	(-9.34, -3.95)	0.191803	0.205456

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 3. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ARB/CCB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.012163	(0.011515, 0.012812)	<.001
Baseline trend	-0.000030	(-0.000054, -0.000007)	;;ew
Level Change (After Intervention 1)	-0.000086	(-0.000395, 0.000223)	0.579
Trend Change (After Intervention 1)	-0.000130	(-0.000189, -0.000072)	<.001
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.012198	(0.011383, 0.013013)	<.001
Baseline trend	-0.000033	(-0.000062, -0.000004)	0.026
Trend Change (After Intervention 1)	-0.000126	(-0.000196, -0.000056)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 4. Absolute and Relative Changes in Proportion of HCTZ/ARB/CCB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	-0.000126	(-0.000211, -0.000040)	0.010592	0.010717
Relative Change (%) at 1 Months after Intervention 1	-1.17	(-1.89, -0.45)	0.010592	0.010717
Absolute Change at 2 Months after Intervention 1	-0.000251	(-0.000422, -0.000081)	0.010433	0.010684
Relative Change (%) at 2 Months after Intervention 1	-2.35	(-3.79, -0.91)	0.010433	0.010684
Absolute Change at 3 Months after Intervention 1	-0.000377	(-0.000632, -0.000121)	0.010275	0.010651
Relative Change (%) at 3 Months after Intervention 1	-3.54	(-5.69, -1.38)	0.010275	0.010651
Absolute Change at 4 Months after Intervention 1	-0.000502	(-0.000843, -0.000161)	0.010116	0.010619
Relative Change (%) at 4 Months after Intervention 1	-4.73	(-7.60, -1.86)	0.010116	0.010619
Absolute Change at 5 Months after Intervention 1	-0.000628	(-0.001054, -0.000202)	0.009958	0.010586
Relative Change (%) at 5 Months after Intervention 1	-5.93	(-9.52, -2.34)	0.009958	0.010586
Absolute Change at 6 Months after Intervention 1	-0.000753	(-0.001265, -0.000242)	0.009799	0.010553
Relative Change (%) at 6 Months after Intervention 1	-7.14	(-11.44, -2.84)	0.009799	0.010553
Absolute Change at 7 Months after Intervention 1	-0.000879	(-0.001475, -0.000282)	0.009641	0.010520
Relative Change (%) at 7 Months after Intervention 1	-8.35	(-13.36, -3.35)	0.009641	0.010520
Absolute Change at 8 Months after Intervention 1	-0.001004	(-0.001686, -0.000323)	0.009483	0.010487
Relative Change (%) at 8 Months after Intervention 1	-9.58	(-15.29, -3.86)	0.009483	0.010487
Absolute Change at 9 Months after Intervention 1	-0.001130	(-0.001897, -0.000363)	0.009324	0.010454
Relative Change (%) at 9 Months after Intervention 1	-10.81	(-17.23, -4.39)	0.009324	0.010454
Absolute Change at 10 Months after Intervention 1	-0.001256	(-0.002108, -0.000403)	0.009166	0.010421
Relative Change (%) at 10 Months after Intervention 1	-12.05	(-19.17, -4.92)	0.009166	0.010421
Absolute Change at 11 Months after Intervention 1	-0.001381	(-0.002318, -0.000444)	0.009007	0.010388
Relative Change (%) at 11 Months after Intervention 1	-13.29	(-21.12, -5.47)	0.009007	0.010388
Absolute Change at 12 Months after Intervention 1	-0.001507	(-0.002529, -0.000484)	0.008849	0.010355
Relative Change (%) at 12 Months after Intervention 1	-14.55	(-23.08, -6.02)	0.008849	0.010355
Absolute Change at 13 Months after Intervention 1	-0.001632	(-0.002740, -0.000525)	0.008690	0.010322
Relative Change (%) at 13 Months after Intervention 1	-15.81	(-25.04, -6.59)	0.008690	0.010322
Absolute Change at 14 Months after Intervention 1	-0.001758	(-0.002951, -0.000565)	0.008532	0.010290
Relative Change (%) at 14 Months after Intervention 1	-17.08	(-27.00, -7.16)	0.008532	0.010290
Absolute Change at 15 Months after Intervention 1	-0.001883	(-0.003161, -0.000605)	0.008373	0.010257
Relative Change (%) at 15 Months after Intervention 1	-18.36	(-28.97, -7.75)	0.008373	0.010257
Absolute Change at 16 Months after Intervention 1	-0.002009	(-0.003372, -0.000646)	0.008215	0.010224
Relative Change (%) at 16 Months after Intervention 1	-19.65	(-30.95, -8.35)	0.008215	0.010224
Absolute Change at 17 Months after Intervention 1	-0.002134	(-0.003583, -0.000686)	0.008056	0.010191
Relative Change (%) at 17 Months after Intervention 1	-20.94	(-32.93, -8.96)	0.008056	0.010191

Table 4. Absolute and Relative Changes in Proportion of HCTZ/ARB/CCB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	-0.002260	(-0.003794, -0.000726)	0.007898	0.010158
Relative Change (%) at 18 Months after Intervention 1	-22.25	(-34.92, -9.58)	0.007898	0.010158
Absolute Change at 19 Months after Intervention 1	-0.002386	(-0.004005, -0.000767)	0.007739	0.010125
Relative Change (%) at 19 Months after Intervention 1	-23.56	(-36.92, -10.21)	0.007739	0.010125
Absolute Change at 20 Months after Intervention 1	-0.002511	(-0.004215, -0.000807)	0.007581	0.010092
Relative Change (%) at 20 Months after Intervention 1	-24.88	(-38.92, -10.85)	0.007581	0.010092
Absolute Change at 21 Months after Intervention 1	-0.002637	(-0.004426, -0.000847)	0.007422	0.010059
Relative Change (%) at 21 Months after Intervention 1	-26.21	(-40.92, -11.50)	0.007422	0.010059
Absolute Change at 22 Months after Intervention 1	-0.002762	(-0.004637, -0.000888)	0.007264	0.010026
Relative Change (%) at 22 Months after Intervention 1	-27.55	(-42.93, -12.16)	0.007264	0.010026
Absolute Change at 23 Months after Intervention 1	-0.002888	(-0.004848, -0.000928)	0.007106	0.009993
Relative Change (%) at 23 Months after Intervention 1	-28.90	(-44.95, -12.84)	0.007106	0.009993
Absolute Change at 24 Months after Intervention 1	-0.003013	(-0.005058, -0.000968)	0.006947	0.009960
Relative Change (%) at 24 Months after Intervention 1	-30.25	(-46.98, -13.53)	0.006947	0.009960
Absolute Change at 25 Months after Intervention 1	-0.003139	(-0.005269, -0.001009)	0.006789	0.009928
Relative Change (%) at 25 Months after Intervention 1	-31.62	(-49.01, -14.23)	0.006789	0.009928
Absolute Change at 26 Months after Intervention 1	-0.003264	(-0.005480, -0.001049)	0.006630	0.009895
Relative Change (%) at 26 Months after Intervention 1	-32.99	(-51.04, -14.94)	0.006630	0.009895
Absolute Change at 27 Months after Intervention 1	-0.003390	(-0.005691, -0.001089)	0.006472	0.009862
Absolute Change at 27 Months after Intervention 1	-0.003390	(-0.005691, -0.001089)	0.006472	0.009862
Relative Change (%) at 27 Months after Intervention 1	-34.38	(-53.08, -15.67)	0.006472	0.009862
Relative Change (%) at 27 Months after Intervention 1	-34.38	(-53.08, -15.67)	0.006472	0.009862

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 5. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/ARB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.293510	(0.275257, 0.311764)	<.001
Baseline trend	-0.001601	(-0.002251, -0.000951)	<.001
Level Change (After Intervention 1)	-0.001049	(-0.004792, 0.002694)	0.578
Trend Change (After Intervention 1)	0.002030	(0.000434, 0.003627)	0.014
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.292862	(0.274452, 0.311272)	<.001
Baseline trend	-0.001574	(-0.002228, -0.000920)	<.001
Trend Change (After Intervention 1)	0.001904	(0.000343, 0.003465)	0.018

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 6. Absolute and Relative Changes in Proportion of HCTZ/ARB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.001904	(0.000330, 0.003478)	0.223950	0.222046
Relative Change (%) at 1 Months after Intervention 1	0.86	(0.09, 1.62)	0.223950	0.222046
Absolute Change at 2 Months after Intervention 1	0.003808	(0.000660, 0.006956)	0.224280	0.220473
Relative Change (%) at 2 Months after Intervention 1	1.73	(0.18, 3.27)	0.224280	0.220473
Absolute Change at 3 Months after Intervention 1	0.005711	(0.000990, 0.010433)	0.224610	0.218899
Relative Change (%) at 3 Months after Intervention 1	2.61	(0.27, 4.95)	0.224610	0.218899
Absolute Change at 4 Months after Intervention 1	0.007615	(0.001320, 0.013911)	0.224941	0.217325
Relative Change (%) at 4 Months after Intervention 1	3.50	(0.35, 6.66)	0.224941	0.217325
Absolute Change at 5 Months after Intervention 1	0.009519	(0.001649, 0.017389)	0.225271	0.215752
Relative Change (%) at 5 Months after Intervention 1	4.41	(0.42, 8.40)	0.225271	0.215752
Absolute Change at 6 Months after Intervention 1	0.011423	(0.001979, 0.020867)	0.225601	0.214178
Relative Change (%) at 6 Months after Intervention 1	5.33	(0.49, 10.17)	0.225601	0.214178
Absolute Change at 7 Months after Intervention 1	0.013327	(0.002309, 0.024344)	0.225931	0.212604
Relative Change (%) at 7 Months after Intervention 1	6.27	(0.56, 11.98)	0.225931	0.212604
Absolute Change at 8 Months after Intervention 1	0.015231	(0.002639, 0.027822)	0.226261	0.211030
Relative Change (%) at 8 Months after Intervention 1	7.22	(0.62, 13.81)	0.226261	0.211030
Absolute Change at 9 Months after Intervention 1	0.017134	(0.002969, 0.031300)	0.226591	0.209457
Relative Change (%) at 9 Months after Intervention 1	8.18	(0.68, 15.68)	0.226591	0.209457
Absolute Change at 10 Months after Intervention 1	0.019038	(0.003299, 0.034778)	0.226921	0.207883
Relative Change (%) at 10 Months after Intervention 1	9.16	(0.73, 17.59)	0.226921	0.207883
Absolute Change at 11 Months after Intervention 1	0.020942	(0.003629, 0.038255)	0.227252	0.206309
Relative Change (%) at 11 Months after Intervention 1	10.15	(0.77, 19.53)	0.227252	0.206309
Absolute Change at 12 Months after Intervention 1	0.022846	(0.003959, 0.041733)	0.227582	0.204736
Relative Change (%) at 12 Months after Intervention 1	11.16	(0.81, 21.51)	0.227582	0.204736
Absolute Change at 13 Months after Intervention 1	0.024750	(0.004288, 0.045211)	0.227912	0.203162
Relative Change (%) at 13 Months after Intervention 1	12.18	(0.84, 23.52)	0.227912	0.203162
Absolute Change at 14 Months after Intervention 1	0.026654	(0.004618, 0.048689)	0.228242	0.201588
Relative Change (%) at 14 Months after Intervention 1	13.22	(0.87, 25.58)	0.228242	0.201588
Absolute Change at 15 Months after Intervention 1	0.028557	(0.004948, 0.052167)	0.228572	0.200015
Relative Change (%) at 15 Months after Intervention 1	14.28	(0.88, 27.67)	0.228572	0.200015
Absolute Change at 16 Months after Intervention 1	0.030461	(0.005278, 0.055644)	0.228902	0.198441
Relative Change (%) at 16 Months after Intervention 1	15.35	(0.89, 29.81)	0.228902	0.198441
Absolute Change at 17 Months after Intervention 1	0.032365	(0.005608, 0.059122)	0.229232	0.196867
Relative Change (%) at 17 Months after Intervention 1	16.44	(0.89, 31.99)	0.229232	0.196867

Table 6. Absolute and Relative Changes in Proportion of HCTZ/ARB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.034269	(0.005938, 0.062600)	0.229562	0.195294
Relative Change (%) at 18 Months after Intervention 1	17.55	(0.89, 34.21)	0.229562	0.195294
Absolute Change at 19 Months after Intervention 1	0.036173	(0.006268, 0.066078)	0.229893	0.193720
Relative Change (%) at 19 Months after Intervention 1	18.67	(0.87, 36.47)	0.229893	0.193720
Absolute Change at 20 Months after Intervention 1	0.038077	(0.006598, 0.069555)	0.230223	0.192146
Relative Change (%) at 20 Months after Intervention 1	19.82	(0.85, 38.79)	0.230223	0.192146
Absolute Change at 21 Months after Intervention 1	0.039980	(0.006927, 0.073033)	0.230553	0.190573
Relative Change (%) at 21 Months after Intervention 1	20.98	(0.81, 41.15)	0.230553	0.190573
Absolute Change at 22 Months after Intervention 1	0.041884	(0.007257, 0.076511)	0.230883	0.188999
Relative Change (%) at 22 Months after Intervention 1	22.16	(0.77, 43.56)	0.230883	0.188999
Absolute Change at 23 Months after Intervention 1	0.043788	(0.007587, 0.079989)	0.231213	0.187425
Relative Change (%) at 23 Months after Intervention 1	23.36	(0.71, 46.02)	0.231213	0.187425
Absolute Change at 24 Months after Intervention 1	0.045692	(0.007917, 0.083467)	0.231543	0.185851
Relative Change (%) at 24 Months after Intervention 1	24.59	(0.64, 48.53)	0.231543	0.185851
Absolute Change at 25 Months after Intervention 1	0.047596	(0.008247, 0.086944)	0.231873	0.184278
Relative Change (%) at 25 Months after Intervention 1	25.83	(0.56, 51.09)	0.231873	0.184278
Absolute Change at 26 Months after Intervention 1	0.049499	(0.008577, 0.090422)	0.232204	0.182704
Relative Change (%) at 26 Months after Intervention 1	27.09	(0.47, 53.71)	0.232204	0.182704
Absolute Change at 27 Months after Intervention 1	0.051403	(0.008907, 0.093900)	0.232534	0.181130
Absolute Change at 27 Months after Intervention 1	0.051403	(0.008907, 0.093900)	0.232534	0.181130
Relative Change (%) at 27 Months after Intervention 1	28.38	(0.37, 56.39)	0.232534	0.181130
Relative Change (%) at 27 Months after Intervention 1	28.38	(0.37, 56.39)	0.232534	0.181130

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 7. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/BB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.026013	(0.025497, 0.026529)	<.001
Baseline trend	-0.000117	(-0.000135, -0.000099)	<.001
Level Change (After Intervention 1)	-0.000015	(-0.000279, 0.000249)	0.908
Trend Change (After Intervention 1)	0.000041	(0.000001, 0.000081)	0.046
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.026013	(0.025506, 0.026520)	<.001
Baseline trend	-0.000117	(-0.000134, -0.000100)	<.001
Trend Change (After Intervention 1)	0.000040	(0.000002, 0.000079)	0.042

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 8. Absolute and Relative Changes in Proportion of HCTZ/BB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000040	(0.000000, 0.000081)	0.020784	0.020744
Relative Change (%) at 1 Months after Intervention 1	0.19	(0.00, 0.39)	0.020784	0.020744
Absolute Change at 2 Months after Intervention 1	0.000081	(0.000000, 0.000161)	0.020707	0.020626
Relative Change (%) at 2 Months after Intervention 1	0.39	(-0.01, 0.79)	0.020707	0.020626
Absolute Change at 3 Months after Intervention 1	0.000121	(0.000000, 0.000242)	0.020630	0.020509
Relative Change (%) at 3 Months after Intervention 1	0.59	(-0.01, 1.19)	0.020630	0.020509
Absolute Change at 4 Months after Intervention 1	0.000161	(0.000000, 0.000323)	0.020553	0.020392
Relative Change (%) at 4 Months after Intervention 1	0.79	(-0.02, 1.60)	0.020553	0.020392
Absolute Change at 5 Months after Intervention 1	0.000201	(-0.000001, 0.000404)	0.020477	0.020275
Relative Change (%) at 5 Months after Intervention 1	0.99	(-0.03, 2.01)	0.020477	0.020275
Absolute Change at 6 Months after Intervention 1	0.000242	(-0.000001, 0.000484)	0.020400	0.020158
Relative Change (%) at 6 Months after Intervention 1	1.20	(-0.03, 2.43)	0.020400	0.020158
Absolute Change at 7 Months after Intervention 1	0.000282	(-0.000001, 0.000565)	0.020323	0.020041
Relative Change (%) at 7 Months after Intervention 1	1.41	(-0.04, 2.85)	0.020323	0.020041
Absolute Change at 8 Months after Intervention 1	0.000322	(-0.000001, 0.000646)	0.020246	0.019924
Relative Change (%) at 8 Months after Intervention 1	1.62	(-0.05, 3.28)	0.020246	0.019924
Absolute Change at 9 Months after Intervention 1	0.000363	(-0.000001, 0.000726)	0.020169	0.019807
Relative Change (%) at 9 Months after Intervention 1	1.83	(-0.05, 3.72)	0.020169	0.019807
Absolute Change at 10 Months after Intervention 1	0.000403	(-0.000001, 0.000807)	0.020093	0.019690
Relative Change (%) at 10 Months after Intervention 1	2.05	(-0.06, 4.16)	0.020093	0.019690
Absolute Change at 11 Months after Intervention 1	0.000443	(-0.000001, 0.000888)	0.020016	0.019573
Relative Change (%) at 11 Months after Intervention 1	2.26	(-0.07, 4.60)	0.020016	0.019573
Absolute Change at 12 Months after Intervention 1	0.000484	(-0.000001, 0.000968)	0.019939	0.019456
Relative Change (%) at 12 Months after Intervention 1	2.49	(-0.08, 5.05)	0.019939	0.019456
Absolute Change at 13 Months after Intervention 1	0.000524	(-0.000001, 0.001049)	0.019862	0.019338
Relative Change (%) at 13 Months after Intervention 1	2.71	(-0.09, 5.51)	0.019862	0.019338
Absolute Change at 14 Months after Intervention 1	0.000564	(-0.000002, 0.001130)	0.019786	0.019221
Relative Change (%) at 14 Months after Intervention 1	2.94	(-0.10, 5.97)	0.019786	0.019221
Absolute Change at 15 Months after Intervention 1	0.000604	(-0.000002, 0.001211)	0.019709	0.019104
Relative Change (%) at 15 Months after Intervention 1	3.16	(-0.11, 6.44)	0.019709	0.019104
Absolute Change at 16 Months after Intervention 1	0.000645	(-0.000002, 0.001291)	0.019632	0.018987
Relative Change (%) at 16 Months after Intervention 1	3.40	(-0.12, 6.91)	0.019632	0.018987
Absolute Change at 17 Months after Intervention 1	0.000685	(-0.000002, 0.001372)	0.019555	0.018870
Relative Change (%) at 17 Months after Intervention 1	3.63	(-0.13, 7.39)	0.019555	0.018870

Table 8. Absolute and Relative Changes in Proportion of HCTZ/BB Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000725	(-0.000002, 0.001453)	0.019478	0.018753
Relative Change (%) at 18 Months after Intervention 1	3.87	(-0.15, 7.88)	0.019478	0.018753
Absolute Change at 19 Months after Intervention 1	0.000766	(-0.000002, 0.001533)	0.019402	0.018636
Relative Change (%) at 19 Months after Intervention 1	4.11	(-0.16, 8.38)	0.019402	0.018636
Absolute Change at 20 Months after Intervention 1	0.000806	(-0.000002, 0.001614)	0.019325	0.018519
Relative Change (%) at 20 Months after Intervention 1	4.35	(-0.17, 8.88)	0.019325	0.018519
Absolute Change at 21 Months after Intervention 1	0.000846	(-0.000002, 0.001695)	0.019248	0.018402
Relative Change (%) at 21 Months after Intervention 1	4.60	(-0.19, 9.39)	0.019248	0.018402
Absolute Change at 22 Months after Intervention 1	0.000887	(-0.000002, 0.001776)	0.019171	0.018285
Relative Change (%) at 22 Months after Intervention 1	4.85	(-0.20, 9.90)	0.019171	0.018285
Absolute Change at 23 Months after Intervention 1	0.000927	(-0.000003, 0.001856)	0.019094	0.018167
Relative Change (%) at 23 Months after Intervention 1	5.10	(-0.22, 10.42)	0.019094	0.018167
Absolute Change at 24 Months after Intervention 1	0.000967	(-0.000003, 0.001937)	0.019018	0.018050
Relative Change (%) at 24 Months after Intervention 1	5.36	(-0.24, 10.95)	0.019018	0.018050
Absolute Change at 25 Months after Intervention 1	0.001007	(-0.000003, 0.002018)	0.018941	0.017933
Relative Change (%) at 25 Months after Intervention 1	5.62	(-0.25, 11.49)	0.018941	0.017933
Absolute Change at 26 Months after Intervention 1	0.001048	(-0.000003, 0.002098)	0.018864	0.017816
Relative Change (%) at 26 Months after Intervention 1	5.88	(-0.27, 12.03)	0.018864	0.017816
Absolute Change at 27 Months after Intervention 1	0.001088	(-0.000003, 0.002179)	0.018787	0.017699
Absolute Change at 27 Months after Intervention 1	0.001088	(-0.000003, 0.002179)	0.018787	0.017699
Relative Change (%) at 27 Months after Intervention 1	6.15	(-0.29, 12.59)	0.018787	0.017699
Relative Change (%) at 27 Months after Intervention 1	6.15	(-0.29, 12.59)	0.018787	0.017699

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 9. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Central Alpha-2 Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.000024	(0.000020, 0.000028)	<.001
Baseline trend	-0.000000	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000005	(-0.000008, -0.000002)	0.004
Trend Change (After Intervention 1)	0.000000	(-0.000000, 0.000001)	0.111
Most Parsimonious Final Model Parameters (df = 69)[2,3]			
Intercept	0.000024	(0.000020, 0.000028)	<.001
Baseline trend	-0.000000	(-0.000001, -0.000000)	<.001
Level Change (After Intervention 1)	-0.000005	(-0.000008, -0.000002)	0.004
Trend Change (After Intervention 1)	0.000000	(-0.000000, 0.000001)	0.111

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 10. Absolute and Relative Changes in Proportion of HCTZ/Central Alpha-2 Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	-0.000004	(-0.000007, -0.000001)	0.000003	0.000007
Relative Change (%) at 1 Months after Intervention 1	-62.76	(-106.14, -19.39)	0.000003	0.000007
Absolute Change at 2 Months after Intervention 1	-0.000004	(-0.000007, -0.000001)	0.000002	0.000006
Relative Change (%) at 2 Months after Intervention 1	-62.48	(-105.78, -19.19)	0.000002	0.000006
Absolute Change at 3 Months after Intervention 1	-0.000004	(-0.000007, -0.000001)	0.000002	0.000006
Relative Change (%) at 3 Months after Intervention 1	-62.16	(-105.62, -18.70)	0.000002	0.000006
Absolute Change at 4 Months after Intervention 1	-0.000004	(-0.000007, 0.000000)	0.000002	0.000006
Relative Change (%) at 4 Months after Intervention 1	-61.80	(-105.77, -17.83)	0.000002	0.000006
Absolute Change at 5 Months after Intervention 1	-0.000003	(-0.000007, 0.000000)	0.000002	0.000005
Relative Change (%) at 5 Months after Intervention 1	-61.39	(-106.37, -16.40)	0.000002	0.000005
Absolute Change at 6 Months after Intervention 1	-0.000003	(-0.000006, 0.000000)	0.000002	0.000005
Relative Change (%) at 6 Months after Intervention 1	-60.91	(-107.60, -14.22)	0.000002	0.000005
Absolute Change at 7 Months after Intervention 1	-0.000003	(-0.000006, 0.000001)	0.000002	0.000005
Relative Change (%) at 7 Months after Intervention 1	-60.35	(-109.72, -10.99)	0.000002	0.000005
Absolute Change at 8 Months after Intervention 1	-0.000002	(-0.000006, 0.000001)	0.000002	0.000004
Relative Change (%) at 8 Months after Intervention 1	-59.70	(-113.04, -6.35)	0.000002	0.000004
Absolute Change at 9 Months after Intervention 1	-0.000002	(-0.000006, 0.000002)	0.000002	0.000004
Relative Change (%) at 9 Months after Intervention 1	-58.90	(-118.03, 0.22)	0.000002	0.000004
Absolute Change at 10 Months after Intervention 1	-0.000002	(-0.000006, 0.000002)	0.000001	0.000003
Relative Change (%) at 10 Months after Intervention 1	-57.93	(-125.30, 9.43)	0.000001	0.000003
Absolute Change at 11 Months after Intervention 1	-0.000002	(-0.000006, 0.000003)	0.000001	0.000003
Relative Change (%) at 11 Months after Intervention 1	-56.72	(-135.78, 22.35)	0.000001	0.000003
Absolute Change at 12 Months after Intervention 1	-0.000001	(-0.000006, 0.000003)	0.000001	0.000003
Relative Change (%) at 12 Months after Intervention 1	-55.15	(-150.96, 40.66)	0.000001	0.000003
Absolute Change at 13 Months after Intervention 1	-0.000001	(-0.000006, 0.000004)	0.000001	0.000002
Relative Change (%) at 13 Months after Intervention 1	-53.05	(-173.41, 67.31)	0.000001	0.000002
Absolute Change at 14 Months after Intervention 1	-0.000001	(-0.000006, 0.000004)	0.000001	0.000002
Relative Change (%) at 14 Months after Intervention 1	-50.10	(-208.22, 108.02)	0.000001	0.000002
Absolute Change at 15 Months after Intervention 1	-0.000001	(-0.000006, 0.000005)	0.000001	0.000001
Relative Change (%) at 15 Months after Intervention 1	-45.63	(-266.74, 175.48)	0.000001	0.000001
Absolute Change at 16 Months after Intervention 1	0.000000	(-0.000006, 0.000005)	0.000001	0.000001
Relative Change (%) at 16 Months after Intervention 1	-38.08	(-380.22, 304.05)	0.000001	0.000001
Absolute Change at 17 Months after Intervention 1	0.000000	(-0.000006, 0.000006)	0.000001	0.000001
Relative Change (%) at 17 Months after Intervention 1	-22.61	(-670.04, 624.83)	0.000001	0.000001

Table 10. Absolute and Relative Changes in Proportion of HCTZ/Central Alpha-2 Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000000	(-0.000006, 0.000006)	0.000000	0.000000
Relative Change (%) at 18 Months after Intervention 1	27.12	(-2148.19, 2202.42)	0.000000	0.000000
Absolute Change at 19 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 19 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 20 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 20 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 21 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 21 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 22 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 22 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 23 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 23 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 24 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 24 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 25 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 25 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 26 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 26 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 11. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.334887	(0.332052, 0.337722)	<.001
Baseline trend	-0.000848	(-0.000951, -0.000745)	<.001
Level Change (After Intervention 1)	-0.000449	(-0.003164, 0.002266)	0.743
Trend Change (After Intervention 1)	-0.000028	(-0.000274, 0.000218)	0.823
Most Parsimonious Final Model Parameters (df = 71)[2,3]			
Intercept	0.335209	(0.332910, 0.337509)	<.001
Baseline trend	-0.000866	(-0.000921, -0.000811)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 12. Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.296236	0.296236
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.296236	0.296236
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.295370	0.295370
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.295370	0.295370
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.294504	0.294504
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.294504	0.294504
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.293638	0.293638
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.293638	0.293638
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.292772	0.292772
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.292772	0.292772
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.291905	0.291905
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.291905	0.291905
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.291039	0.291039
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.291039	0.291039
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.290173	0.290173
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.290173	0.290173
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.289307	0.289307
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.289307	0.289307
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.288441	0.288441
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.288441	0.288441
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.287575	0.287575
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.287575	0.287575
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.286709	0.286709
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.286709	0.286709
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.285843	0.285843
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.285843	0.285843
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.284977	0.284977
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.284977	0.284977
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.284111	0.284111
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.284111	0.284111
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.283245	0.283245
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.283245	0.283245
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.282379	0.282379
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.282379	0.282379

Table 12. Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.281513	0.281513
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.281513	0.281513
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.280646	0.280646
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.280646	0.280646
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.279780	0.279780
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.279780	0.279780
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.278914	0.278914
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.278914	0.278914
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.278048	0.278048
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.278048	0.278048
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.277182	0.277182
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.277182	0.277182
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.276316	0.276316
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.276316	0.276316
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.275450	0.275450
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.275450	0.275450
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.274584	0.274584
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.274584	0.274584
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.273718	0.273718
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.273718	0.273718
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.273718	0.273718
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.273718	0.273718

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 13. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.956923	(0.955606, 0.958241)	<.001
Baseline trend	-0.000451	(-0.000498, -0.000405)	<.001
Level Change (After Intervention 1)	-0.000096	(-0.000712, 0.000520)	0.756
Trend Change (After Intervention 1)	0.000089	(-0.000023, 0.000202)	0.116
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.956570	(0.954920, 0.958220)	<.001
Baseline trend	-0.000446	(-0.000500, -0.000393)	<.001
Trend Change (After Intervention 1)	0.000097	(-0.000018, 0.000211)	0.097

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 14. Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000097	(-0.000024, 0.000217)	0.936590	0.936493
Relative Change (%) at 1 Months after Intervention 1	0.01	(0.00, 0.02)	0.936590	0.936493
Absolute Change at 2 Months after Intervention 1	0.000193	(-0.000047, 0.000434)	0.936240	0.936047
Relative Change (%) at 2 Months after Intervention 1	0.02	(-0.01, 0.05)	0.936240	0.936047
Absolute Change at 3 Months after Intervention 1	0.000290	(-0.000071, 0.000651)	0.935891	0.935601
Relative Change (%) at 3 Months after Intervention 1	0.03	(-0.01, 0.07)	0.935891	0.935601
Absolute Change at 4 Months after Intervention 1	0.000387	(-0.000095, 0.000868)	0.935541	0.935154
Relative Change (%) at 4 Months after Intervention 1	0.04	(-0.01, 0.09)	0.935541	0.935154
Absolute Change at 5 Months after Intervention 1	0.000483	(-0.000119, 0.001085)	0.935192	0.934708
Relative Change (%) at 5 Months after Intervention 1	0.05	(-0.01, 0.12)	0.935192	0.934708
Absolute Change at 6 Months after Intervention 1	0.000580	(-0.000142, 0.001302)	0.934842	0.934262
Relative Change (%) at 6 Months after Intervention 1	0.06	(-0.02, 0.14)	0.934842	0.934262
Absolute Change at 7 Months after Intervention 1	0.000677	(-0.000166, 0.001520)	0.934493	0.933816
Relative Change (%) at 7 Months after Intervention 1	0.07	(-0.02, 0.16)	0.934493	0.933816
Absolute Change at 8 Months after Intervention 1	0.000774	(-0.000190, 0.001737)	0.934143	0.933370
Relative Change (%) at 8 Months after Intervention 1	0.08	(-0.02, 0.19)	0.934143	0.933370
Absolute Change at 9 Months after Intervention 1	0.000870	(-0.000213, 0.001954)	0.933794	0.932924
Relative Change (%) at 9 Months after Intervention 1	0.09	(-0.02, 0.21)	0.933794	0.932924
Absolute Change at 10 Months after Intervention 1	0.000967	(-0.000237, 0.002171)	0.933444	0.932477
Relative Change (%) at 10 Months after Intervention 1	0.10	(-0.03, 0.23)	0.933444	0.932477
Absolute Change at 11 Months after Intervention 1	0.001064	(-0.000261, 0.002388)	0.933095	0.932031
Relative Change (%) at 11 Months after Intervention 1	0.11	(-0.03, 0.26)	0.933095	0.932031
Absolute Change at 12 Months after Intervention 1	0.001160	(-0.000284, 0.002605)	0.932745	0.931585
Relative Change (%) at 12 Months after Intervention 1	0.12	(-0.03, 0.28)	0.932745	0.931585
Absolute Change at 13 Months after Intervention 1	0.001257	(-0.000308, 0.002822)	0.932396	0.931139
Relative Change (%) at 13 Months after Intervention 1	0.13	(-0.03, 0.30)	0.932396	0.931139
Absolute Change at 14 Months after Intervention 1	0.001354	(-0.000332, 0.003039)	0.932047	0.930693
Relative Change (%) at 14 Months after Intervention 1	0.15	(-0.04, 0.33)	0.932047	0.930693
Absolute Change at 15 Months after Intervention 1	0.001450	(-0.000356, 0.003256)	0.931697	0.930247
Relative Change (%) at 15 Months after Intervention 1	0.16	(-0.04, 0.35)	0.931697	0.930247
Absolute Change at 16 Months after Intervention 1	0.001547	(-0.000379, 0.003473)	0.931348	0.929801
Relative Change (%) at 16 Months after Intervention 1	0.17	(-0.04, 0.37)	0.931348	0.929801
Absolute Change at 17 Months after Intervention 1	0.001644	(-0.000403, 0.003690)	0.930998	0.929354
Relative Change (%) at 17 Months after Intervention 1	0.18	(-0.04, 0.40)	0.930998	0.929354

Table 14. Absolute and Relative Changes in Proportion of HCTZ-Containing Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.001740	(-0.000427, 0.003907)	0.930649	0.928908
Relative Change (%) at 18 Months after Intervention 1	0.19	(-0.05, 0.42)	0.930649	0.928908
Absolute Change at 19 Months after Intervention 1	0.001837	(-0.000450, 0.004125)	0.930299	0.928462
Relative Change (%) at 19 Months after Intervention 1	0.20	(-0.05, 0.44)	0.930299	0.928462
Absolute Change at 20 Months after Intervention 1	0.001934	(-0.000474, 0.004342)	0.929950	0.928016
Relative Change (%) at 20 Months after Intervention 1	0.21	(-0.05, 0.47)	0.929950	0.928016
Absolute Change at 21 Months after Intervention 1	0.002031	(-0.000498, 0.004559)	0.929600	0.927570
Relative Change (%) at 21 Months after Intervention 1	0.22	(-0.05, 0.49)	0.929600	0.927570
Absolute Change at 22 Months after Intervention 1	0.002127	(-0.000521, 0.004776)	0.929251	0.927124
Relative Change (%) at 22 Months after Intervention 1	0.23	(-0.06, 0.52)	0.929251	0.927124
Absolute Change at 23 Months after Intervention 1	0.002224	(-0.000545, 0.004993)	0.928901	0.926677
Relative Change (%) at 23 Months after Intervention 1	0.24	(-0.06, 0.54)	0.928901	0.926677
Absolute Change at 24 Months after Intervention 1	0.002321	(-0.000569, 0.005210)	0.928552	0.926231
Relative Change (%) at 24 Months after Intervention 1	0.25	(-0.06, 0.56)	0.928552	0.926231
Absolute Change at 25 Months after Intervention 1	0.002417	(-0.000593, 0.005427)	0.928202	0.925785
Relative Change (%) at 25 Months after Intervention 1	0.26	(-0.06, 0.59)	0.928202	0.925785
Absolute Change at 26 Months after Intervention 1	0.002514	(-0.000616, 0.005644)	0.927853	0.925339
Relative Change (%) at 26 Months after Intervention 1	0.27	(-0.07, 0.61)	0.927853	0.925339
Absolute Change at 27 Months after Intervention 1	0.002611	(-0.000640, 0.005861)	0.927503	0.924893
Absolute Change at 27 Months after Intervention 1	0.002611	(-0.000640, 0.005861)	0.927503	0.924893
Relative Change (%) at 27 Months after Intervention 1	0.28	(-0.07, 0.63)	0.927503	0.924893
Relative Change (%) at 27 Months after Intervention 1	0.28	(-0.07, 0.63)	0.927503	0.924893

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 15. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Direct Renin Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.000631	(0.000589, 0.000672)	<.001
Baseline trend	-0.000009	(-0.000011, -0.000008)	<.001
Level Change (After Intervention 1)	0.000000	(-0.000019, 0.000020)	0.978
Trend Change (After Intervention 1)	0.000005	(0.000002, 0.000008)	0.002
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.000630	(0.000590, 0.000671)	<.001
Baseline trend	-0.000009	(-0.000011, -0.000008)	<.001
Trend Change (After Intervention 1)	0.000005	(0.000002, 0.000008)	0.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 16. Absolute and Relative Changes in Proportion of HCTZ/Direct Renin Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000005	(0.000002, 0.000008)	0.000215	0.000210
Relative Change (%) at 1 Months after Intervention 1	2.41	(0.48, 4.35)	0.000215	0.000210
Absolute Change at 2 Months after Intervention 1	0.000010	(0.000004, 0.000017)	0.000211	0.000201
Relative Change (%) at 2 Months after Intervention 1	5.05	(0.94, 9.17)	0.000211	0.000201
Absolute Change at 3 Months after Intervention 1	0.000015	(0.000006, 0.000025)	0.000207	0.000192
Relative Change (%) at 3 Months after Intervention 1	7.94	(1.35, 14.54)	0.000207	0.000192
Absolute Change at 4 Months after Intervention 1	0.000020	(0.000007, 0.000033)	0.000203	0.000182
Relative Change (%) at 4 Months after Intervention 1	11.14	(1.71, 20.56)	0.000203	0.000182
Absolute Change at 5 Months after Intervention 1	0.000025	(0.000009, 0.000042)	0.000198	0.000173
Relative Change (%) at 5 Months after Intervention 1	14.67	(1.97, 27.36)	0.000198	0.000173
Absolute Change at 6 Months after Intervention 1	0.000030	(0.000011, 0.000050)	0.000194	0.000164
Relative Change (%) at 6 Months after Intervention 1	18.61	(2.11, 35.10)	0.000194	0.000164
Absolute Change at 7 Months after Intervention 1	0.000036	(0.000013, 0.000058)	0.000190	0.000154
Relative Change (%) at 7 Months after Intervention 1	23.02	(2.07, 43.96)	0.000190	0.000154
Absolute Change at 8 Months after Intervention 1	0.000041	(0.000015, 0.000066)	0.000186	0.000145
Relative Change (%) at 8 Months after Intervention 1	28.00	(1.78, 54.22)	0.000186	0.000145
Absolute Change at 9 Months after Intervention 1	0.000046	(0.000017, 0.000075)	0.000181	0.000136
Relative Change (%) at 9 Months after Intervention 1	33.66	(1.11, 66.22)	0.000181	0.000136
Absolute Change at 10 Months after Intervention 1	0.000051	(0.000019, 0.000083)	0.000177	0.000126
Relative Change (%) at 10 Months after Intervention 1	40.17	(-0.08, 80.42)	0.000177	0.000126
Absolute Change at 11 Months after Intervention 1	0.000056	(0.000020, 0.000091)	0.000173	0.000117
Relative Change (%) at 11 Months after Intervention 1	47.70	(-2.05, 97.46)	0.000173	0.000117
Absolute Change at 12 Months after Intervention 1	0.000061	(0.000022, 0.000100)	0.000169	0.000108
Relative Change (%) at 12 Months after Intervention 1	56.55	(-5.15, 118.25)	0.000169	0.000108
Absolute Change at 13 Months after Intervention 1	0.000066	(0.000024, 0.000108)	0.000164	0.000098
Relative Change (%) at 13 Months after Intervention 1	67.07	(-9.96, 144.10)	0.000164	0.000098
Absolute Change at 14 Months after Intervention 1	0.000071	(0.000026, 0.000116)	0.000160	0.000089
Relative Change (%) at 14 Months after Intervention 1	79.79	(-17.43, 177.01)	0.000160	0.000089
Absolute Change at 15 Months after Intervention 1	0.000076	(0.000028, 0.000125)	0.000156	0.000080
Relative Change (%) at 15 Months after Intervention 1	95.49	(-29.12, 220.11)	0.000156	0.000080
Absolute Change at 16 Months after Intervention 1	0.000081	(0.000030, 0.000133)	0.000152	0.000070
Relative Change (%) at 16 Months after Intervention 1	115.36	(-47.86, 278.57)	0.000152	0.000070
Absolute Change at 17 Months after Intervention 1	0.000086	(0.000031, 0.000141)	0.000147	0.000061
Relative Change (%) at 17 Months after Intervention 1	141.28	(-79.00, 361.56)	0.000147	0.000061

Table 16. Absolute and Relative Changes in Proportion of HCTZ/Direct Renin Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000091	(0.000033, 0.000149)	0.000143	0.000052
Relative Change (%) at 18 Months after Intervention 1	176.56	(-133.52, 486.64)	0.000143	0.000052
Absolute Change at 19 Months after Intervention 1	0.000096	(0.000035, 0.000158)	0.000139	0.000042
Relative Change (%) at 19 Months after Intervention 1	227.35	(-236.72, 691.42)	0.000139	0.000042
Absolute Change at 20 Months after Intervention 1	0.000102	(0.000037, 0.000166)	0.000135	0.000033
Relative Change (%) at 20 Months after Intervention 1	306.78	(-456.69, 1070.24)	0.000135	0.000033
Absolute Change at 21 Months after Intervention 1	0.000107	(0.000039, 0.000174)	0.000130	0.000024
Relative Change (%) at 21 Months after Intervention 1	448.56	(-1027.36, 1924.47)	0.000130	0.000024
Absolute Change at 22 Months after Intervention 1	0.000112	(0.000041, 0.000183)	0.000126	0.000014
Relative Change (%) at 22 Months after Intervention 1	773.57	(-3197.74, 4744.87)	0.000126	0.000014
Absolute Change at 23 Months after Intervention 1	0.000117	(0.000043, 0.000191)	0.000122	0.000005
Relative Change (%) at 23 Months after Intervention 1	2285.67	(-29094.3, 33665.68)	0.000122	0.000005
Absolute Change at 24 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 24 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 25 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 25 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 26 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 26 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Absolute Change at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A
Relative Change (%) at 27 Months after Intervention 1	N/A	(N/A, N/A)	N/A	N/A

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 17. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ Single Ingredient Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.307809	(0.288917, 0.326702)	<.001
Baseline trend	0.002251	(0.001582, 0.002920)	<.001
Level Change (After Intervention 1)	0.000302	(-0.002714, 0.003318)	0.842
Trend Change (After Intervention 1)	-0.002323	(-0.003961, -0.000685)	0.006
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.308103	(0.289442, 0.326763)	<.001
Baseline trend	0.002238	(0.001582, 0.002893)	<.001
Trend Change (After Intervention 1)	-0.002271	(-0.003825, -0.000716)	0.005

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 18. Absolute and Relative Changes in Proportion of HCTZ Single Ingredient Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	-0.002271	(-0.003811, -0.000731)	0.406521	0.408791
Relative Change (%) at 1 Months after Intervention 1	-0.56	(-0.91, -0.20)	0.406521	0.408791
Absolute Change at 2 Months after Intervention 1	-0.004541	(-0.007622, -0.001461)	0.406487	0.411029
Relative Change (%) at 2 Months after Intervention 1	-1.10	(-1.82, -0.39)	0.406487	0.411029
Absolute Change at 3 Months after Intervention 1	-0.006812	(-0.011432, -0.002192)	0.406454	0.413266
Relative Change (%) at 3 Months after Intervention 1	-1.65	(-2.71, -0.59)	0.406454	0.413266
Absolute Change at 4 Months after Intervention 1	-0.009083	(-0.015243, -0.002922)	0.406421	0.415504
Relative Change (%) at 4 Months after Intervention 1	-2.19	(-3.59, -0.78)	0.406421	0.415504
Absolute Change at 5 Months after Intervention 1	-0.011353	(-0.019054, -0.003653)	0.406388	0.417741
Relative Change (%) at 5 Months after Intervention 1	-2.72	(-4.46, -0.98)	0.406388	0.417741
Absolute Change at 6 Months after Intervention 1	-0.013624	(-0.022865, -0.004384)	0.406355	0.419979
Relative Change (%) at 6 Months after Intervention 1	-3.24	(-5.32, -1.17)	0.406355	0.419979
Absolute Change at 7 Months after Intervention 1	-0.015895	(-0.026675, -0.005114)	0.406322	0.422216
Relative Change (%) at 7 Months after Intervention 1	-3.76	(-6.17, -1.36)	0.406322	0.422216
Absolute Change at 8 Months after Intervention 1	-0.018166	(-0.030486, -0.005845)	0.406288	0.424454
Relative Change (%) at 8 Months after Intervention 1	-4.28	(-7.00, -1.55)	0.406288	0.424454
Absolute Change at 9 Months after Intervention 1	-0.020436	(-0.034297, -0.006575)	0.406255	0.426691
Relative Change (%) at 9 Months after Intervention 1	-4.79	(-7.83, -1.74)	0.406255	0.426691
Absolute Change at 10 Months after Intervention 1	-0.022707	(-0.038108, -0.007306)	0.406222	0.428929
Relative Change (%) at 10 Months after Intervention 1	-5.29	(-8.65, -1.93)	0.406222	0.428929
Absolute Change at 11 Months after Intervention 1	-0.024978	(-0.041919, -0.008037)	0.406189	0.431166
Relative Change (%) at 11 Months after Intervention 1	-5.79	(-9.46, -2.12)	0.406189	0.431166
Absolute Change at 12 Months after Intervention 1	-0.027248	(-0.045729, -0.008767)	0.406156	0.433404
Relative Change (%) at 12 Months after Intervention 1	-6.29	(-10.27, -2.31)	0.406156	0.433404
Absolute Change at 13 Months after Intervention 1	-0.029519	(-0.049540, -0.009498)	0.406122	0.435641
Relative Change (%) at 13 Months after Intervention 1	-6.78	(-11.06, -2.50)	0.406122	0.435641
Absolute Change at 14 Months after Intervention 1	-0.031790	(-0.053351, -0.010228)	0.406089	0.437879
Relative Change (%) at 14 Months after Intervention 1	-7.26	(-11.84, -2.68)	0.406089	0.437879
Absolute Change at 15 Months after Intervention 1	-0.034060	(-0.057162, -0.010959)	0.406056	0.440116
Relative Change (%) at 15 Months after Intervention 1	-7.74	(-12.61, -2.86)	0.406056	0.440116
Absolute Change at 16 Months after Intervention 1	-0.036331	(-0.060972, -0.011690)	0.406023	0.442354
Relative Change (%) at 16 Months after Intervention 1	-8.21	(-13.38, -3.05)	0.406023	0.442354
Absolute Change at 17 Months after Intervention 1	-0.038602	(-0.064783, -0.012420)	0.405990	0.444592
Relative Change (%) at 17 Months after Intervention 1	-8.68	(-14.14, -3.23)	0.405990	0.444592

Table 18. Absolute and Relative Changes in Proportion of HCTZ Single Ingredient Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	-0.040872	(-0.068594, -0.013151)	0.405957	0.446829
Relative Change (%) at 18 Months after Intervention 1	-9.15	(-14.88, -3.41)	0.405957	0.446829
Absolute Change at 19 Months after Intervention 1	-0.043143	(-0.072405, -0.013882)	0.405923	0.449067
Relative Change (%) at 19 Months after Intervention 1	-9.61	(-15.62, -3.59)	0.405923	0.449067
Absolute Change at 20 Months after Intervention 1	-0.045414	(-0.076216, -0.014612)	0.405890	0.451304
Relative Change (%) at 20 Months after Intervention 1	-10.06	(-16.36, -3.77)	0.405890	0.451304
Absolute Change at 21 Months after Intervention 1	-0.047685	(-0.080026, -0.015343)	0.405857	0.453542
Relative Change (%) at 21 Months after Intervention 1	-10.51	(-17.08, -3.95)	0.405857	0.453542
Absolute Change at 22 Months after Intervention 1	-0.049955	(-0.083837, -0.016073)	0.405824	0.455779
Relative Change (%) at 22 Months after Intervention 1	-10.96	(-17.79, -4.13)	0.405824	0.455779
Absolute Change at 23 Months after Intervention 1	-0.052226	(-0.087648, -0.016804)	0.405791	0.458017
Relative Change (%) at 23 Months after Intervention 1	-11.40	(-18.50, -4.30)	0.405791	0.458017
Absolute Change at 24 Months after Intervention 1	-0.054497	(-0.091459, -0.017535)	0.405758	0.460254
Relative Change (%) at 24 Months after Intervention 1	-11.84	(-19.20, -4.48)	0.405758	0.460254
Absolute Change at 25 Months after Intervention 1	-0.056767	(-0.095269, -0.018265)	0.405724	0.462492
Relative Change (%) at 25 Months after Intervention 1	-12.27	(-19.90, -4.65)	0.405724	0.462492
Absolute Change at 26 Months after Intervention 1	-0.059038	(-0.099080, -0.018996)	0.405691	0.464729
Relative Change (%) at 26 Months after Intervention 1	-12.70	(-20.58, -4.83)	0.405691	0.464729
Absolute Change at 27 Months after Intervention 1	-0.061309	(-0.102891, -0.019726)	0.405658	0.466967
Absolute Change at 27 Months after Intervention 1	-0.061309	(-0.102891, -0.019726)	0.405658	0.466967
Relative Change (%) at 27 Months after Intervention 1	-13.13	(-21.26, -5.00)	0.405658	0.466967
Relative Change (%) at 27 Months after Intervention 1	-13.13	(-21.26, -5.00)	0.405658	0.466967

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 19. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of HCTZ/Potassium-Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.098664	(0.095923, 0.101405)	<.001
Baseline trend	-0.000415	(-0.000512, -0.000318)	<.001
Level Change (After Intervention 1)	0.000096	(-0.001042, 0.001234)	0.867
Trend Change (After Intervention 1)	0.000246	(0.000015, 0.000478)	0.038
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.098761	(0.095888, 0.101634)	<.001
Baseline trend	-0.000415	(-0.000516, -0.000315)	<.001
Trend Change (After Intervention 1)	0.000245	(0.000012, 0.000478)	0.040

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 20. Absolute and Relative Changes in Proportion of HCTZ/Potassium-Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000245	(-0.000012, 0.000503)	0.080318	0.080073
Relative Change (%) at 1 Months after Intervention 1	0.31	(-0.02, 0.64)	0.080318	0.080073
Absolute Change at 2 Months after Intervention 1	0.000491	(-0.000024, 0.001005)	0.080148	0.079658
Relative Change (%) at 2 Months after Intervention 1	0.62	(-0.05, 1.28)	0.080148	0.079658
Absolute Change at 3 Months after Intervention 1	0.000736	(-0.000036, 0.001508)	0.079978	0.079242
Relative Change (%) at 3 Months after Intervention 1	0.93	(-0.08, 1.93)	0.079978	0.079242
Absolute Change at 4 Months after Intervention 1	0.000982	(-0.000047, 0.002011)	0.079809	0.078827
Relative Change (%) at 4 Months after Intervention 1	1.25	(-0.10, 2.59)	0.079809	0.078827
Absolute Change at 5 Months after Intervention 1	0.001227	(-0.000059, 0.002513)	0.079639	0.078412
Relative Change (%) at 5 Months after Intervention 1	1.56	(-0.13, 3.26)	0.079639	0.078412
Absolute Change at 6 Months after Intervention 1	0.001472	(-0.000071, 0.003016)	0.079469	0.077996
Relative Change (%) at 6 Months after Intervention 1	1.89	(-0.16, 3.94)	0.079469	0.077996
Absolute Change at 7 Months after Intervention 1	0.001718	(-0.000083, 0.003518)	0.079299	0.077581
Relative Change (%) at 7 Months after Intervention 1	2.21	(-0.19, 4.62)	0.079299	0.077581
Absolute Change at 8 Months after Intervention 1	0.001963	(-0.000095, 0.004021)	0.079129	0.077166
Relative Change (%) at 8 Months after Intervention 1	2.54	(-0.23, 5.31)	0.079129	0.077166
Absolute Change at 9 Months after Intervention 1	0.002209	(-0.000107, 0.004524)	0.078959	0.076750
Relative Change (%) at 9 Months after Intervention 1	2.88	(-0.26, 6.01)	0.078959	0.076750
Absolute Change at 10 Months after Intervention 1	0.002454	(-0.000118, 0.005026)	0.078789	0.076335
Relative Change (%) at 10 Months after Intervention 1	3.21	(-0.29, 6.72)	0.078789	0.076335
Absolute Change at 11 Months after Intervention 1	0.002699	(-0.000130, 0.005529)	0.078619	0.075920
Relative Change (%) at 11 Months after Intervention 1	3.56	(-0.33, 7.44)	0.078619	0.075920
Absolute Change at 12 Months after Intervention 1	0.002945	(-0.000142, 0.006032)	0.078449	0.075505
Relative Change (%) at 12 Months after Intervention 1	3.90	(-0.37, 8.17)	0.078449	0.075505
Absolute Change at 13 Months after Intervention 1	0.003190	(-0.000154, 0.006534)	0.078279	0.075089
Relative Change (%) at 13 Months after Intervention 1	4.25	(-0.41, 8.90)	0.078279	0.075089
Absolute Change at 14 Months after Intervention 1	0.003436	(-0.000166, 0.007037)	0.078110	0.074674
Relative Change (%) at 14 Months after Intervention 1	4.60	(-0.45, 9.65)	0.078110	0.074674
Absolute Change at 15 Months after Intervention 1	0.003681	(-0.000178, 0.007540)	0.077940	0.074259
Relative Change (%) at 15 Months after Intervention 1	4.96	(-0.49, 10.40)	0.077940	0.074259
Absolute Change at 16 Months after Intervention 1	0.003926	(-0.000189, 0.008042)	0.077770	0.073843
Relative Change (%) at 16 Months after Intervention 1	5.32	(-0.53, 11.17)	0.077770	0.073843
Absolute Change at 17 Months after Intervention 1	0.004172	(-0.000201, 0.008545)	0.077600	0.073428
Relative Change (%) at 17 Months after Intervention 1	5.68	(-0.58, 11.94)	0.077600	0.073428

Table 20. Absolute and Relative Changes in Proportion of HCTZ/Potassium-Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or thiazide-like diuretics after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.004417	(-0.000213, 0.009047)	0.077430	0.073013
Relative Change (%) at 18 Months after Intervention 1	6.05	(-0.63, 12.73)	0.077430	0.073013
Absolute Change at 19 Months after Intervention 1	0.004663	(-0.000225, 0.009550)	0.077260	0.072597
Relative Change (%) at 19 Months after Intervention 1	6.42	(-0.68, 13.52)	0.077260	0.072597
Absolute Change at 20 Months after Intervention 1	0.004908	(-0.000237, 0.010053)	0.077090	0.072182
Relative Change (%) at 20 Months after Intervention 1	6.80	(-0.73, 14.32)	0.077090	0.072182
Absolute Change at 21 Months after Intervention 1	0.005153	(-0.000249, 0.010555)	0.076920	0.071767
Relative Change (%) at 21 Months after Intervention 1	7.18	(-0.78, 15.14)	0.076920	0.071767
Absolute Change at 22 Months after Intervention 1	0.005399	(-0.000260, 0.011058)	0.076750	0.071352
Relative Change (%) at 22 Months after Intervention 1	7.57	(-0.83, 15.96)	0.076750	0.071352
Absolute Change at 23 Months after Intervention 1	0.005644	(-0.000272, 0.011561)	0.076581	0.070936
Relative Change (%) at 23 Months after Intervention 1	7.96	(-0.89, 16.80)	0.076581	0.070936
Absolute Change at 24 Months after Intervention 1	0.005890	(-0.000284, 0.012063)	0.076411	0.070521
Relative Change (%) at 24 Months after Intervention 1	8.35	(-0.95, 17.65)	0.076411	0.070521
Absolute Change at 25 Months after Intervention 1	0.006135	(-0.000296, 0.012566)	0.076241	0.070106
Relative Change (%) at 25 Months after Intervention 1	8.75	(-1.01, 18.51)	0.076241	0.070106
Absolute Change at 26 Months after Intervention 1	0.006380	(-0.000308, 0.013068)	0.076071	0.069690
Relative Change (%) at 26 Months after Intervention 1	9.16	(-1.07, 19.38)	0.076071	0.069690
Absolute Change at 27 Months after Intervention 1	0.006626	(-0.000320, 0.013571)	0.075901	0.069275
Absolute Change at 27 Months after Intervention 1	0.006626	(-0.000320, 0.013571)	0.075901	0.069275
Relative Change (%) at 27 Months after Intervention 1	9.56	(-1.13, 20.26)	0.075901	0.069275
Relative Change (%) at 27 Months after Intervention 1	9.56	(-1.13, 20.26)	0.075901	0.069275

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 21. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of ACEI Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.303850	(0.302387, 0.305313)	<.001
Baseline trend	-0.000501	(-0.000553, -0.000449)	<.001
Level Change (After Intervention 1)	0.001923	(0.000333, 0.003514)	0.019
Trend Change (After Intervention 1)	-0.000327	(-0.000441, -0.000212)	<.001
Most Parsimonious Final Model Parameters (df = 69)[2,3]			
Intercept	0.303850	(0.302387, 0.305313)	<.001
Baseline trend	-0.000501	(-0.000553, -0.000449)	<.001
Level Change (After Intervention 1)	0.001923	(0.000333, 0.003514)	0.019
Trend Change (After Intervention 1)	-0.000327	(-0.000441, -0.000212)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 22. Absolute and Relative Changes in Proportion of ACEI Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.001597	(-0.000009, 0.003203)	0.282909	0.281313
Relative Change (%) at 1 Months after Intervention 1	0.57	(-0.01, 1.14)	0.282909	0.281313
Absolute Change at 2 Months after Intervention 1	0.001270	(-0.000333, 0.002872)	0.282082	0.280812
Relative Change (%) at 2 Months after Intervention 1	0.45	(-0.12, 1.02)	0.282082	0.280812
Absolute Change at 3 Months after Intervention 1	0.000943	(-0.000665, 0.002551)	0.281254	0.280311
Relative Change (%) at 3 Months after Intervention 1	0.34	(-0.24, 0.91)	0.281254	0.280311
Absolute Change at 4 Months after Intervention 1	0.000616	(-0.001008, 0.002240)	0.280426	0.279810
Relative Change (%) at 4 Months after Intervention 1	0.22	(-0.36, 0.80)	0.280426	0.279810
Absolute Change at 5 Months after Intervention 1	0.000289	(-0.001360, 0.001939)	0.279599	0.279309
Relative Change (%) at 5 Months after Intervention 1	0.10	(-0.49, 0.69)	0.279599	0.279309
Absolute Change at 6 Months after Intervention 1	-0.000037	(-0.001721, 0.001646)	0.278771	0.278808
Relative Change (%) at 6 Months after Intervention 1	-0.01	(-0.62, 0.59)	0.278771	0.278808
Absolute Change at 7 Months after Intervention 1	-0.000364	(-0.002090, 0.001362)	0.277943	0.278308
Relative Change (%) at 7 Months after Intervention 1	-0.13	(-0.75, 0.49)	0.277943	0.278308
Absolute Change at 8 Months after Intervention 1	-0.000691	(-0.002467, 0.001085)	0.277116	0.277807
Relative Change (%) at 8 Months after Intervention 1	-0.25	(-0.89, 0.39)	0.277116	0.277807
Absolute Change at 9 Months after Intervention 1	-0.001018	(-0.002851, 0.000816)	0.276288	0.277306
Relative Change (%) at 9 Months after Intervention 1	-0.37	(-1.03, 0.29)	0.276288	0.277306
Absolute Change at 10 Months after Intervention 1	-0.001344	(-0.003242, 0.000553)	0.275461	0.276805
Relative Change (%) at 10 Months after Intervention 1	-0.49	(-1.17, 0.20)	0.275461	0.276805
Absolute Change at 11 Months after Intervention 1	-0.001671	(-0.003639, 0.000296)	0.274633	0.276304
Relative Change (%) at 11 Months after Intervention 1	-0.60	(-1.31, 0.10)	0.274633	0.276304
Absolute Change at 12 Months after Intervention 1	-0.001998	(-0.004040, 0.000044)	0.273805	0.275803
Relative Change (%) at 12 Months after Intervention 1	-0.72	(-1.46, 0.01)	0.273805	0.275803
Absolute Change at 13 Months after Intervention 1	-0.002325	(-0.004447, -0.000203)	0.272978	0.275303
Relative Change (%) at 13 Months after Intervention 1	-0.84	(-1.61, -0.08)	0.272978	0.275303
Absolute Change at 14 Months after Intervention 1	-0.002652	(-0.004858, -0.000445)	0.272150	0.274802
Relative Change (%) at 14 Months after Intervention 1	-0.96	(-1.76, -0.17)	0.272150	0.274802
Absolute Change at 15 Months after Intervention 1	-0.002978	(-0.005272, -0.000684)	0.271323	0.274301
Relative Change (%) at 15 Months after Intervention 1	-1.09	(-1.91, -0.26)	0.271323	0.274301
Absolute Change at 16 Months after Intervention 1	-0.003305	(-0.005690, -0.000920)	0.270495	0.273800
Relative Change (%) at 16 Months after Intervention 1	-1.21	(-2.07, -0.35)	0.270495	0.273800
Absolute Change at 17 Months after Intervention 1	-0.003632	(-0.006111, -0.001153)	0.269667	0.273299
Relative Change (%) at 17 Months after Intervention 1	-1.33	(-2.23, -0.43)	0.269667	0.273299

Table 22. Absolute and Relative Changes in Proportion of ACEI Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	-0.003959	(-0.006535, -0.001383)	0.268840	0.272798
Relative Change (%) at 18 Months after Intervention 1	-1.45	(-2.38, -0.52)	0.268840	0.272798
Absolute Change at 19 Months after Intervention 1	-0.004285	(-0.006961, -0.001610)	0.268012	0.272298
Relative Change (%) at 19 Months after Intervention 1	-1.57	(-2.54, -0.60)	0.268012	0.272298
Absolute Change at 20 Months after Intervention 1	-0.004612	(-0.007388, -0.001836)	0.267185	0.271797
Relative Change (%) at 20 Months after Intervention 1	-1.70	(-2.70, -0.69)	0.267185	0.271797
Absolute Change at 21 Months after Intervention 1	-0.004939	(-0.007818, -0.002060)	0.266357	0.271296
Relative Change (%) at 21 Months after Intervention 1	-1.82	(-2.87, -0.77)	0.266357	0.271296
Absolute Change at 22 Months after Intervention 1	-0.005266	(-0.008250, -0.002282)	0.265529	0.270795
Relative Change (%) at 22 Months after Intervention 1	-1.94	(-3.03, -0.86)	0.265529	0.270795
Absolute Change at 23 Months after Intervention 1	-0.005593	(-0.008683, -0.002502)	0.264702	0.270294
Relative Change (%) at 23 Months after Intervention 1	-2.07	(-3.19, -0.94)	0.264702	0.270294
Absolute Change at 24 Months after Intervention 1	-0.005919	(-0.009117, -0.002721)	0.263874	0.269793
Relative Change (%) at 24 Months after Intervention 1	-2.19	(-3.36, -1.03)	0.263874	0.269793
Absolute Change at 25 Months after Intervention 1	-0.006246	(-0.009553, -0.002939)	0.263046	0.269293
Relative Change (%) at 25 Months after Intervention 1	-2.32	(-3.53, -1.11)	0.263046	0.269293
Absolute Change at 26 Months after Intervention 1	-0.006573	(-0.009990, -0.003156)	0.262219	0.268792
Relative Change (%) at 26 Months after Intervention 1	-2.45	(-3.69, -1.20)	0.262219	0.268792
Absolute Change at 27 Months after Intervention 1	-0.006900	(-0.010427, -0.003372)	0.261391	0.268291
Absolute Change at 27 Months after Intervention 1	-0.006900	(-0.010427, -0.003372)	0.261391	0.268291
Relative Change (%) at 27 Months after Intervention 1	-2.57	(-3.86, -1.28)	0.261391	0.268291
Relative Change (%) at 27 Months after Intervention 1	-2.57	(-3.86, -1.28)	0.261391	0.268291

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 23. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of ARB Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.280616	(0.275434, 0.285797)	<.001
Baseline trend	0.000200	(0.000017, 0.000383)	0.033
Level Change (After Intervention 1)	-0.000519	(-0.004098, 0.003060)	0.773
Trend Change (After Intervention 1)	0.000733	(0.000309, 0.001157)	<.001
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.280593	(0.275290, 0.285895)	<.001
Baseline trend	0.000197	(0.000013, 0.000381)	0.036
Trend Change (After Intervention 1)	0.000720	(0.000295, 0.001145)	0.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 24. Absolute and Relative Changes in Proportion of ARB Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000720	(0.000291, 0.001149)	0.290189	0.289469
Relative Change (%) at 1 Months after Intervention 1	0.25	(0.10, 0.40)	0.290189	0.289469
Absolute Change at 2 Months after Intervention 1	0.001440	(0.000581, 0.002298)	0.291106	0.289666
Relative Change (%) at 2 Months after Intervention 1	0.50	(0.19, 0.80)	0.291106	0.289666
Absolute Change at 3 Months after Intervention 1	0.002159	(0.000872, 0.003447)	0.292023	0.289863
Relative Change (%) at 3 Months after Intervention 1	0.74	(0.29, 1.20)	0.292023	0.289863
Absolute Change at 4 Months after Intervention 1	0.002879	(0.001162, 0.004596)	0.292940	0.290061
Relative Change (%) at 4 Months after Intervention 1	0.99	(0.39, 1.60)	0.292940	0.290061
Absolute Change at 5 Months after Intervention 1	0.003599	(0.001453, 0.005745)	0.293857	0.290258
Relative Change (%) at 5 Months after Intervention 1	1.24	(0.48, 2.00)	0.293857	0.290258
Absolute Change at 6 Months after Intervention 1	0.004319	(0.001743, 0.006894)	0.294774	0.290455
Relative Change (%) at 6 Months after Intervention 1	1.49	(0.58, 2.40)	0.294774	0.290455
Absolute Change at 7 Months after Intervention 1	0.005038	(0.002034, 0.008043)	0.295691	0.290652
Relative Change (%) at 7 Months after Intervention 1	1.73	(0.67, 2.80)	0.295691	0.290652
Absolute Change at 8 Months after Intervention 1	0.005758	(0.002324, 0.009192)	0.296608	0.290850
Relative Change (%) at 8 Months after Intervention 1	1.98	(0.76, 3.20)	0.296608	0.290850
Absolute Change at 9 Months after Intervention 1	0.006478	(0.002615, 0.010341)	0.297525	0.291047
Relative Change (%) at 9 Months after Intervention 1	2.23	(0.86, 3.59)	0.297525	0.291047
Absolute Change at 10 Months after Intervention 1	0.007198	(0.002905, 0.011490)	0.298442	0.291244
Relative Change (%) at 10 Months after Intervention 1	2.47	(0.95, 3.99)	0.298442	0.291244
Absolute Change at 11 Months after Intervention 1	0.007917	(0.003196, 0.012639)	0.299359	0.291441
Relative Change (%) at 11 Months after Intervention 1	2.72	(1.04, 4.39)	0.299359	0.291441
Absolute Change at 12 Months after Intervention 1	0.008637	(0.003486, 0.013788)	0.300276	0.291639
Relative Change (%) at 12 Months after Intervention 1	2.96	(1.14, 4.79)	0.300276	0.291639
Absolute Change at 13 Months after Intervention 1	0.009357	(0.003777, 0.014937)	0.301193	0.291836
Relative Change (%) at 13 Months after Intervention 1	3.21	(1.23, 5.18)	0.301193	0.291836
Absolute Change at 14 Months after Intervention 1	0.010077	(0.004067, 0.016086)	0.302110	0.292033
Relative Change (%) at 14 Months after Intervention 1	3.45	(1.32, 5.58)	0.302110	0.292033
Absolute Change at 15 Months after Intervention 1	0.010796	(0.004358, 0.017235)	0.303027	0.292230
Relative Change (%) at 15 Months after Intervention 1	3.69	(1.41, 5.98)	0.303027	0.292230
Absolute Change at 16 Months after Intervention 1	0.011516	(0.004648, 0.018384)	0.303944	0.292428
Relative Change (%) at 16 Months after Intervention 1	3.94	(1.50, 6.37)	0.303944	0.292428
Absolute Change at 17 Months after Intervention 1	0.012236	(0.004939, 0.019533)	0.304861	0.292625
Relative Change (%) at 17 Months after Intervention 1	4.18	(1.59, 6.77)	0.304861	0.292625

Table 24. Absolute and Relative Changes in Proportion of ARB Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.012956	(0.005229, 0.020682)	0.305778	0.292822
Relative Change (%) at 18 Months after Intervention 1	4.42	(1.69, 7.16)	0.305778	0.292822
Absolute Change at 19 Months after Intervention 1	0.013676	(0.005520, 0.021831)	0.306695	0.293019
Relative Change (%) at 19 Months after Intervention 1	4.67	(1.78, 7.56)	0.306695	0.293019
Absolute Change at 20 Months after Intervention 1	0.014395	(0.005810, 0.022980)	0.307612	0.293217
Relative Change (%) at 20 Months after Intervention 1	4.91	(1.87, 7.95)	0.307612	0.293217
Absolute Change at 21 Months after Intervention 1	0.015115	(0.006101, 0.024129)	0.308529	0.293414
Relative Change (%) at 21 Months after Intervention 1	5.15	(1.95, 8.35)	0.308529	0.293414
Absolute Change at 22 Months after Intervention 1	0.015835	(0.006391, 0.025278)	0.309446	0.293611
Relative Change (%) at 22 Months after Intervention 1	5.39	(2.04, 8.74)	0.309446	0.293611
Absolute Change at 23 Months after Intervention 1	0.016555	(0.006682, 0.026427)	0.310363	0.293808
Relative Change (%) at 23 Months after Intervention 1	5.63	(2.13, 9.14)	0.310363	0.293808
Absolute Change at 24 Months after Intervention 1	0.017274	(0.006972, 0.027576)	0.311280	0.294006
Relative Change (%) at 24 Months after Intervention 1	5.88	(2.22, 9.53)	0.311280	0.294006
Absolute Change at 25 Months after Intervention 1	0.017994	(0.007263, 0.028725)	0.312197	0.294203
Relative Change (%) at 25 Months after Intervention 1	6.12	(2.31, 9.92)	0.312197	0.294203
Absolute Change at 26 Months after Intervention 1	0.018714	(0.007553, 0.029874)	0.313114	0.294400
Relative Change (%) at 26 Months after Intervention 1	6.36	(2.40, 10.32)	0.313114	0.294400
Absolute Change at 27 Months after Intervention 1	0.019434	(0.007844, 0.031023)	0.314031	0.294597
Absolute Change at 27 Months after Intervention 1	0.019434	(0.007844, 0.031023)	0.314031	0.294597
Relative Change (%) at 27 Months after Intervention 1	6.60	(2.48, 10.71)	0.314031	0.294597
Relative Change (%) at 27 Months after Intervention 1	6.60	(2.48, 10.71)	0.314031	0.294597

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 25. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Beta Blocker Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.350909	(0.340006, 0.361812)	<.001
Baseline trend	-0.000404	(-0.000780, -0.000028)	0.036
Level Change (After Intervention 1)	0.000671	(-0.005236, 0.006577)	0.822
Trend Change (After Intervention 1)	0.000630	(-0.000224, 0.001484)	0.146
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.350858	(0.339885, 0.361831)	<.001
Baseline trend	-0.000397	(-0.000772, -0.000022)	0.039
Trend Change (After Intervention 1)	0.000641	(-0.000205, 0.001486)	0.135

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 26. Absolute and Relative Changes in Proportion of Beta Blocker Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000641	(-0.000261, 0.001542)	0.333649	0.333008
Relative Change (%) at 1 Months after Intervention 1	0.19	(-0.08, 0.47)	0.333649	0.333008
Absolute Change at 2 Months after Intervention 1	0.001281	(-0.000521, 0.003084)	0.333893	0.332611
Relative Change (%) at 2 Months after Intervention 1	0.39	(-0.17, 0.94)	0.333893	0.332611
Absolute Change at 3 Months after Intervention 1	0.001922	(-0.000782, 0.004626)	0.334137	0.332214
Relative Change (%) at 3 Months after Intervention 1	0.58	(-0.25, 1.41)	0.334137	0.332214
Absolute Change at 4 Months after Intervention 1	0.002563	(-0.001042, 0.006168)	0.334381	0.331818
Relative Change (%) at 4 Months after Intervention 1	0.77	(-0.34, 1.88)	0.334381	0.331818
Absolute Change at 5 Months after Intervention 1	0.003204	(-0.001303, 0.007711)	0.334625	0.331421
Relative Change (%) at 5 Months after Intervention 1	0.97	(-0.42, 2.36)	0.334625	0.331421
Absolute Change at 6 Months after Intervention 1	0.003844	(-0.001564, 0.009253)	0.334869	0.331024
Relative Change (%) at 6 Months after Intervention 1	1.16	(-0.51, 2.83)	0.334869	0.331024
Absolute Change at 7 Months after Intervention 1	0.004485	(-0.001824, 0.010795)	0.335113	0.330628
Relative Change (%) at 7 Months after Intervention 1	1.36	(-0.60, 3.31)	0.335113	0.330628
Absolute Change at 8 Months after Intervention 1	0.005126	(-0.002085, 0.012337)	0.335357	0.330231
Relative Change (%) at 8 Months after Intervention 1	1.55	(-0.69, 3.79)	0.335357	0.330231
Absolute Change at 9 Months after Intervention 1	0.005767	(-0.002346, 0.013879)	0.335601	0.329834
Relative Change (%) at 9 Months after Intervention 1	1.75	(-0.77, 4.27)	0.335601	0.329834
Absolute Change at 10 Months after Intervention 1	0.006407	(-0.002606, 0.015421)	0.335845	0.329438
Relative Change (%) at 10 Months after Intervention 1	1.94	(-0.86, 4.75)	0.335845	0.329438
Absolute Change at 11 Months after Intervention 1	0.007048	(-0.002867, 0.016963)	0.336089	0.329041
Relative Change (%) at 11 Months after Intervention 1	2.14	(-0.95, 5.24)	0.336089	0.329041
Absolute Change at 12 Months after Intervention 1	0.007689	(-0.003127, 0.018505)	0.336333	0.328644
Relative Change (%) at 12 Months after Intervention 1	2.34	(-1.04, 5.72)	0.336333	0.328644
Absolute Change at 13 Months after Intervention 1	0.008330	(-0.003388, 0.020047)	0.336577	0.328248
Relative Change (%) at 13 Months after Intervention 1	2.54	(-1.13, 6.21)	0.336577	0.328248
Absolute Change at 14 Months after Intervention 1	0.008970	(-0.003649, 0.021590)	0.336822	0.327851
Relative Change (%) at 14 Months after Intervention 1	2.74	(-1.22, 6.70)	0.336822	0.327851
Absolute Change at 15 Months after Intervention 1	0.009611	(-0.003909, 0.023132)	0.337066	0.327454
Relative Change (%) at 15 Months after Intervention 1	2.94	(-1.32, 7.19)	0.337066	0.327454
Absolute Change at 16 Months after Intervention 1	0.010252	(-0.004170, 0.024674)	0.337310	0.327058
Relative Change (%) at 16 Months after Intervention 1	3.13	(-1.41, 7.68)	0.337310	0.327058
Absolute Change at 17 Months after Intervention 1	0.010893	(-0.004431, 0.026216)	0.337554	0.326661
Relative Change (%) at 17 Months after Intervention 1	3.33	(-1.50, 8.17)	0.337554	0.326661

Table 26. Absolute and Relative Changes in Proportion of Beta Blocker Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.011533	(-0.004691, 0.027758)	0.337798	0.326264
Relative Change (%) at 18 Months after Intervention 1	3.54	(-1.60, 8.67)	0.337798	0.326264
Absolute Change at 19 Months after Intervention 1	0.012174	(-0.004952, 0.029300)	0.338042	0.325868
Relative Change (%) at 19 Months after Intervention 1	3.74	(-1.69, 9.16)	0.338042	0.325868
Absolute Change at 20 Months after Intervention 1	0.012815	(-0.005212, 0.030842)	0.338286	0.325471
Relative Change (%) at 20 Months after Intervention 1	3.94	(-1.79, 9.66)	0.338286	0.325471
Absolute Change at 21 Months after Intervention 1	0.013456	(-0.005473, 0.032384)	0.338530	0.325074
Relative Change (%) at 21 Months after Intervention 1	4.14	(-1.88, 10.16)	0.338530	0.325074
Absolute Change at 22 Months after Intervention 1	0.014096	(-0.005734, 0.033927)	0.338774	0.324678
Relative Change (%) at 22 Months after Intervention 1	4.34	(-1.98, 10.66)	0.338774	0.324678
Absolute Change at 23 Months after Intervention 1	0.014737	(-0.005994, 0.035469)	0.339018	0.324281
Relative Change (%) at 23 Months after Intervention 1	4.54	(-2.08, 11.17)	0.339018	0.324281
Absolute Change at 24 Months after Intervention 1	0.015378	(-0.006255, 0.037011)	0.339262	0.323884
Relative Change (%) at 24 Months after Intervention 1	4.75	(-2.18, 11.67)	0.339262	0.323884
Absolute Change at 25 Months after Intervention 1	0.016019	(-0.006515, 0.038553)	0.339506	0.323488
Relative Change (%) at 25 Months after Intervention 1	4.95	(-2.27, 12.18)	0.339506	0.323488
Absolute Change at 26 Months after Intervention 1	0.016659	(-0.006776, 0.040095)	0.339750	0.323091
Relative Change (%) at 26 Months after Intervention 1	5.16	(-2.37, 12.69)	0.339750	0.323091
Absolute Change at 27 Months after Intervention 1	0.017300	(-0.007037, 0.041637)	0.339995	0.322694
Absolute Change at 27 Months after Intervention 1	0.017300	(-0.007037, 0.041637)	0.339995	0.322694
Relative Change (%) at 27 Months after Intervention 1	5.36	(-2.47, 13.20)	0.339995	0.322694
Relative Change (%) at 27 Months after Intervention 1	5.36	(-2.47, 13.20)	0.339995	0.322694

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 27. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of CCB Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.227425	(0.219245, 0.235604)	<.001
Baseline trend	0.000537	(0.000260, 0.000814)	<.001
Level Change (After Intervention 1)	0.000272	(-0.003604, 0.004148)	0.889
Trend Change (After Intervention 1)	0.000141	(-0.000479, 0.000761)	0.651
Most Parsimonious Final Model Parameters (df = 71)[2,3]			
Intercept	0.226715	(0.218930, 0.234500)	<.001
Baseline trend	0.000589	(0.000416, 0.000763)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 28. Absolute and Relative Changes in Proportion of CCB Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.253231	0.253231
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.253231	0.253231
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.253821	0.253821
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.253821	0.253821
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.254410	0.254410
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.254410	0.254410
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.254999	0.254999
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.254999	0.254999
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.255588	0.255588
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.255588	0.255588
Absolute Change at 6 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.256178	0.256178
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.256178	0.256178
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.256767	0.256767
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.256767	0.256767
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.257356	0.257356
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.257356	0.257356
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.257946	0.257946
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.257946	0.257946
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.258535	0.258535
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.258535	0.258535
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.259124	0.259124
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.259124	0.259124
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.259713	0.259713
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.259713	0.259713
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.260303	0.260303
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.260303	0.260303
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.260892	0.260892
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.260892	0.260892
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.261481	0.261481
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.261481	0.261481
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.262070	0.262070
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.262070	0.262070
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.262660	0.262660
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.262660	0.262660

Table 28. Absolute and Relative Changes in Proportion of CCB Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.263249	0.263249
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.263249	0.263249
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.263838	0.263838
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.263838	0.263838
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.264427	0.264427
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.264427	0.264427
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.265017	0.265017
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.265017	0.265017
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.265606	0.265606
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.265606	0.265606
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.266195	0.266195
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.266195	0.266195
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.266784	0.266784
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.266784	0.266784
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.267374	0.267374
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.267374	0.267374
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.267963	0.267963
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.267963	0.267963
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.268552	0.268552
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.268552	0.268552
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.268552	0.268552
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.268552	0.268552

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 29. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Loop Diuretics Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.058827	(0.052100, 0.065555)	<.001
Baseline trend	-0.000129	(-0.000365, 0.000108)	0.281
Level Change (After Intervention 1)	0.000061	(-0.003006, 0.003128)	0.968
Trend Change (After Intervention 1)	0.000259	(-0.000295, 0.000812)	0.355
Most Parsimonious Final Model Parameters (df = 72)[2,3]			
Intercept	0.056644	(0.051496, 0.061792)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 30. Absolute and Relative Changes in Proportion of Loop Diuretics Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 1 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 2 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 2 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 3 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 3 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 4 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 4 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 5 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 5 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 6 Months after Intervention 1	0.000000	Q	0.056644	0.056644
Relative Change (%) at 6 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 7 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 7 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 8 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 8 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 9 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 9 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 10 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 10 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 11 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 11 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 12 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 12 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 13 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 13 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 14 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 14 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 15 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 15 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 16 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 16 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 17 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 17 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644

Table 30. Absolute and Relative Changes in Proportion of Loop Diuretics Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056644	0.056644
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.056644	0.056644

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 31. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Potassium Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.037381	(0.036939, 0.037823)	<.001
Baseline trend	0.000313	(0.000296, 0.000329)	<.001
Level Change (After Intervention 1)	-0.000062	(-0.000554, 0.000430)	0.802
Trend Change (After Intervention 1)	0.000016	(-0.000024, 0.000056)	0.438
Most Parsimonious Final Model Parameters (df = 71)[2,3]			
Intercept	0.037296	(0.036944, 0.037649)	<.001
Baseline trend	0.000317	(0.000308, 0.000325)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 32. Absolute and Relative Changes in Proportion of Potassium Sparing Combination Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.056927	0.056927
Relative Change (%) at 18 Months after Intervention 1	0.00	(0.00, 0.00)	0.056927	0.056927
Absolute Change at 19 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.057243	0.057243
Relative Change (%) at 19 Months after Intervention 1	0.00	(0.00, 0.00)	0.057243	0.057243
Absolute Change at 20 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.057560	0.057560
Relative Change (%) at 20 Months after Intervention 1	0.00	(0.00, 0.00)	0.057560	0.057560
Absolute Change at 21 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.057877	0.057877
Relative Change (%) at 21 Months after Intervention 1	0.00	(0.00, 0.00)	0.057877	0.057877
Absolute Change at 22 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.058193	0.058193
Relative Change (%) at 22 Months after Intervention 1	0.00	(0.00, 0.00)	0.058193	0.058193
Absolute Change at 23 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.058510	0.058510
Relative Change (%) at 23 Months after Intervention 1	0.00	(0.00, 0.00)	0.058510	0.058510
Absolute Change at 24 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.058827	0.058827
Relative Change (%) at 24 Months after Intervention 1	0.00	(0.00, 0.00)	0.058827	0.058827
Absolute Change at 25 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.059143	0.059143
Relative Change (%) at 25 Months after Intervention 1	0.00	(0.00, 0.00)	0.059143	0.059143
Absolute Change at 26 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.059460	0.059460
Relative Change (%) at 26 Months after Intervention 1	0.00	(0.00, 0.00)	0.059460	0.059460
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.059776	0.059776
Absolute Change at 27 Months after Intervention 1	0.000000	(0.000000, 0.000000)	0.059776	0.059776
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.059776	0.059776
Relative Change (%) at 27 Months after Intervention 1	0.00	(0.00, 0.00)	0.059776	0.059776

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Table 33. Parameter Estimates from the Segmented Regression Model of Monthly Proportion of Thiazide-like Diuretics Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1]

	Estimate	95% CI	Approximate Pr > |t|
Initial Model Parameters (df = 69)[2]			
Intercept	0.015759	(0.015404, 0.016115)	<.001
Baseline trend	0.000112	(0.000103, 0.000122)	<.001
Level Change (After Intervention 1)	0.000090	(-0.000115, 0.000294)	0.385
Trend Change (After Intervention 1)	-0.000069	(-0.000088, -0.000051)	<.001
Most Parsimonious Final Model Parameters (df = 70)[2,3]			
Intercept	0.015750	(0.015396, 0.016103)	<.001
Baseline trend	0.000113	(0.000104, 0.000123)	<.001
Trend Change (After Intervention 1)	-0.000068	(-0.000087, -0.000049)	<.001

[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

[2]Maximum likelihood estimation method is used to obtain the estimates here. Maximum likelihood estimation method adjusts for autocorrelation. The p-value is calculated under the assumption of asymptotic normality.

[3]Most parsimonious final model parameters were selected from initial model parameters using backwards selection with a cutoff of 0.2

Table 34. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

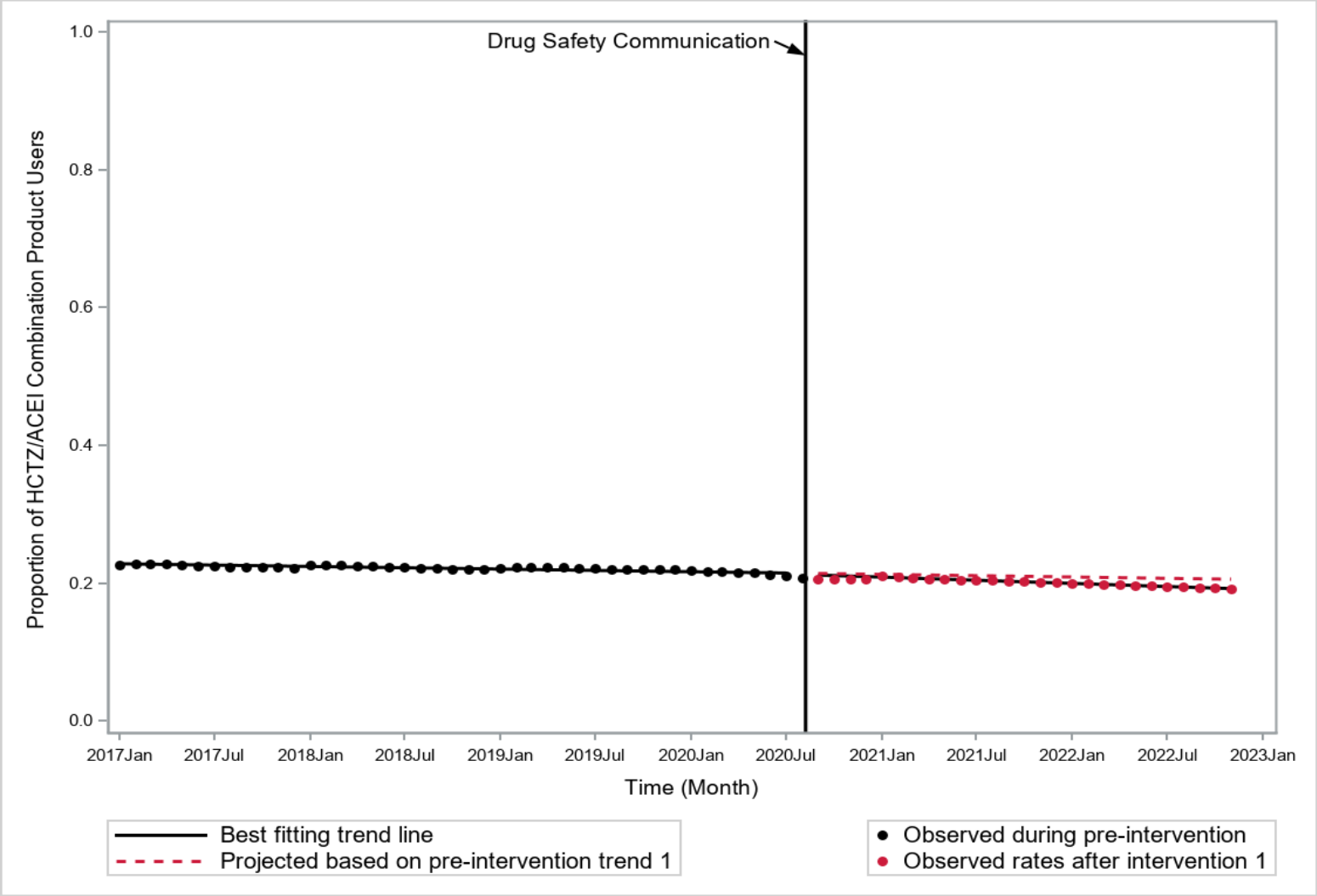
Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 1 Months after Intervention 1	-0.000068	(-0.000090, -0.000045)	0.020770	0.020837
Relative Change (%) at 1 Months after Intervention 1	-0.33	(-0.43, -0.22)	0.020770	0.020837
Absolute Change at 2 Months after Intervention 1	-0.000136	(-0.000181, -0.000091)	0.020815	0.020951
Relative Change (%) at 2 Months after Intervention 1	-0.65	(-0.85, -0.44)	0.020815	0.020951
Absolute Change at 3 Months after Intervention 1	-0.000204	(-0.000271, -0.000136)	0.020860	0.021064
Relative Change (%) at 3 Months after Intervention 1	-0.97	(-1.27, -0.66)	0.020860	0.021064
Absolute Change at 4 Months after Intervention 1	-0.000271	(-0.000362, -0.000181)	0.020905	0.021177
Relative Change (%) at 4 Months after Intervention 1	-1.28	(-1.69, -0.87)	0.020905	0.021177
Absolute Change at 5 Months after Intervention 1	-0.000339	(-0.000452, -0.000226)	0.020950	0.021290
Relative Change (%) at 5 Months after Intervention 1	-1.59	(-2.10, -1.09)	0.020950	0.021290
Absolute Change at 6 Months after Intervention 1	-0.000407	(-0.000543, -0.000272)	0.020996	0.021403
Relative Change (%) at 6 Months after Intervention 1	-1.90	(-2.51, -1.30)	0.020996	0.021403
Absolute Change at 7 Months after Intervention 1	-0.000475	(-0.000633, -0.000317)	0.021041	0.021516
Relative Change (%) at 7 Months after Intervention 1	-2.21	(-2.91, -1.51)	0.021041	0.021516
Absolute Change at 8 Months after Intervention 1	-0.000543	(-0.000724, -0.000362)	0.021086	0.021629
Relative Change (%) at 8 Months after Intervention 1	-2.51	(-3.31, -1.71)	0.021086	0.021629
Absolute Change at 9 Months after Intervention 1	-0.000611	(-0.000814, -0.000407)	0.021131	0.021742
Relative Change (%) at 9 Months after Intervention 1	-2.81	(-3.70, -1.92)	0.021131	0.021742
Absolute Change at 10 Months after Intervention 1	-0.000679	(-0.000904, -0.000453)	0.021176	0.021855
Relative Change (%) at 10 Months after Intervention 1	-3.11	(-4.09, -2.12)	0.021176	0.021855
Absolute Change at 11 Months after Intervention 1	-0.000746	(-0.000995, -0.000498)	0.021222	0.021968
Relative Change (%) at 11 Months after Intervention 1	-3.40	(-4.47, -2.32)	0.021222	0.021968
Absolute Change at 12 Months after Intervention 1	-0.000814	(-0.001085, -0.000543)	0.021267	0.022081
Relative Change (%) at 12 Months after Intervention 1	-3.69	(-4.85, -2.52)	0.021267	0.022081
Absolute Change at 13 Months after Intervention 1	-0.000882	(-0.001176, -0.000589)	0.021312	0.022194
Relative Change (%) at 13 Months after Intervention 1	-3.97	(-5.23, -2.72)	0.021312	0.022194
Absolute Change at 14 Months after Intervention 1	-0.000950	(-0.001266, -0.000634)	0.021357	0.022307
Relative Change (%) at 14 Months after Intervention 1	-4.26	(-5.60, -2.92)	0.021357	0.022307
Absolute Change at 15 Months after Intervention 1	-0.001018	(-0.001357, -0.000679)	0.021402	0.022420
Relative Change (%) at 15 Months after Intervention 1	-4.54	(-5.97, -3.11)	0.021402	0.022420
Absolute Change at 16 Months after Intervention 1	-0.001086	(-0.001447, -0.000724)	0.021448	0.022533
Relative Change (%) at 16 Months after Intervention 1	-4.82	(-6.33, -3.30)	0.021448	0.022533
Absolute Change at 17 Months after Intervention 1	-0.001154	(-0.001538, -0.000770)	0.021493	0.022646
Relative Change (%) at 17 Months after Intervention 1	-5.09	(-6.70, -3.49)	0.021493	0.022646

Table 34. Absolute and Relative Changes in Proportion of Thiazide-like Diuretics Product Users among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives after August 8, 2020[1] Compared with Expected Rates Derived from Baseline Trend

Outcome Measure	Estimate	95% CI	Predicted Rate (With Intervention)	Extrapolated Rate (Without Intervention)
Absolute Change at 18 Months after Intervention 1	-0.001221	(-0.001628, -0.000815)	0.021538	0.022759
Relative Change (%) at 18 Months after Intervention 1	-5.37	(-7.05, -3.68)	0.021538	0.022759
Absolute Change at 19 Months after Intervention 1	-0.001289	(-0.001718, -0.000860)	0.021583	0.022873
Relative Change (%) at 19 Months after Intervention 1	-5.64	(-7.41, -3.87)	0.021583	0.022873
Absolute Change at 20 Months after Intervention 1	-0.001357	(-0.001809, -0.000906)	0.021628	0.022986
Relative Change (%) at 20 Months after Intervention 1	-5.90	(-7.76, -4.05)	0.021628	0.022986
Absolute Change at 21 Months after Intervention 1	-0.001425	(-0.001899, -0.000951)	0.021674	0.023099
Relative Change (%) at 21 Months after Intervention 1	-6.17	(-8.10, -4.24)	0.021674	0.023099
Absolute Change at 22 Months after Intervention 1	-0.001493	(-0.001990, -0.000996)	0.021719	0.023212
Relative Change (%) at 22 Months after Intervention 1	-6.43	(-8.44, -4.42)	0.021719	0.023212
Absolute Change at 23 Months after Intervention 1	-0.001561	(-0.002080, -0.001041)	0.021764	0.023325
Relative Change (%) at 23 Months after Intervention 1	-6.69	(-8.78, -4.60)	0.021764	0.023325
Absolute Change at 24 Months after Intervention 1	-0.001629	(-0.002171, -0.001087)	0.021809	0.023438
Relative Change (%) at 24 Months after Intervention 1	-6.95	(-9.12, -4.78)	0.021809	0.023438
Absolute Change at 25 Months after Intervention 1	-0.001697	(-0.002261, -0.001132)	0.021854	0.023551
Relative Change (%) at 25 Months after Intervention 1	-7.20	(-9.45, -4.96)	0.021854	0.023551
Absolute Change at 26 Months after Intervention 1	-0.001764	(-0.002352, -0.001177)	0.021900	0.023664
Relative Change (%) at 26 Months after Intervention 1	-7.46	(-9.78, -5.13)	0.021900	0.023664
Absolute Change at 27 Months after Intervention 1	-0.001832	(-0.002442, -0.001222)	0.021945	0.023777
Absolute Change at 27 Months after Intervention 1	-0.001832	(-0.002442, -0.001222)	0.021945	0.023777
Relative Change (%) at 27 Months after Intervention 1	-7.71	(-10.11, -5.31)	0.021945	0.023777
Relative Change (%) at 27 Months after Intervention 1	-7.71	(-10.11, -5.31)	0.021945	0.023777

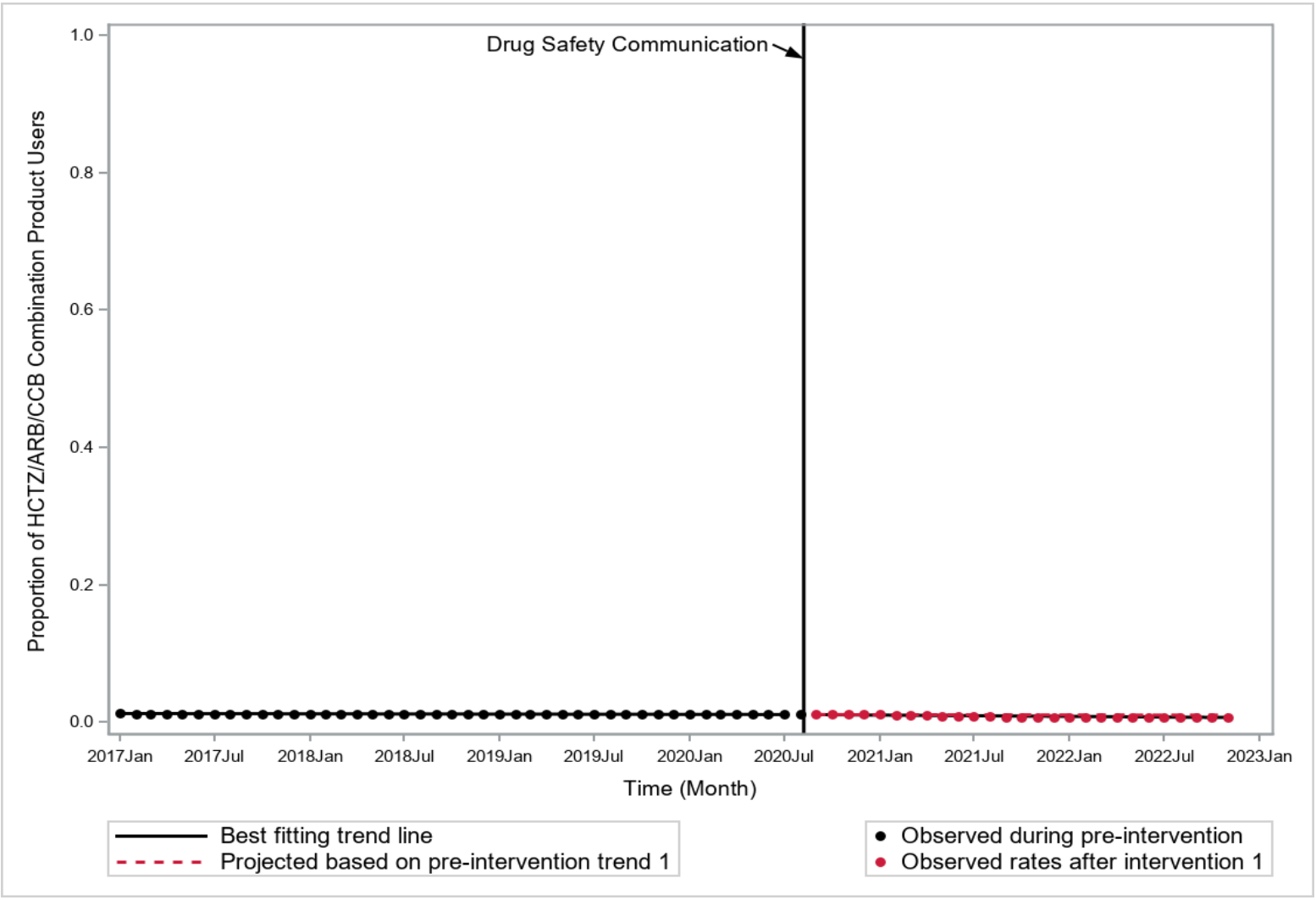
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 1. Proportion of HCTZ/ACEI Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



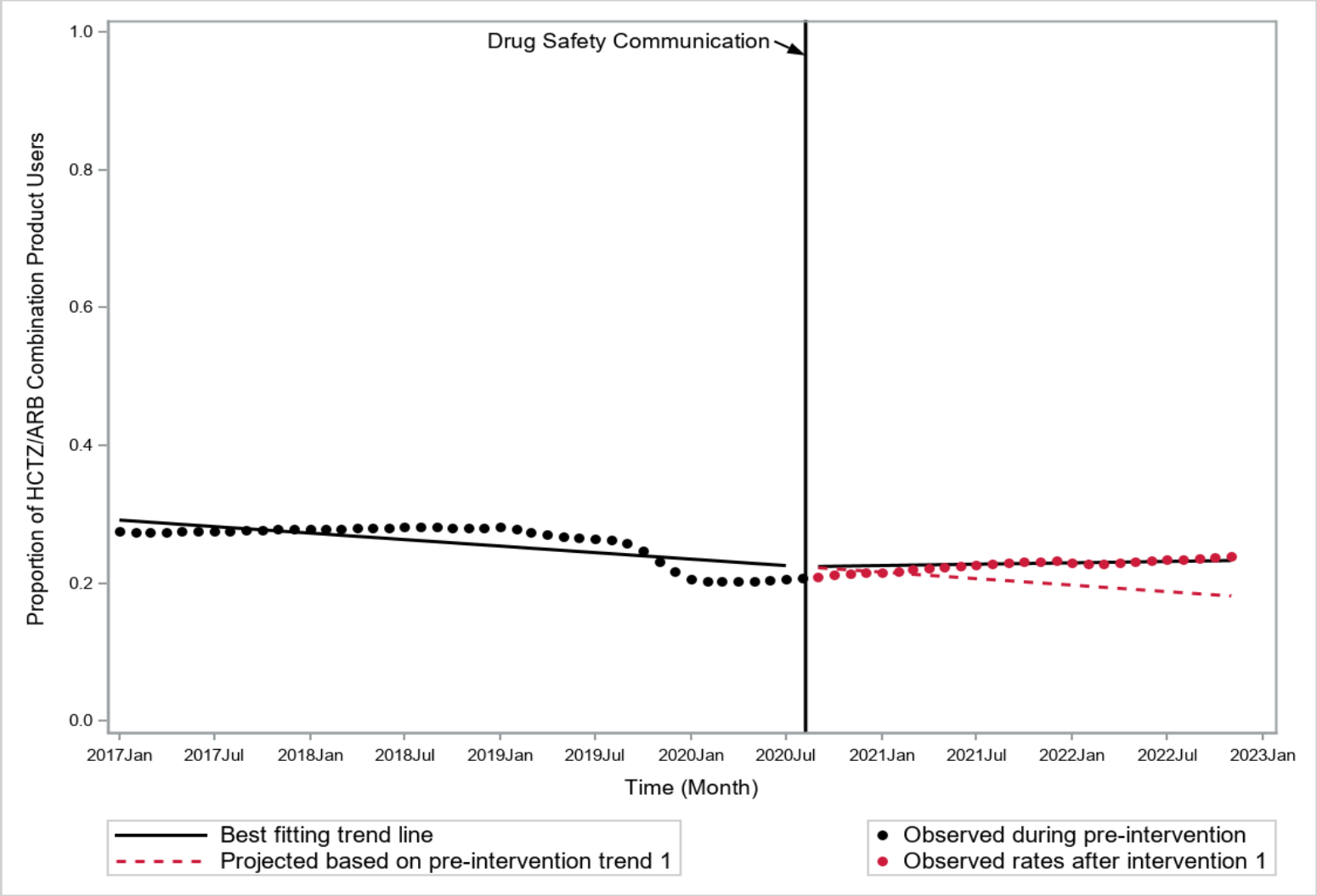
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 2. Proportion of HCTZ/ARB/CCB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



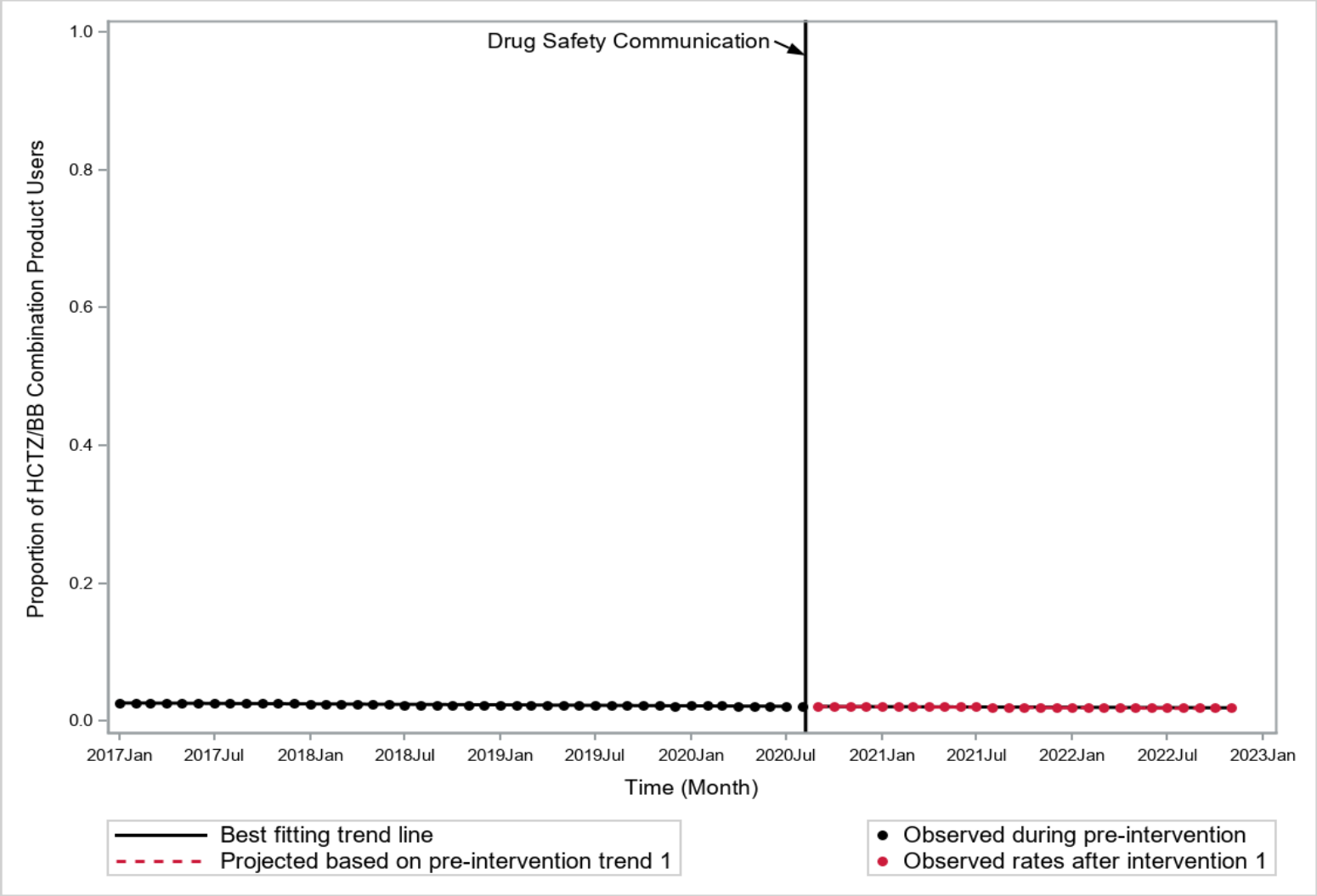
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 3. Proportion of HCTZ/ARB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



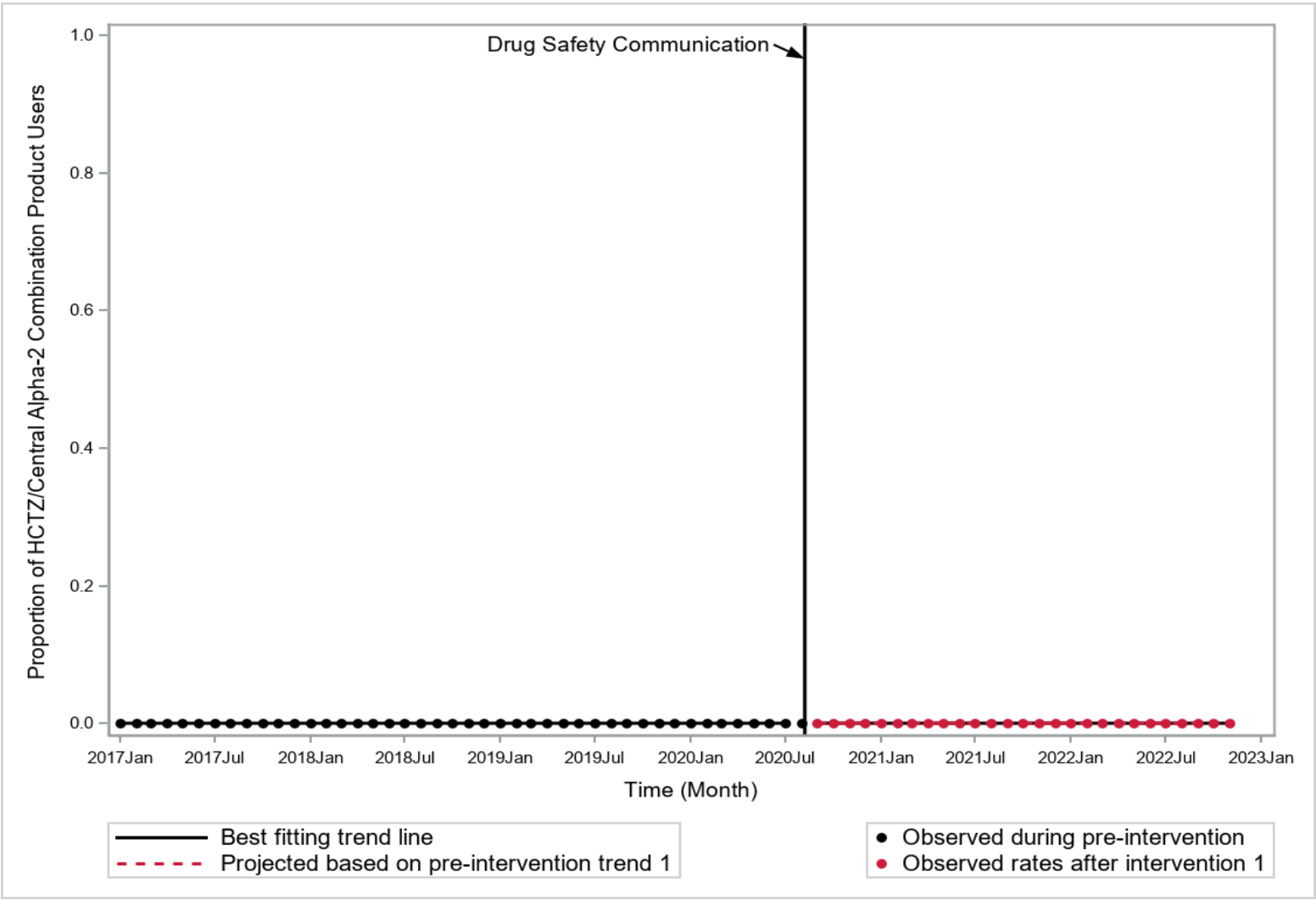
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 4. Proportion of HCTZ/BB Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



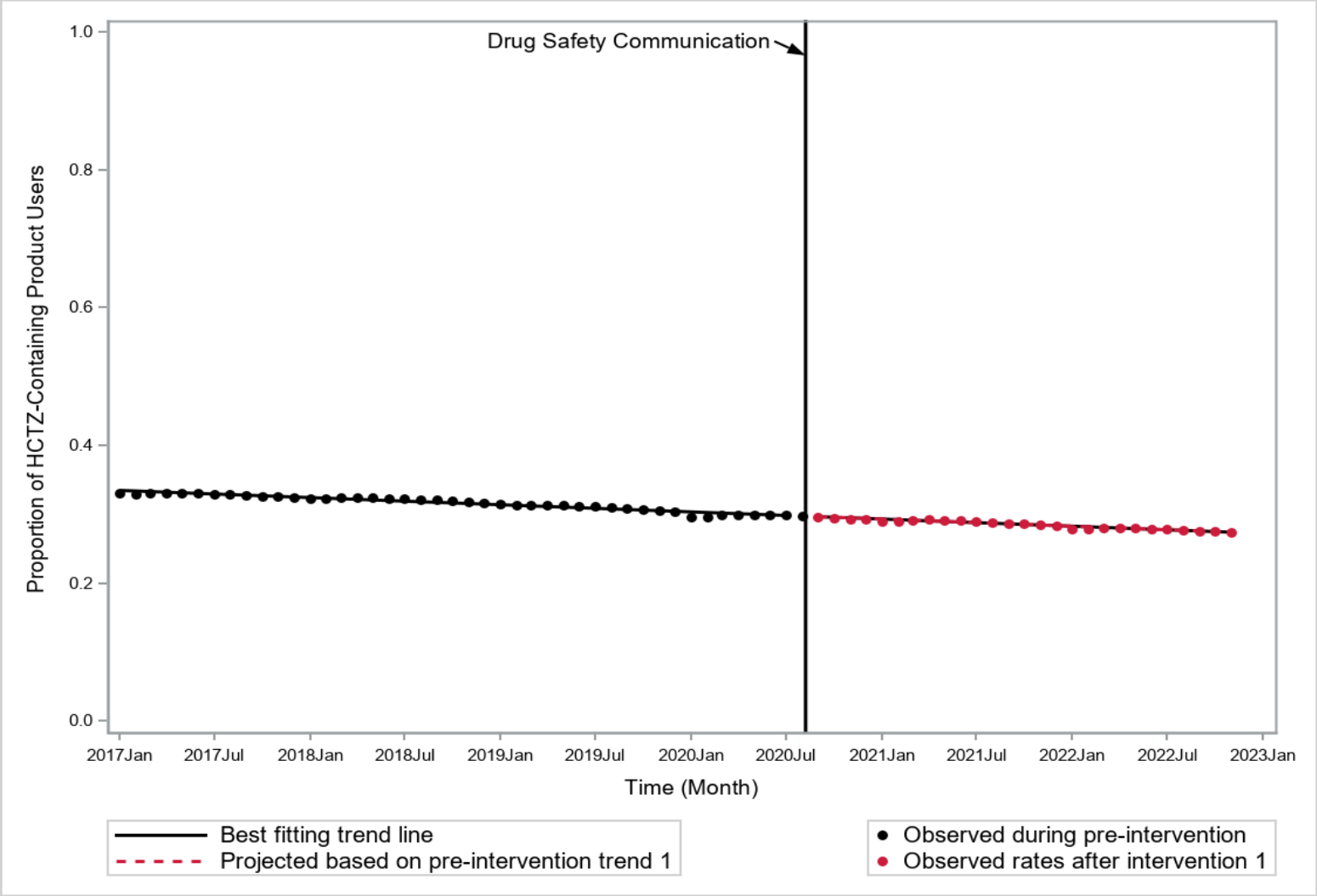
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 5. Proportion of HCTZ/Central Alpha-2 Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



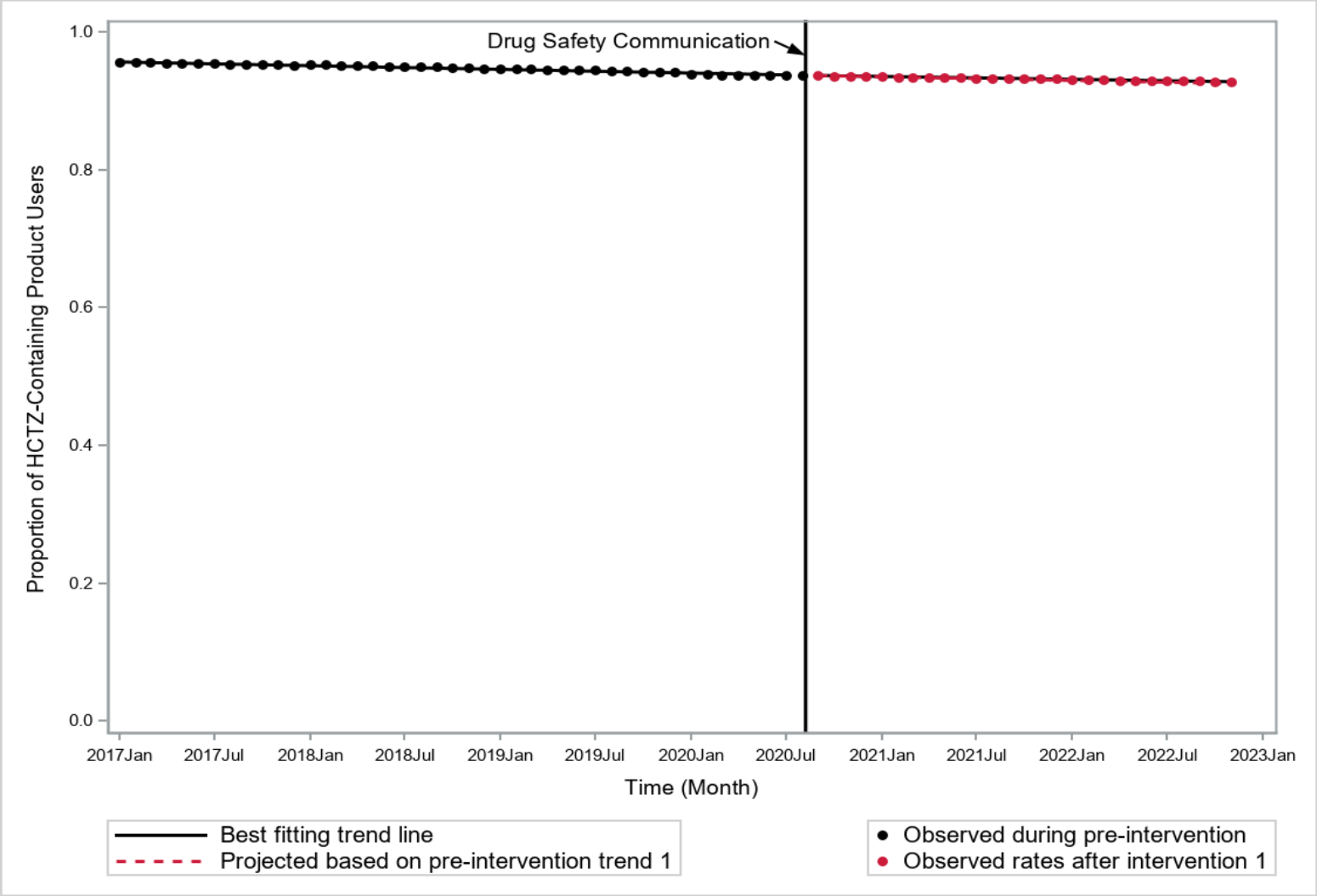
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 6. Proportion of HCTZ-Containing Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



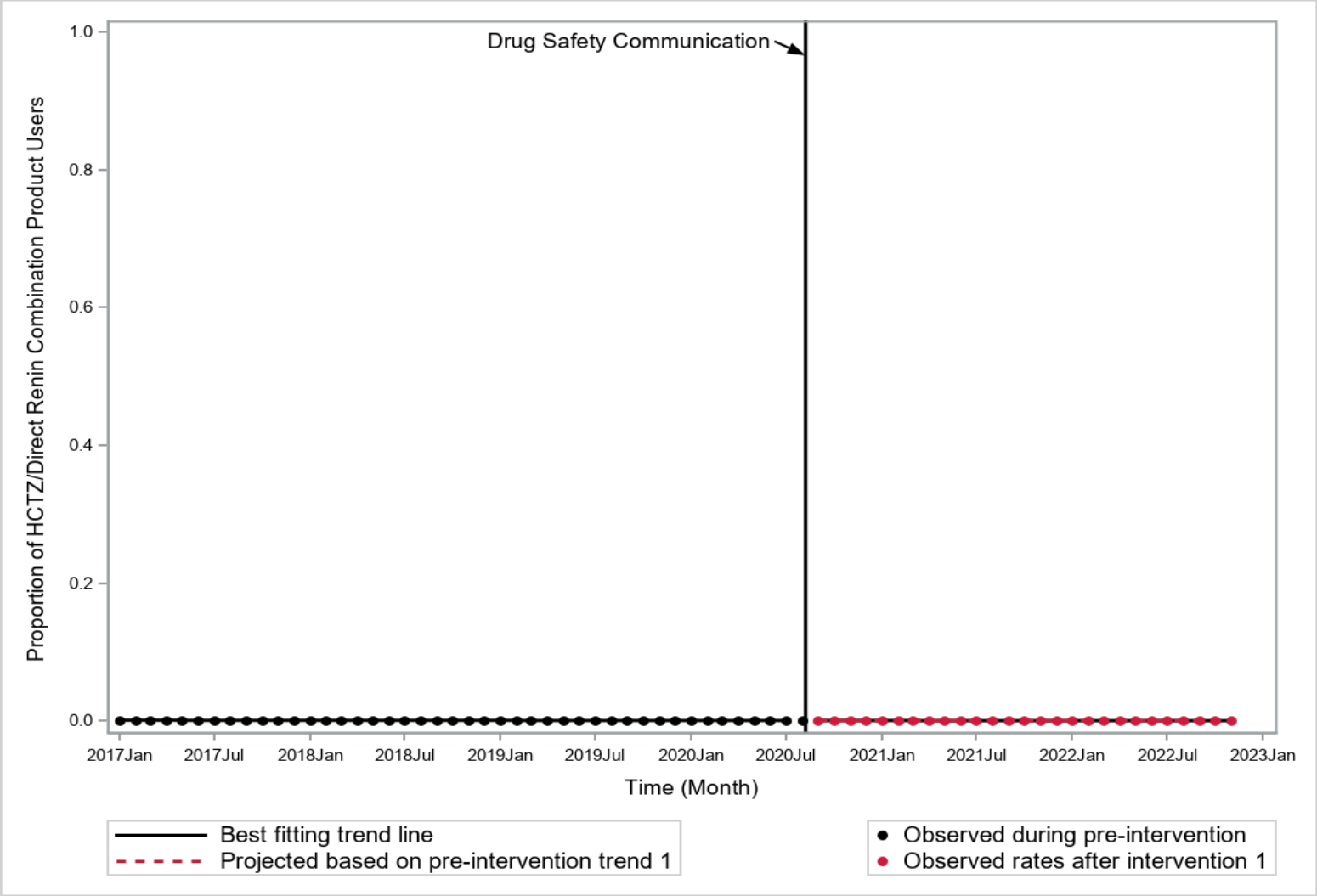
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 7. Proportion of HCTZ-Containing Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



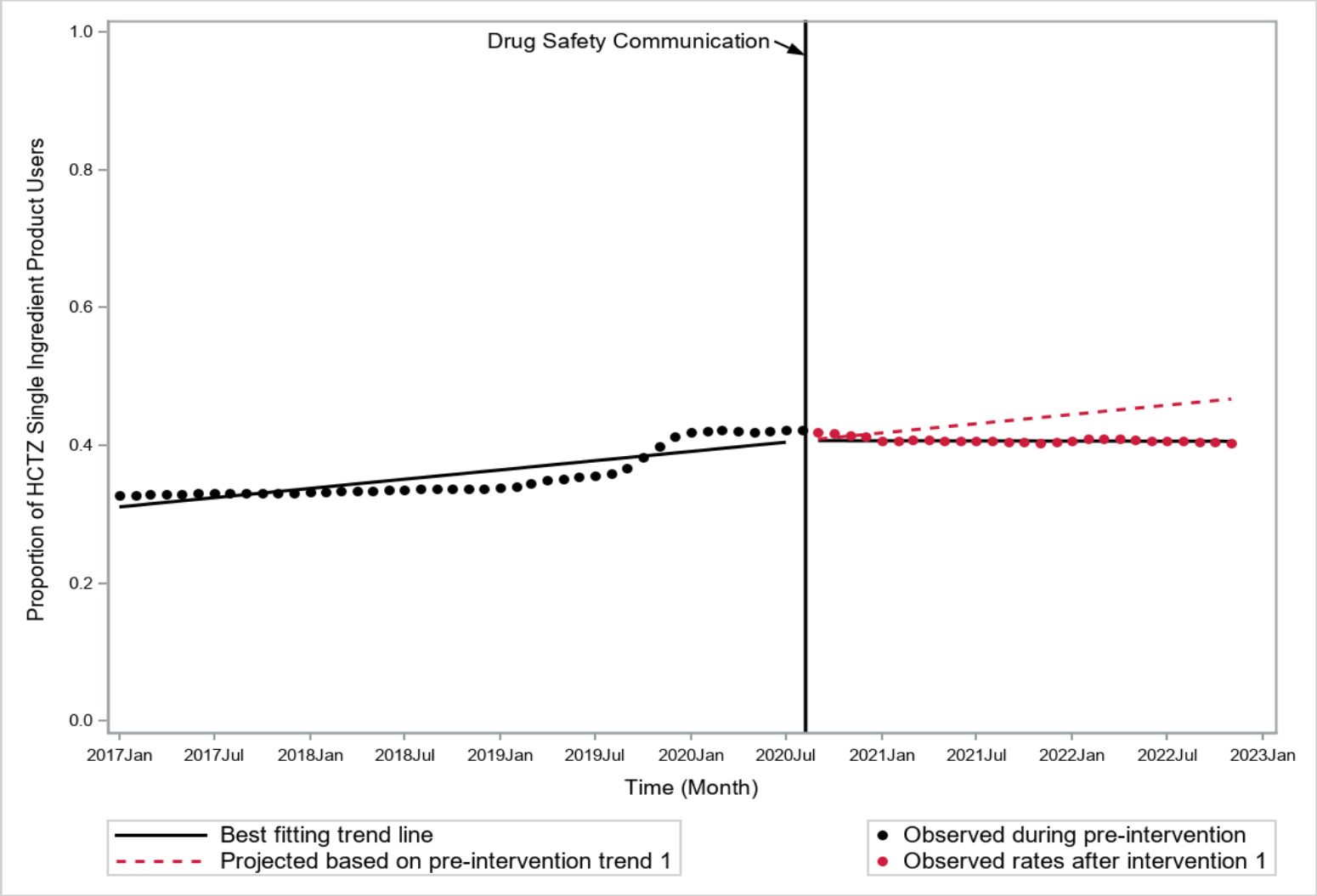
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 8. Proportion of HCTZ/Direct Renin Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



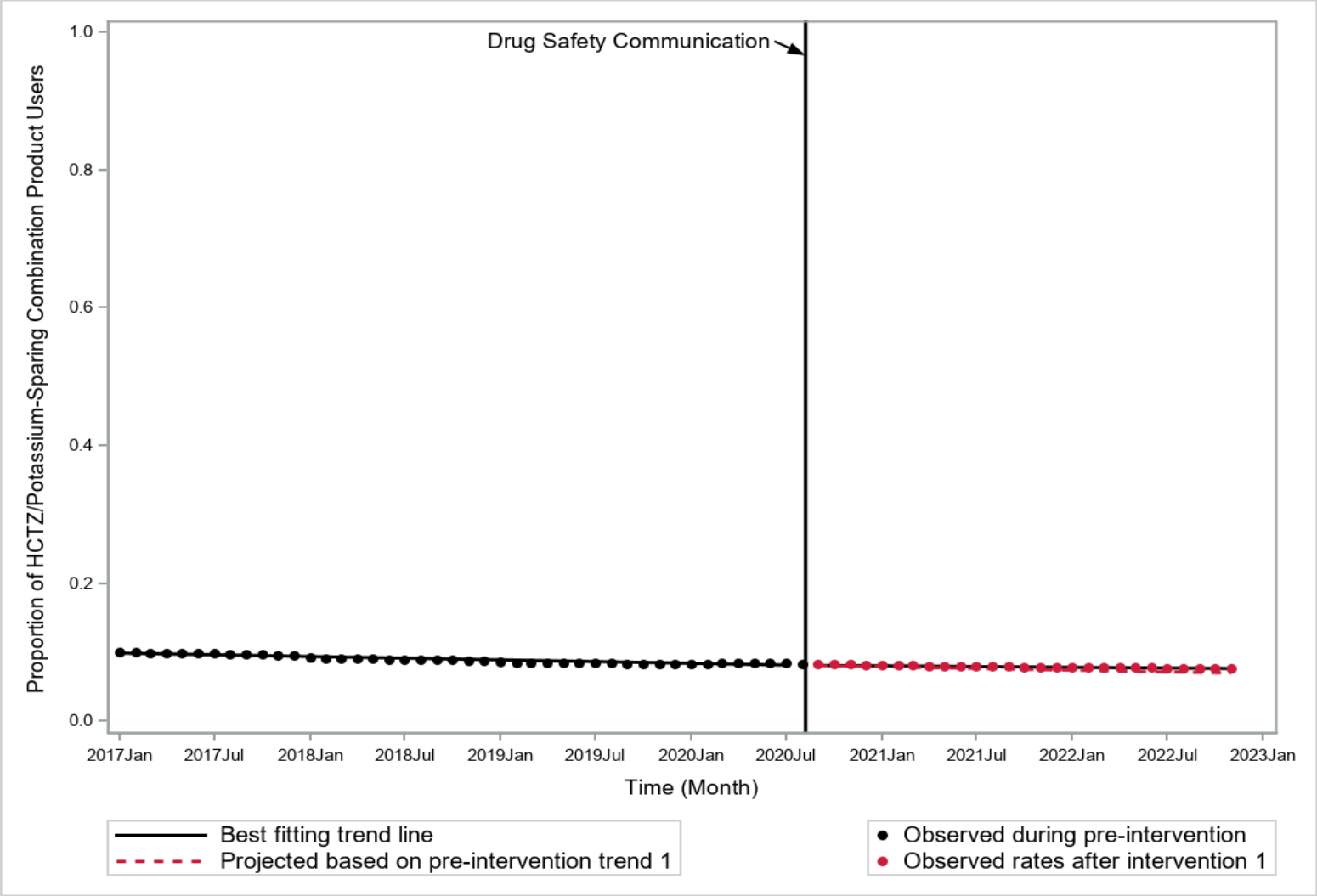
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 9. Proportion of HCTZ Single Ingredient Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



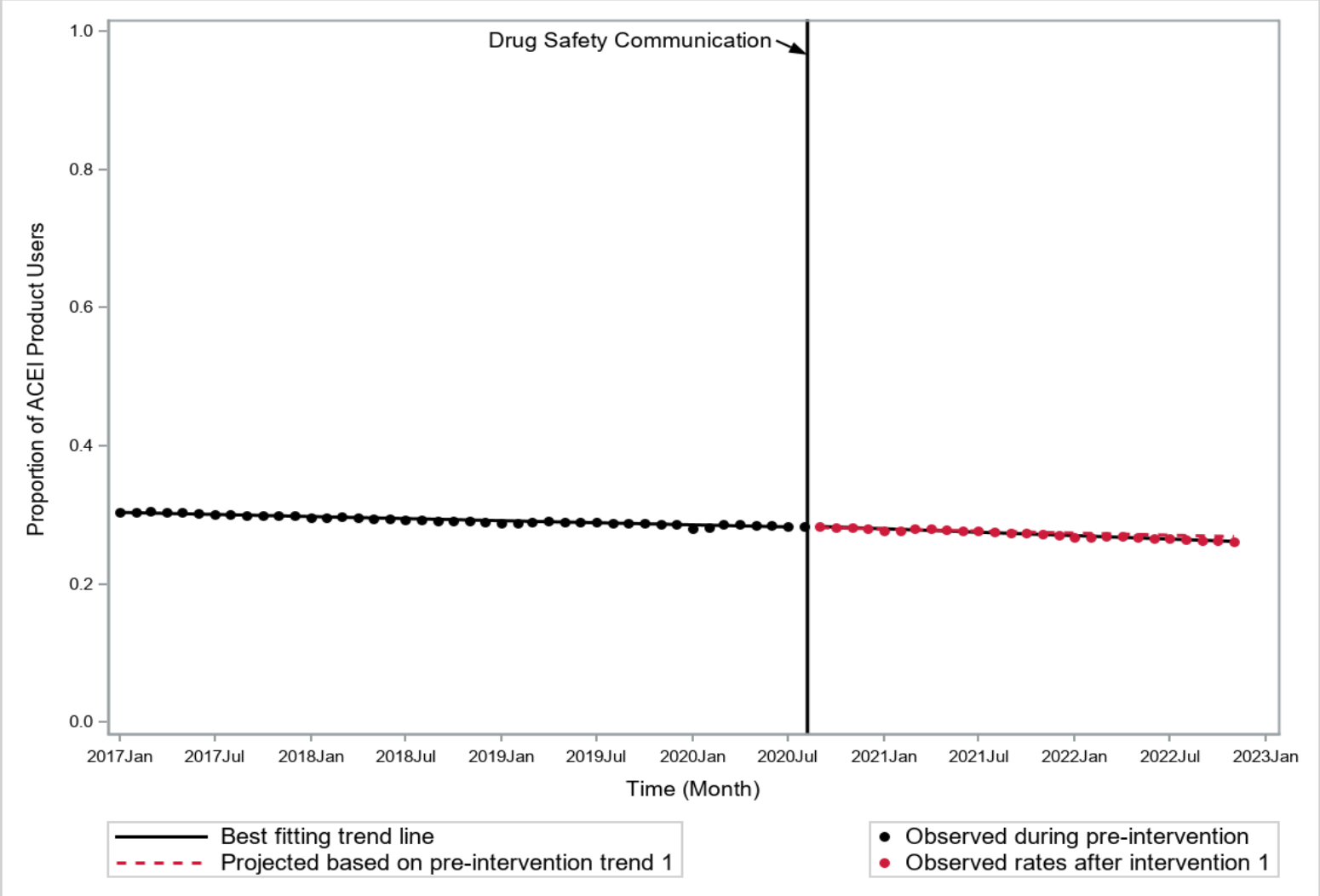
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 10. Proportion of HCTZ/Potassium-Sparing Combination Product Users Among Number of patients with use of HCTZ-containing products or thiazide-like diuretics Before and After August 8, 2020[1]



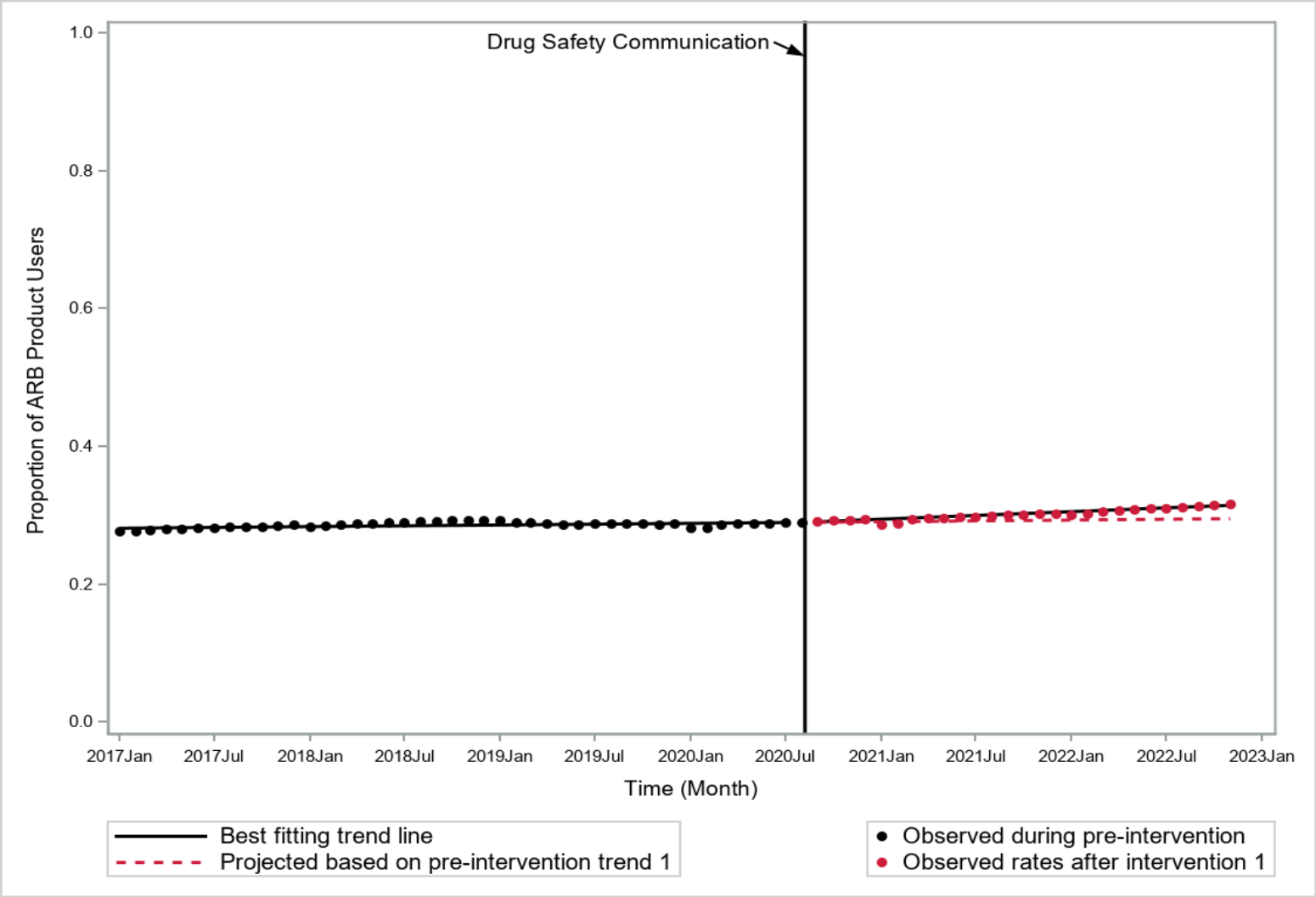
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 11. Proportion of ACEI Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



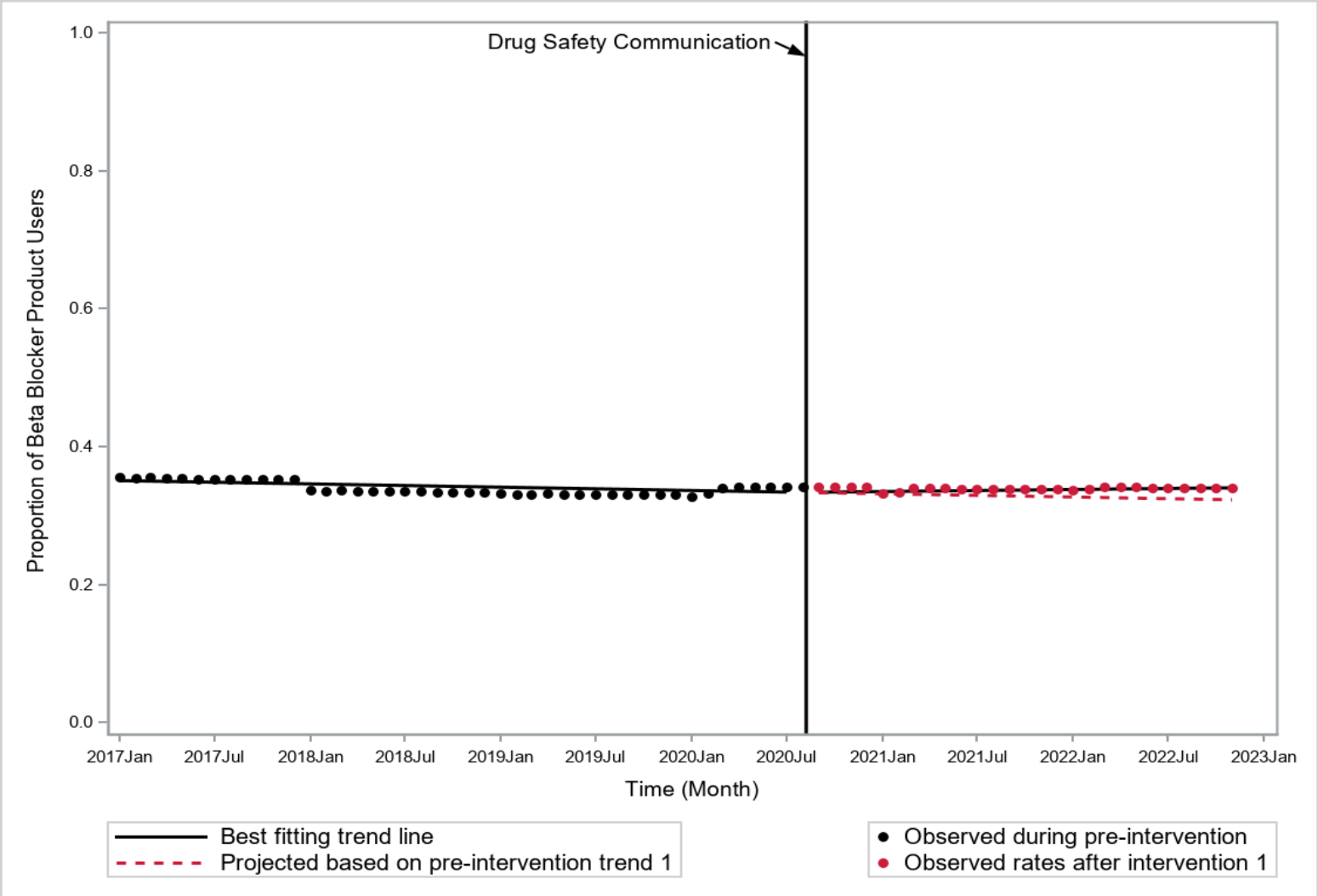
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 12. Proportion of ARB Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



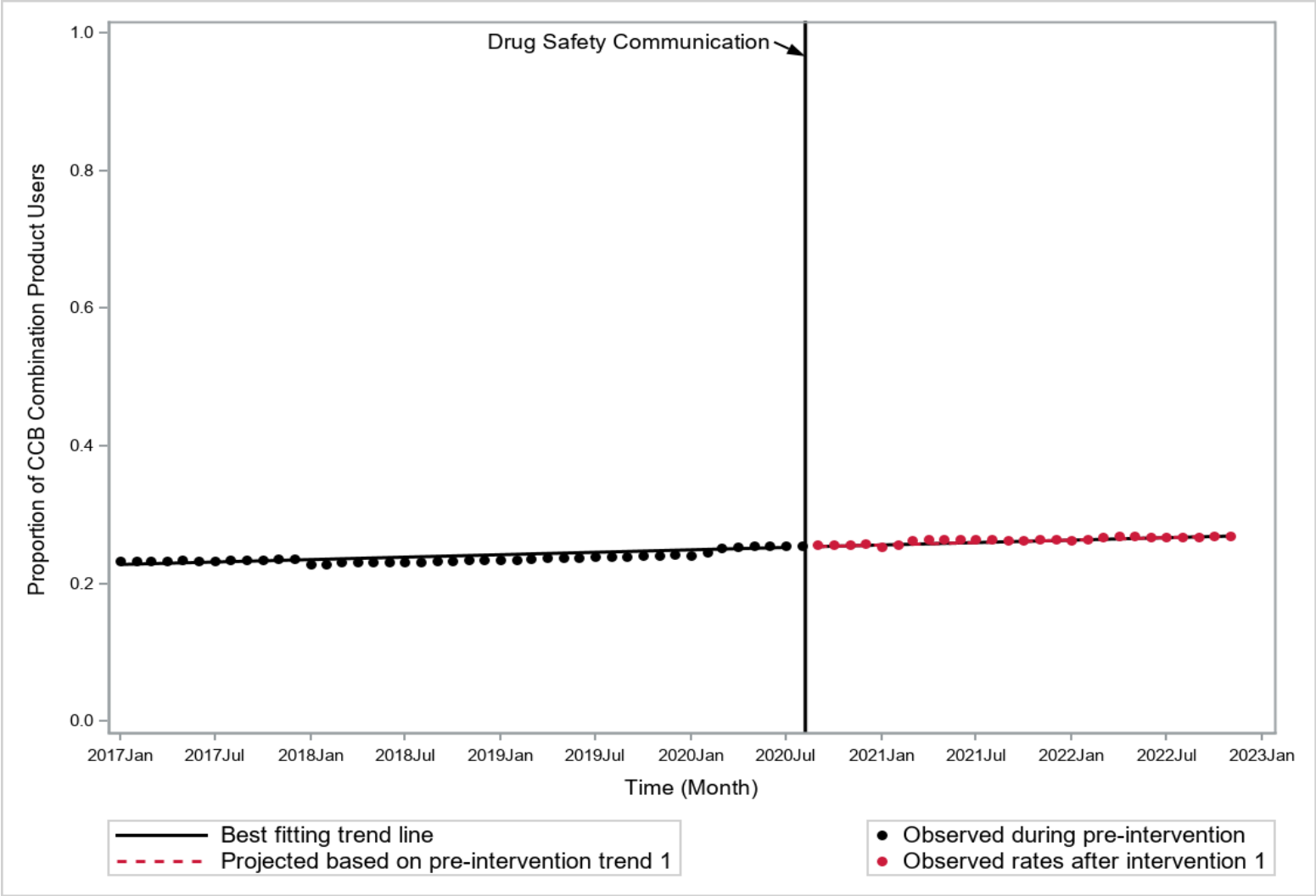
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 13. Proportion of Beta Blocker Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



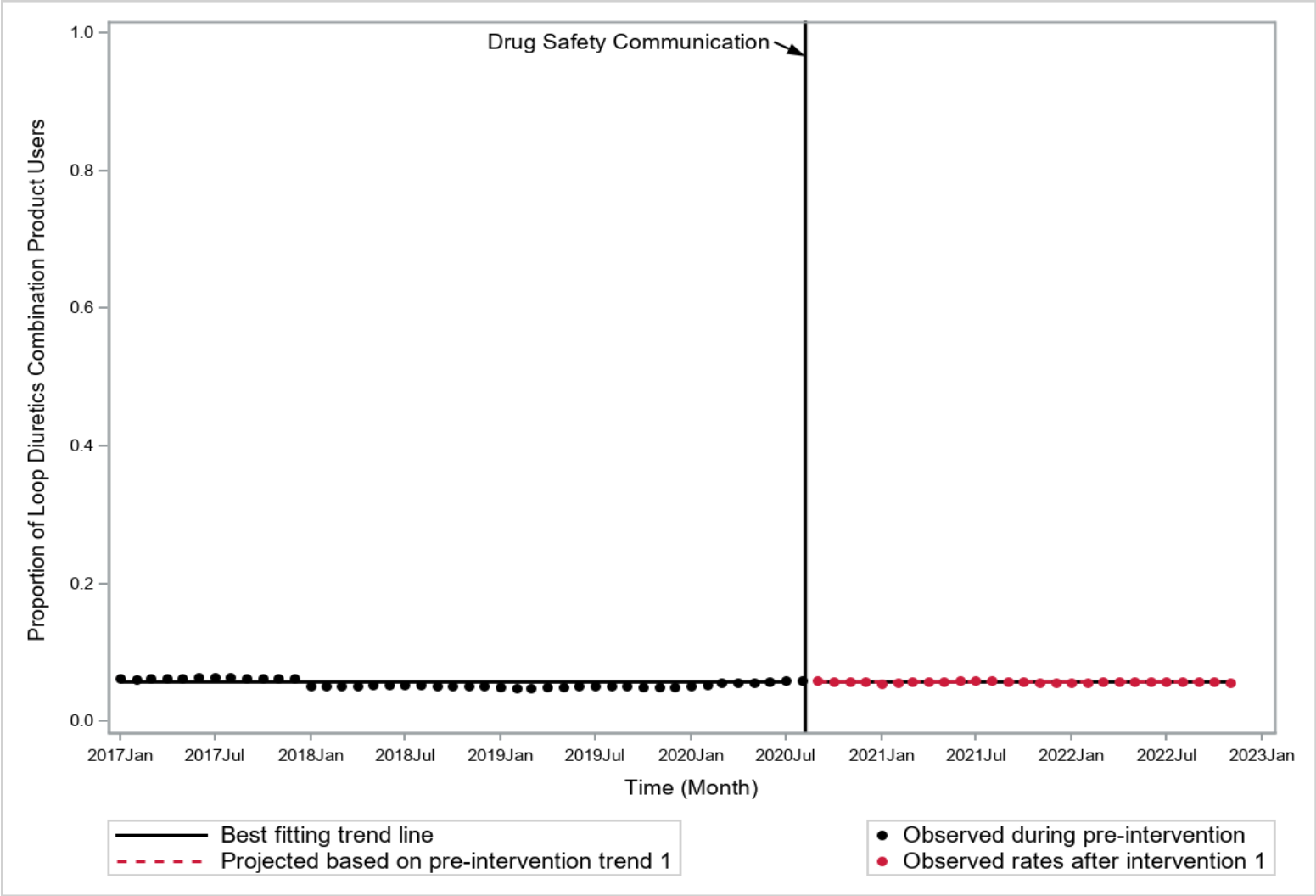
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 14. Proportion of CCB Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



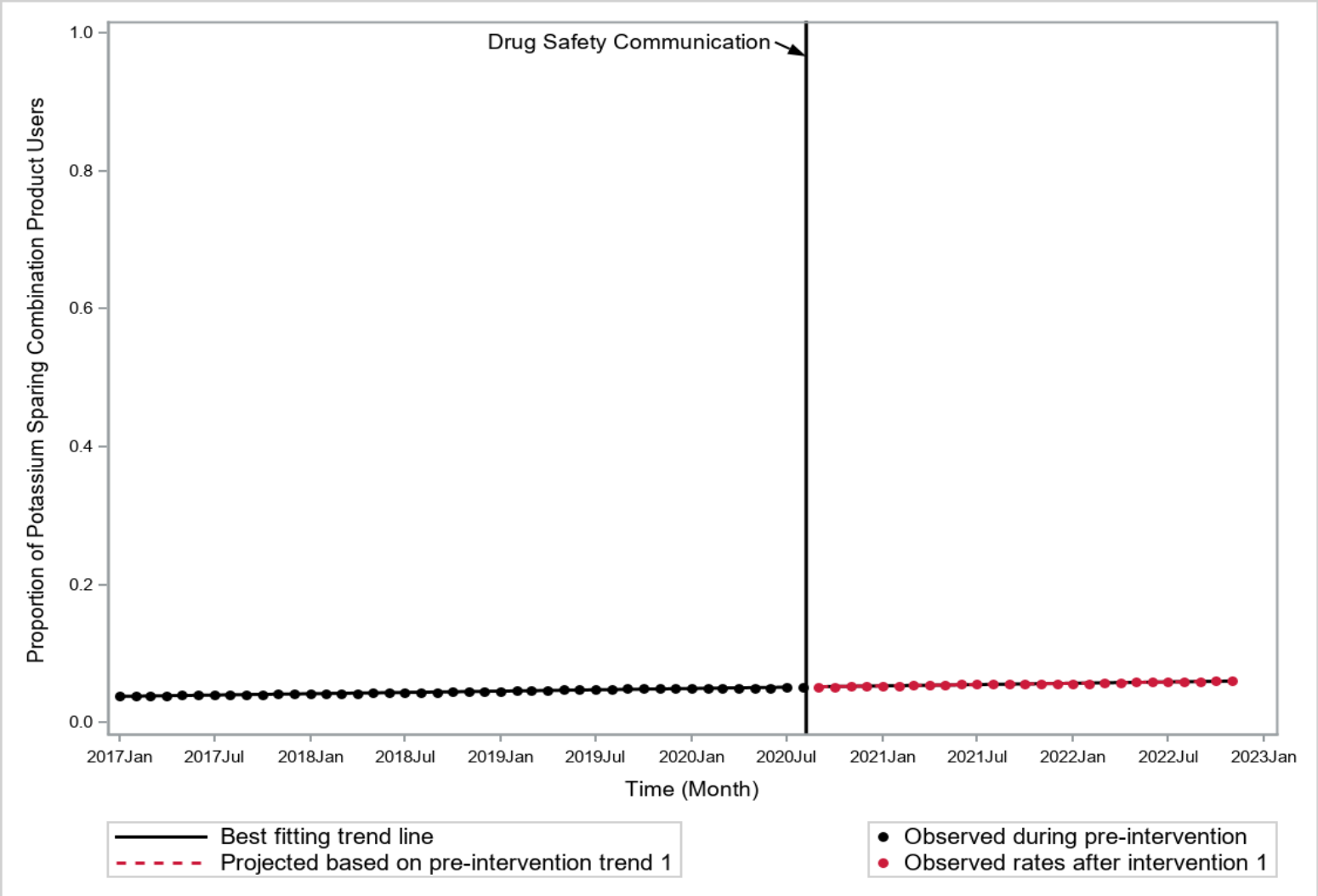
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 15. Proportion of Loop Diuretics Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



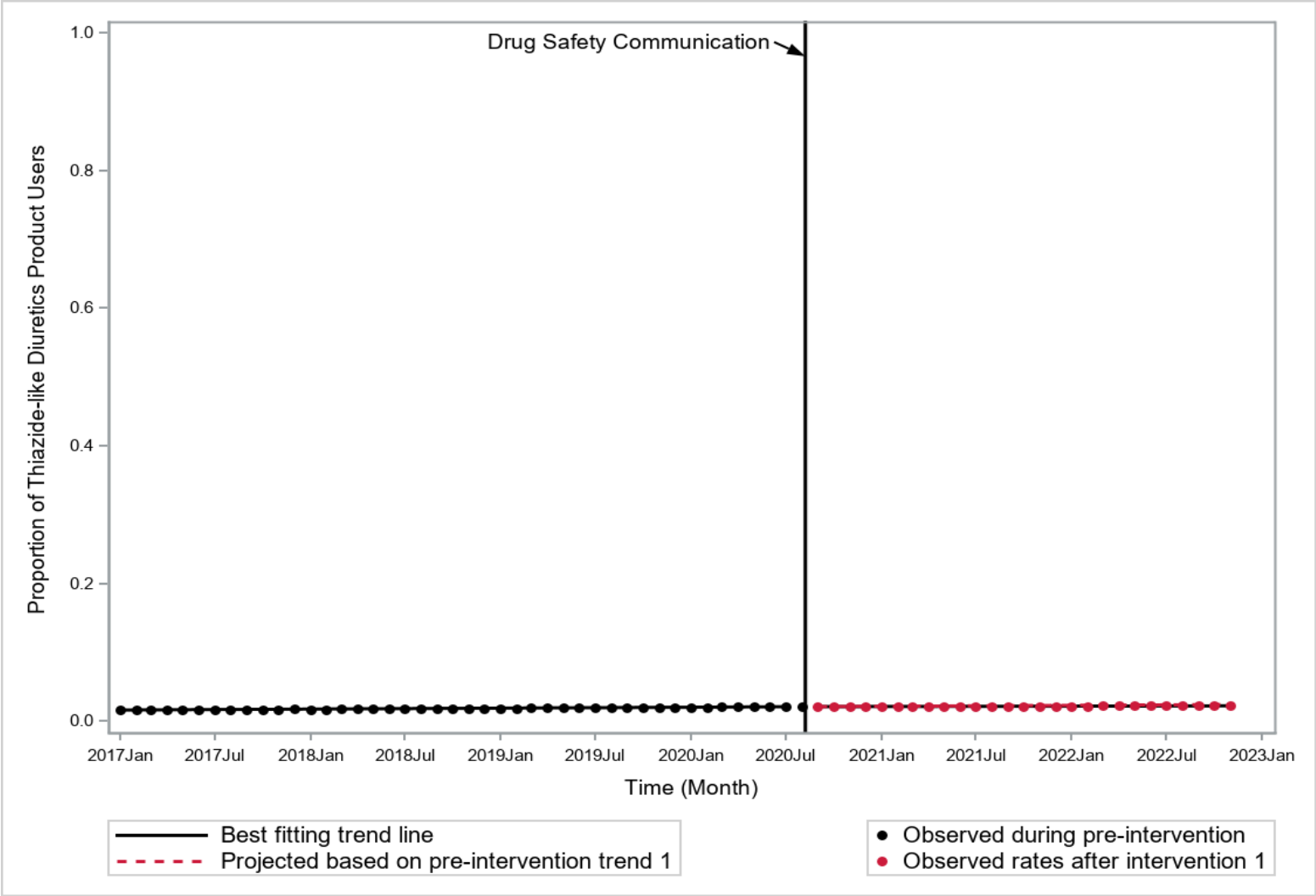
[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 16. Proportion of Potassium Sparing Combination Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Figure 17. Proportion of Thiazide-like Diuretics Product Users Among Number of patients with use of HCTZ-containing products or any diuretics or any antihypertensives Before and After August 8, 2020[1]



[1]The ITS model is performed with rounding to the nearest subsequent month for August 8, 2020 as the start of Drug Safety Communication. Data from January 1, 2017 to November 30, 2022 is used to create the model.

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
HCTZ single ingredient/monotherapy	
hydrochlorothiazide	hydrochlorothiazide
hydrochlorothiazide	Microzide
HCTZ combination products	
benazepril HCl/hydrochlorothiazide	benazepril-hydrochlorothiazide
benazepril HCl/hydrochlorothiazide	Lotensin HCT
captopril/hydrochlorothiazide	captopril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	enalapril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	Vaseretic
fosinopril sodium/hydrochlorothiazide	fosinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	lisinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	Zestoretic
moexipril HCl/hydrochlorothiazide	moexipril-hydrochlorothiazide
quinapril HCl/hydrochlorothiazide	Accuretic
quinapril HCl/hydrochlorothiazide	quinapril-hydrochlorothiazide
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	Ziac
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid
methyldopa/hydrochlorothiazide	methyldopa-hydrochlorothiazide
aliskiren hemifumarate/hydrochlorothiazide	Tekturna HCT

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
amiloride HCl/hydrochlorothiazide	amiloride-hydrochlorothiazide
spironolactone/hydrochlorothiazide	Aldactazide
spironolactone/hydrochlorothiazide	spironolacton-hydrochlorothiaz
triamterene/hydrochlorothiazide	Dyazide
triamterene/hydrochlorothiazide	Maxzide
triamterene/hydrochlorothiazide	Maxzide-25mg
triamterene/hydrochlorothiazide	triamterene-hydrochlorothiazid
HCTZ ACE inhibitor combination	
benazepril HCl/hydrochlorothiazide	benazepril-hydrochlorothiazide
benazepril HCl/hydrochlorothiazide	Lotensin HCT
captopril/hydrochlorothiazide	captopril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	enalapril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	Vaseretic
fosinopril sodium/hydrochlorothiazide	fosinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	lisinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	Zestoretic
moexipril HCl/hydrochlorothiazide	moexipril-hydrochlorothiazide
quinapril HCl/hydrochlorothiazide	Accuretic
quinapril HCl/hydrochlorothiazide	quinapril-hydrochlorothiazide
HCTZ ARB combination	
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
HCTZ potassium sparing diuretics combination	
amiloride HCl/hydrochlorothiazide	amiloride-hydrochlorothiazide
spironolactone/hydrochlorothiazide	Aldactazide
spironolactone/hydrochlorothiazide	spironolacton-hydrochlorothiaz
triamterene/hydrochlorothiazide	Dyazide
triamterene/hydrochlorothiazide	Maxzide
triamterene/hydrochlorothiazide	Maxzide-25mg
triamterene/hydrochlorothiazide	triamterene-hydrochlorothiazid

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
HCTZ beta blocker combination	
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	Ziac
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid
HCTZ ARB calcium channel blocker combination	
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
Chlorothiazide, Bendroflumethiazide, or Thiazide-like diuretics	
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
chlorothiazide	chlorothiazide
chlorothiazide	Diuril
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
Chlorothiazide	
chlorothiazide	chlorothiazide
chlorothiazide	Diuril
Bendroflumethiazide	
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
Thiazide-like diuretics	
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
ACE inhibitors	
amlodipine besylate/benazepril HCl	amlodipine-benazepril
amlodipine besylate/benazepril HCl	Lotrel
benazepril HCl	benazepril
benazepril HCl	Lotensin
captopril	captopril

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
enalapril maleate	enalapril maleate
enalapril maleate	Epaned
enalapril maleate	Vasotec
fosinopril sodium	fosinopril
lisinopril	lisinopril
lisinopril	Prinivil
lisinopril	Qbrelis
lisinopril	Zestril
moexipril HCl	moexipril
perindopril arginine/amlodipine besylate	Prestalia
perindopril erbumine	Aceon
perindopril erbumine	perindopril erbumine
quinapril HCl	Accupril
quinapril HCl	quinapril
ramipril	Altace
ramipril	ramipril
trandolapril	Mavik
trandolapril	trandolapril
trandolapril/verapamil HCl	Tarka
trandolapril/verapamil HCl	trandolapril-verapamil
Calcium channel blockers	
amlodipine benzoate	Katerzia
amlodipine besylate	amlodipine
amlodipine besylate	Norliqva
amlodipine besylate	Norvasc
amlodipine besylate/celecoxib	Consensi
diltiazem HCl	Cardizem
diltiazem HCl	Cardizem CD
diltiazem HCl	Cardizem LA
diltiazem HCl	Cartia XT
diltiazem HCl	diltiazem HCl
diltiazem HCl	DILT-XR
diltiazem HCl	Matzim LA
diltiazem HCl	Taztia XT
diltiazem HCl	Tiadylt ER
diltiazem HCl	Tiazac
felodipine	felodipine
isradipine	isradipine
levamlodipine maleate	Conjupri
levamlodipine maleate	levamlodipine
nicardipine HCl	nicardipine
nifedipine	Adalat CC

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
nifedipine	Afeditab CR
nifedipine	Nifedical XL
nifedipine	nifedipine
nifedipine	Procardia
nifedipine	Procardia XL
nimodipine	nimodipine
nimodipine	Nymalize
nisoldipine	nisoldipine
nisoldipine	Sular
verapamil HCl	Calan
verapamil HCl	Calan SR
verapamil HCl	verapamil
verapamil HCl	Verelan
verapamil HCl	Verelan PM
Potassium-sparing diuretics	
amiloride HCl	amiloride
eplerenone	eplerenone
eplerenone	Inspra
spironolactone	Aldactone
spironolactone	CaroSpir
spironolactone	spironolactone
triamterene	Dyrenium
triamterene	triamterene
Loop diuretics	
bumetanide	bumetanide
ethacrynic acid	Edecrin
ethacrynic acid	ethacrynic acid
furosemide	furosemide
furosemide	Lasix
torsemide	Demadex
torsemide	Soaanz
torsemide	torsemide
Limited denominator (any HCTZ-containing product, chlorothiazide, bendroflumethiazide or thiazide-like diuretics)	
aliskiren hemifumarate/hydrochlorothiazide	Tekturna HCT
amiloride HCl/hydrochlorothiazide	amiloride-hydrochlorothiazide
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
benazepril HCl/hydrochlorothiazide	benazepril-hydrochlorothiazide

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
benazepril HCl/hydrochlorothiazide	Lotensin HCT
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	Ziac
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
captopril/hydrochlorothiazide	captopril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	enalapril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	Vaseretic
fosinopril sodium/hydrochlorothiazide	fosinopril-hydrochlorothiazide
hydrochlorothiazide	hydrochlorothiazide
hydrochlorothiazide	Microzide
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
lisinopril/hydrochlorothiazide	lisinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	Zestoretic
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
methyldopa/hydrochlorothiazide	methyldopa-hydrochlorothiazide
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
moexipril HCl/hydrochlorothiazide	moexipril-hydrochlorothiazide
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid
quinapril HCl/hydrochlorothiazide	Accuretic
quinapril HCl/hydrochlorothiazide	quinapril-hydrochlorothiazide
spironolactone/hydrochlorothiazide	Aldactazide
spironolactone/hydrochlorothiazide	spironolacton-hydrochlorothiaz
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
triamterene/hydrochlorothiazide	Dyazide
triamterene/hydrochlorothiazide	Maxzide
triamterene/hydrochlorothiazide	Maxzide-25mg
triamterene/hydrochlorothiazide	triamterene-hydrochlorothiazid
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
chlorothiazide	chlorothiazide

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
chlorothiazide	Diuril
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
Full denominator (any HCTZ-containing products, any thiazide diuretics, any diuretics or any antihypertensives)	
aliskiren hemifumarate/hydrochlorothiazide	Tekturna HCT
amiloride HCl/hydrochlorothiazide	amiloride-hydrochlorothiazide
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
benazepril HCl/hydrochlorothiazide	benazepril-hydrochlorothiazide
benazepril HCl/hydrochlorothiazide	Lotensin HCT
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	Ziac
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
captopril/hydrochlorothiazide	captopril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	enalapril-hydrochlorothiazide
enalapril maleate/hydrochlorothiazide	Vaseretic
fosinopril sodium/hydrochlorothiazide	fosinopril-hydrochlorothiazide
hydrochlorothiazide	hydrochlorothiazide
hydrochlorothiazide	Microzide
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
lisinopril/hydrochlorothiazide	lisinopril-hydrochlorothiazide
lisinopril/hydrochlorothiazide	Zestoretic
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
methyldopa/hydrochlorothiazide	methyldopa-hydrochlorothiazide
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
moexipril HCl/hydrochlorothiazide	moexipril-hydrochlorothiazide
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid
quinapril HCl/hydrochlorothiazide	Accuretic
quinapril HCl/hydrochlorothiazide	quinapril-hydrochlorothiazide
spironolactone/hydrochlorothiazide	Aldactazide
spironolactone/hydrochlorothiazide	spironolacton-hydrochlorothiaz
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
triamterene/hydrochlorothiazide	Dyazide
triamterene/hydrochlorothiazide	Maxzide
triamterene/hydrochlorothiazide	Maxzide-25mg
triamterene/hydrochlorothiazide	triamterene-hydrochlorothiazid
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
chlorothiazide	chlorothiazide
chlorothiazide	Diuril
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
chlorthalidone	chlorthalidone
chlorthalidone	Thalitone
indapamide	indapamide
metolazone	metolazone
amlodipine besylate/benazepril HCl	amlodipine-benazepril
amlodipine besylate/benazepril HCl	Lotrel
benazepril HCl	benazepril
benazepril HCl	Lotensin
captopril	captopril
enalapril maleate	enalapril maleate
enalapril maleate	Epaned
enalapril maleate	Vasotec
fosinopril sodium	fosinopril
lisinopril	lisinopril
lisinopril	Prinivil
lisinopril	Qbrelis
lisinopril	Zestril
moexipril HCl	moexipril
perindopril arginine/amlodipine besylate	Prestalia
perindopril erbumine	Aceon
perindopril erbumine	perindopril erbumine
quinapril HCl	Accupril
quinapril HCl	quinapril

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
ramipril	Altace
ramipril	ramipril
trandolapril	Mavik
trandolapril	trandolapril
trandolapril/verapamil HCl	Tarka
trandolapril/verapamil HCl	trandolapril-verapamil
amlodipine benzoate	Katerzia
amlodipine besylate	amlodipine
amlodipine besylate	Norliqva
amlodipine besylate	Norvasc
amlodipine besylate/celecoxib	Consensi
diltiazem HCl	Cardizem
diltiazem HCl	Cardizem CD
diltiazem HCl	Cardizem LA
diltiazem HCl	Cartia XT
diltiazem HCl	diltiazem HCl
diltiazem HCl	DILT-XR
diltiazem HCl	Matzim LA
diltiazem HCl	Taztia XT
diltiazem HCl	Tiadylt ER
diltiazem HCl	Tiazac
felodipine	felodipine
isradipine	isradipine
levamlodipine maleate	Conjupri
levamlodipine maleate	levamlodipine
nicardipine HCl	nicardipine
nifedipine	Adalat CC
nifedipine	Afeditab CR
nifedipine	Nifedical XL
nifedipine	nifedipine
nifedipine	Procardia
nifedipine	Procardia XL
nimodipine	nimodipine
nimodipine	Nymalize
nisoldipine	nisoldipine
nisoldipine	Sular
verapamil HCl	Calan
verapamil HCl	Calan SR
verapamil HCl	verapamil
verapamil HCl	Verelan
verapamil HCl	Verelan PM
amiloride HCl	amiloride

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
eplerenone	eplerenone
eplerenone	Inspra
spironolactone	Aldactone
spironolactone	CaroSpir
spironolactone	spironolactone
triamterene	Dyrenium
triamterene	triamterene
bumetanide	bumetanide
ethacrynic acid	Edecrin
ethacrynic acid	ethacrynic acid
furosemide	furosemide
furosemide	Lasix
torsemide	Demadex
torsemide	Soaanz
torsemide	torsemide
	ARB Generics
amlodipine besylate/olmesartan medoxomil	amlodipine-olmesartan
amlodipine besylate/olmesartan medoxomil	amlodipine-olmesartan
amlodipine besylate/olmesartan medoxomil	amlodipine-olmesartan
amlodipine besylate/olmesartan medoxomil	amlodipine-olmesartan
amlodipine besylate/olmesartan medoxomil	Azor
amlodipine besylate/olmesartan medoxomil	Azor
amlodipine besylate/olmesartan medoxomil	Azor
amlodipine besylate/olmesartan medoxomil	Azor
amlodipine besylate/valsartan	amlodipine-valsartan
amlodipine besylate/valsartan	amlodipine-valsartan
amlodipine besylate/valsartan	amlodipine-valsartan
amlodipine besylate/valsartan	amlodipine-valsartan
amlodipine besylate/valsartan	Exforge
amlodipine besylate/valsartan	Exforge
amlodipine besylate/valsartan	Exforge
amlodipine besylate/valsartan	Exforge
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	amlodipine-valsartan-hcthiazid
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT
amlodipine besylate/valsartan/hydrochlorothiazide	Exforge HCT

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
azilsartan medoxomil	Edarbi
azilsartan medoxomil	Edarbi
azilsartan medoxomil/chlorthalidone	Edarbyclor
azilsartan medoxomil/chlorthalidone	Edarbyclor
candesartan cilexetil	Atacand
candesartan cilexetil	Atacand
candesartan cilexetil	Atacand
candesartan cilexetil	Atacand
candesartan cilexetil	candesartan
candesartan cilexetil	candesartan
candesartan cilexetil	candesartan
candesartan cilexetil	candesartan
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	Atacand HCT
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
candesartan cilexetil/hydrochlorothiazide	candesartan-hydrochlorothiazid
eprosartan mesylate	eprosartan
irbesartan	Avapro
irbesartan	Avapro
irbesartan	Avapro
irbesartan	irbesartan
irbesartan	irbesartan
irbesartan	irbesartan
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	Avalide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
irbesartan/hydrochlorothiazide	irbesartan-hydrochlorothiazide
losartan potassium	Cozaar
losartan potassium	Cozaar
losartan potassium	Cozaar
losartan potassium	losartan
losartan potassium	losartan
losartan potassium	losartan
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	Hyzaar
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
losartan potassium/hydrochlorothiazide	losartan-hydrochlorothiazide
nebivolol HCl/valsartan	Byvalson

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
olmesartan medoxomil	Benicar
olmesartan medoxomil	Benicar
olmesartan medoxomil	Benicar
olmesartan medoxomil	olmesartan
olmesartan medoxomil	olmesartan
olmesartan medoxomil	olmesartan
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	olmesartan-amlodipin-hcthiazid
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/amlodipine besylate/hydrochlorothiazide	Tribenzor
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	Benicar HCT
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
olmesartan medoxomil/hydrochlorothiazide	olmesartan-hydrochlorothiazide
sacubitril/valsartan	Entresto
sacubitril/valsartan	Entresto
sacubitril/valsartan	Entresto
telmisartan	Micardis
telmisartan	Micardis
telmisartan	Micardis
telmisartan	telmisartan
telmisartan	telmisartan
telmisartan	telmisartan
telmisartan/amlodipine besylate	telmisartan-amlodipine

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
telmisartan/amlodipine besylate	telmisartan-amlodipine
telmisartan/amlodipine besylate	telmisartan-amlodipine
telmisartan/amlodipine besylate	telmisartan-amlodipine
telmisartan/amlodipine besylate	Twynsta
telmisartan/amlodipine besylate	Twynsta
telmisartan/amlodipine besylate	Twynsta
telmisartan/amlodipine besylate	Twynsta
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	Micardis HCT
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
telmisartan/hydrochlorothiazide	telmisartan-hydrochlorothiazid
valsartan	Diovan
valsartan	Diovan
valsartan	Diovan
valsartan	Diovan
valsartan	valsartan
valsartan	valsartan
valsartan	valsartan
valsartan	valsartan
valsartan	valsartan
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	Diovan HCT
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
valsartan/hydrochlorothiazide	valsartan-hydrochlorothiazide
Beta Blockers Generic	
acebutolol HCl	acebutolol
acebutolol HCl	acebutolol
acebutolol HCl	Sectral
acebutolol HCl	Sectral
atenolol	atenolol
atenolol	atenolol
atenolol	atenolol
atenolol	Tenormin
atenolol	Tenormin

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
atenolol	Tenormin
atenolol/chlorthalidone	atenolol-chlorthalidone
atenolol/chlorthalidone	atenolol-chlorthalidone
atenolol/chlorthalidone	Tenoretic 100
atenolol/chlorthalidone	Tenoretic 50
betaxolol HCl	betaxolol
betaxolol HCl	betaxolol
bisoprolol fumarate	bisoprolol fumarate
bisoprolol fumarate	bisoprolol fumarate
bisoprolol fumarate	Zebeta
bisoprolol fumarate	Zebeta
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	bisoprolol-hydrochlorothiazide
bisoprolol fumarate/hydrochlorothiazide	Ziac
bisoprolol fumarate/hydrochlorothiazide	Ziac
bisoprolol fumarate/hydrochlorothiazide	Ziac
carvedilol	carvedilol
carvedilol	carvedilol
carvedilol	carvedilol
carvedilol	carvedilol
carvedilol	Coreg
carvedilol	Coreg
carvedilol	Coreg
carvedilol	Coreg
carvedilol phosphate	carvedilol phosphate
carvedilol phosphate	carvedilol phosphate
carvedilol phosphate	carvedilol phosphate
carvedilol phosphate	carvedilol phosphate
carvedilol phosphate	Coreg CR
carvedilol phosphate	Coreg CR
carvedilol phosphate	Coreg CR
carvedilol phosphate	Coreg CR
esmolol HCl	Brevibloc
esmolol HCl	esmolol
esmolol HCl	esmolol
esmolol HCl in sodium chloride, iso-osmotic	Brevibloc in NaCl (iso-osm)
esmolol HCl in sodium chloride, iso-osmotic	Brevibloc in NaCl (iso-osm)
esmolol HCl in sodium chloride, iso-osmotic	esmolol in NaCl (iso-osm)
esmolol HCl in sodium chloride, iso-osmotic	esmolol in NaCl (iso-osm)
esmolol HCl in sterile water	esmolol in sterile water
esmolol HCl in sterile water	esmolol in sterile water

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl	labetalol
labetalol HCl in dextrose, iso-osmotic	labetalol in dextrose,iso-osm
labetalol HCl in sodium chloride, iso-osmotic	labetalol in NaCl (iso-osmot)
labetalol in dextrose 5 % in water	labetalol in dextrose 5 %
metoprolol succinate	Kapspargo Sprinkle
metoprolol succinate	Kapspargo Sprinkle
metoprolol succinate	Kapspargo Sprinkle
metoprolol succinate	Kapspargo Sprinkle
metoprolol succinate	metoprolol succinate
metoprolol succinate	metoprolol succinate
metoprolol succinate	metoprolol succinate
metoprolol succinate	metoprolol succinate
metoprolol succinate	Toprol XL
metoprolol succinate	Toprol XL
metoprolol succinate	Toprol XL
metoprolol succinate	Toprol XL
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	Dutoprol
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol succinate/hydrochlorothiazide	metoprolol su-hydrochlorothiaz
metoprolol tartrate	Lopressor
metoprolol tartrate	Lopressor
metoprolol tartrate	Lopressor
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate	metoprolol tartrate
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz
metoprolol tartrate/hydrochlorothiazide	metoprolol ta-hydrochlorothiaz

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
nadolol	Corgard
nadolol	Corgard
nadolol	Corgard
nadolol	nadolol
nadolol	nadolol
nadolol	nadolol
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	Corzide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
nadolol/bendroflumethiazide	nadolol-bendroflumethiazide
nebivolol HCl	Bystolic
nebivolol HCl	Bystolic
nebivolol HCl	Bystolic
nebivolol HCl	Bystolic
nebivolol HCl	nebivolol
nebivolol HCl	nebivolol
nebivolol HCl	nebivolol
nebivolol HCl	nebivolol
pindolol	pindolol
pindolol	pindolol
propranolol HCl	Hemangeol
propranolol HCl	Inderal LA
propranolol HCl	Inderal LA
propranolol HCl	Inderal LA
propranolol HCl	Inderal LA
propranolol HCl	Inderal XL
propranolol HCl	Inderal XL
propranolol HCl	InnoPran XL
propranolol HCl	InnoPran XL
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl	propranolol
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid

Appendix B. Generic and Brand Names of Medical Products Used to Define Exposures in this Request

Generic Name	Brand Name
propranolol HCl/hydrochlorothiazide	propranolol-hydrochlorothiazid
sotalol HCl	Betapace
sotalol HCl	Betapace
sotalol HCl	Betapace
sotalol HCl	Betapace
sotalol HCl	Betapace AF
sotalol HCl	Betapace AF
sotalol HCl	Betapace AF
sotalol HCl	Sorine
sotalol HCl	Sorine
sotalol HCl	Sorine
sotalol HCl	Sorine
sotalol HCl	sotalol
sotalol HCl	sotalol
sotalol HCl	sotalol
sotalol HCl	sotalol
sotalol HCl	sotalol
sotalol HCl	Sotalol AF
sotalol HCl	Sotalol AF
sotalol HCl	Sotalol AF
sotalol HCl	Sotylize
timolol maleate	timolol maleate
timolol maleate	timolol maleate
timolol maleate	timolol maleate

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

		Multiple Events Group 1	Multiple Events Group 2
		Numerator: HCTZ-containing products	**Numerator: HCTZ single ingredient/monotherapy**
Multiple Events	**Multiple Events Composition (Primary)**	denom_limited	denom_limited
	Multiple Events Composition (Secondary)	hctz_containing_all	hctz_mono_all
	ITS Denominator	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics
	ITS Numerator	Number of patients with use of any HCTZ-containing product	Number of patients with use of HCTZ single ingredient
	Observation window around primary episode	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
	Secondary episode to use for time metrics	First occurrence of secondary index	First occurrence of secondary index
	Minimum cutoff to be considered adherent	1 adherent episode	1 adherent episode
	Categories for length of primary episode	N/A	N/A
		ITS Analysis 1A	**ITS Analysis 2A**
		Intervention date 8/8/2020	**Intervention date 8/8/2020**
ITS Analysis	**Data range start, end**	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory date period	N/A	N/A
	Intervention date	20/08/08	20/08/08
	Truncation of exposure episode at intervention date?	Yes	Yes
	Interval length	Monthly	Monthly
	p-value	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2
	Time points at which to report difference metrics	All available months between intervention date and data range end	All available months between intervention date and data range end
	Continuous enrollment required?	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

		ITS Analysis 1B	ITS Analysis 2B
		Anticipatory/lag period from 6/1/2020 - 10/1/2020	Anticipatory/lag period from 6/1/2020 - 10/1/2020
ITS Analysis	Data range start, end	1/1/2017 - most recent available data	1/1/2017 - most recent available data
	Anticipatory/lag period	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
	Intervention date	20/08/08	20/08/08
	Truncation of exposure episode at intervention date?	Yes	Yes
	Interval length	Monthly	Monthly
	p-value	0.05	0.05
	Autoregression lag	12 (12 months)	12 (12 months)
	Autoregression model parameter cutoff	0.2	0.2
	Time points at which to report difference metrics	All available months between intervention date and data range end	All available months between intervention date and data range end
	Continuous enrollment required?	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

Multiple Events Group 3	Multiple Events Group 4	Multiple Events Group 5
Numerator: ACEI + HCTZ	**Numerator: ARB + HCTZ**	**Numerator: Potassium-sparing diuretic + HCTZ**
denom_limited	denom_limited	denom_limited
hctz_acei_combo	hctz_arb_combo	hctz_potass_combo
Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics
Number of patients with use of ACEI + HCTZ combo product	Number of patients with use of ARB + HCTZ combo product	Number of patients with use of potassium-sparing diuretic + HCTZ combo product
Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
1 adherent episode	1 adherent episode	1 adherent episode
N/A	N/A	N/A

ITS Analysis 3A	ITS Analysis 4A	ITS Analysis 5A
Intervention date 8/8/2020	**Intervention date 8/8/2020**	**Intervention date 8/8/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
N/A	N/A	N/A
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

ITS Analysis 3B	ITS Analysis 4B	ITS Analysis 5B
Anticipatory/lag period from 6/1/2020 - 10/1/2020	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

Multiple Events Group 6	Multiple Events Group 7	Multiple Events Group 8
Numerator: Beta blocker + HCTZ	**Numerator: ARB + CCB + HCTZ**	**Numerator: Direct renin inhibitor + HCTZ**
denom_limited	denom_limited	denom_limited
hctz_beta_combo	hctz_arb_ccb_combo	hctz_direct
Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics
Number of patients with use of beta blocker + HCTZ combo product	Number of patients with use of ARB + CCB + HCTZ combo product	Number of patients with use of direct renin inhibitor + HCTZ combo product
Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
1 adherent episode	1 adherent episode	1 adherent episode
N/A	N/A	N/A

ITS Analysis 6A	ITS Analysis 7A	ITS Analysis 8A
Intervention date 8/8/2020	**Intervention date 8/8/2020**	**Intervention date 8/8/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
N/A	N/A	N/A
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

ITS Analysis 6B	ITS Analysis 7B	ITS Analysis 8B
Anticipatory/lag period from 6/1/2020 - 10/1/2020	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

Multiple Events Group 9	Multiple Events Group 10	Multiple Events Group 11
Numerator: Central alpha 2 agonist + HCTZ	**Numerator: HCTZ-containing products**	**Numerator: Chlorothiazide, bendroflumethiazide, or thiazide-like diuretics**
denom_limited	denom_all	denom_all
hctz_central	hctz_containing_all	other_thiazide_plus
Number of patients with use of HCTZ-containing products, chlorothiazide, bendroflumethiazide, or thiazide-like diuretics	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives
Number of patients with use of central alpha 2 agonist + HCTZ combo product	Number of patients with use of HCTZ-containing products	Number of patients with use of chlorothiazide, bendroflumethiazide, or thiazide-like diuretics
All enrollment history before and after index date	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
1 adherent episode	1 adherent episode	1 adherent episode
N/A	N/A	N/A

ITS Analysis 9A	ITS Analysis 10A	ITS Analysis 11A
Intervention date 8/8/2020	**Intervention date 8/8/2020**	**Intervention date 8/8/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
N/A	N/A	N/A
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

ITS Analysis 9B	ITS Analysis 10B	ITS Analysis 11B
Anticipatory/lag period from 6/1/2020 - 10/1/2020	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

Multiple Events Group 12	Multiple Events Group 13	Multiple Events Group 14
Numerator: ACEIs (non-HCTZ combination)	**Numerator: CCBs (non-HCTZ combination)**	**Numerator: Potassium-sparing diuretics (non-HCTZ combination)**
denom_all	denom_all	denom_all
other_acei	other_ccb	other_potass
Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives
Number of patients with use of ACEIs (non-HCTZ combination)	Number of patients with use of CCBs (non-HCTZ combination)	Number of patients with use of potassium-sparing diuretics (non-HCTZ combination)
Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
1 adherent episode	1 adherent episode	1 adherent episode
N/A	N/A	N/A

ITS Analysis 12A	ITS Analysis 13A	ITS Analysis 14A
Intervention date 8/8/2020	**Intervention date 8/8/2020**	**Intervention date 8/8/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
N/A	N/A	N/A
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

ITS Analysis 12B	ITS Analysis 13B	ITS Analysis 14B
Anticipatory/lag period from 6/1/2020 - 10/1/2020	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

Multiple Events Group 15	Multiple Events Group 16	Multiple Events Group 17
Numerator: Loop diuretics	**Numerator: ARBs (non-HCTZ combination)**	**Numerator: Beta blockers (non-HCTZ combination)**
denom_all	denom_all	denom_all
other_loop	other_arbs	other_bb
Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives	Number of patients with use of HCTZ-containing products, any thiazide diuretics, any diuretics, or any antihypertensives
Number of patients with use of loop diuretics	Number of patients with use of ARBs (non-HCTZ combination)	Number of patients with use of beta blockers (non-HCTZ combination)
Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode	Start of primary episode (index date) to end of primary episode
First occurrence of secondary index	First occurrence of secondary index	First occurrence of secondary index
1 adherent episode	1 adherent episode	1 adherent episode
N/A	N/A	N/A

ITS Analysis 15A	ITS Analysis 14A	ITS Analysis 15A
Intervention date 8/8/2020	**Intervention date 8/8/2020**	**Intervention date 8/8/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
N/A	N/A	N/A
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No

Appendix C. Specifications for Type 2, Interrupted Time Series Request, Overall Analysis, Limited Denominator

ITS Analysis 15B	ITS Analysis 14B	ITS Analysis 15B
Anticipatory/lag period from 6/1/2020 - 10/1/2020	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**	**Anticipatory/lag period from 6/1/2020 - 10/1/2020**
1/1/2017 - most recent available data	1/1/2017 - most recent available data	1/1/2017 - most recent available data
6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020	6/1/2020 - 10/1/2020
20/08/08	20/08/08	20/08/08
Yes	Yes	Yes
Monthly	Monthly	Monthly
0.05	0.05	0.05
12 (12 months)	12 (12 months)	12 (12 months)
0.2	0.2	0.2
All available months between intervention date and data range end	All available months between intervention date and data range end	All available months between intervention date and data range end
No	No	No