Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial (VERtebral fracture treatment comparisons in Osteoporotic women, VERO trial)

DUPLICATE VERO

April 30, 2021

NCT01709110

1. RCT Details

This section provides a high-level overview of a **published** RCT that the described real-world evidence study is trying to replicate as closely as possible given the remaining limitations inherent in the healthcare databases.

1.1 Title

Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial (VERtebral fracture treatment comparisons in Osteoporotic women, VERO trial - NCT01709110)

1.2 Intended aim(s)

To assess the effects of 24 months of treatment with teriparatide compared with risedronate on the incidence of new fractures in post-menopausal women with preexisting vertebral fractures, regardless of previous osteoporosis treatment.

1.3 Primary endpoint for replication

New vertebral fracture.

1.4 Required power for primary endpoint and noninferiority margin (if applicable)

Assuming a 24-month new vertebral fracture incidence of 4.5% in the teriparatide group and 10% in the risedronate group, 466 patients per group would provide 90% power to detect a difference between groups in the incidence of new vertebral fractures using a Pearson χ^2 test (two-sided α of 0.05).

1.5 Secondary endpoint for replication (assay sensitivity) and RCT finding

Non-vertebral fracture.

1.6 Trial estimate

Hazard Ratio, HR = 0.44 (95% CI, 0.29 to 0.68) comparing teriparatide vs. risedronate group during a 24-month period (Kendler et al., 2007).

2. Person responsible for implementation of replication in Aetion

Elvira D'Andrea, MD, MPH, implemented the study design in the Aetion Evidence Platform. She is not responsible for the validity of the design and analytic choices. All implementation steps are recorded, and the implementation history is archived in the platform.

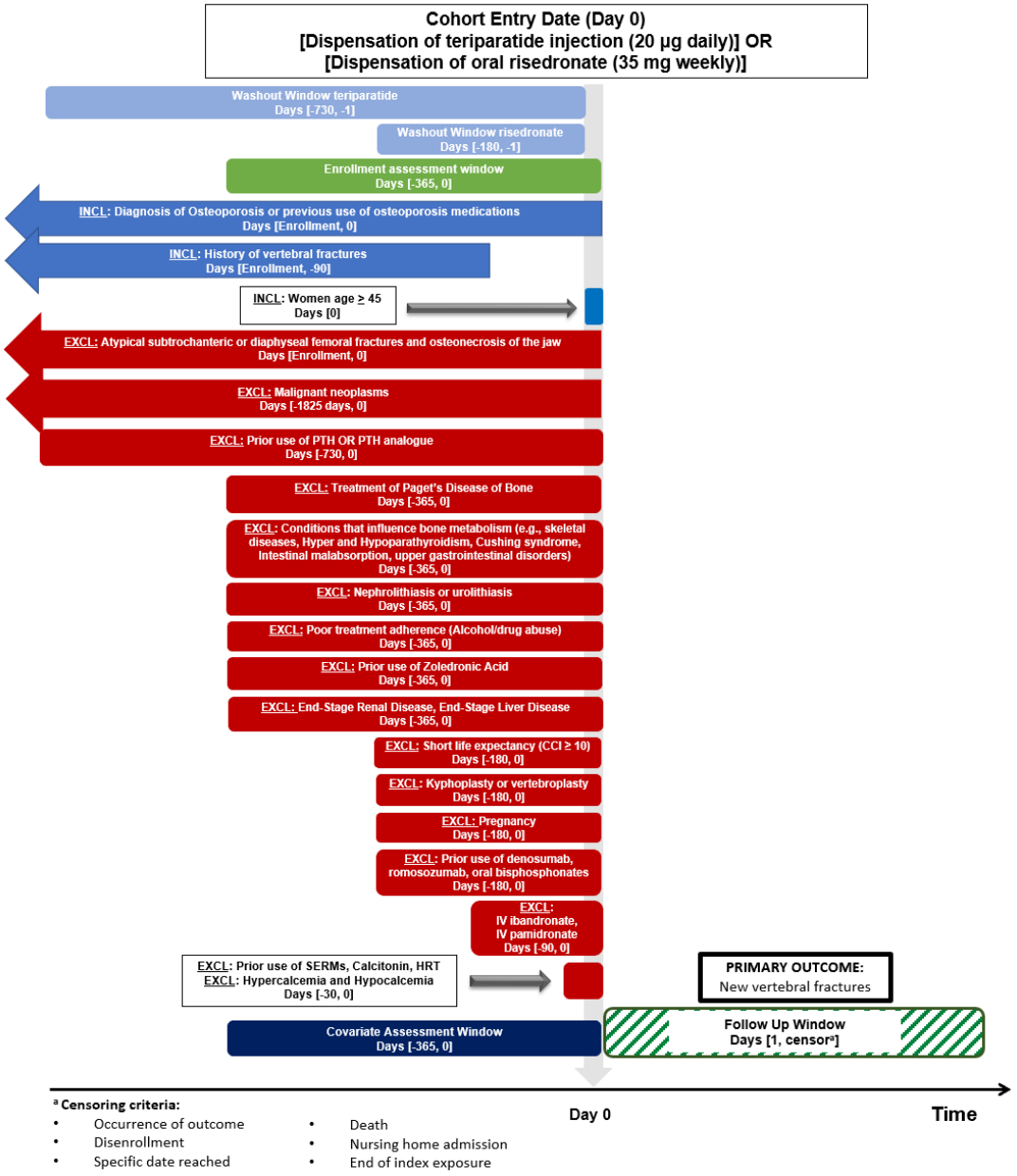
3. Data Source(s)

Optum CDM, IBM® MarketScan®

4. Study Design Diagram

The study design diagram visualizes key aspects of the longitudinal study design for expedited review.

Figure 1. Design Diagram – VERO TRIAL REPLICATION


Cohort Entry Date (Day 0)
[Dispensation of teriparatide injection (20 µg daily)] OR
[Dispensation of oral risedronate (35 mg weekly)]
Washout Window teriparatide
Days [-730, -1]
Washout Window risedronate
Days [-180, -1]
Enrollment assessment window
Days [-365, 0]
INCL: Diagnosis of Osteoporosis or previous use of osteoporosis medications
Days [Enrollment, 0]
INCL: History of vertebral fractures
Days [Enrollment, -90]
INCL: Women age ≥ 45
Days [0]
EXCL: Atypical subtrochanteric or diaphyseal femoral fractures and osteonecrosis of the jaw
Days [Enrollment, 0]
EXCL: Malignant neoplasms
Days [-1825 days, 0]
EXCL: Prior use of PTH OR PTH analogue
Days [-730, 0]
EXCL: Treatment of Paget's Disease of Bone
Days [-365, 0]
EXCL: Conditions that influence bone metabolism (e.g., skeletal diseases, Hyper and Hypoparathyroidism, Cushing syndrome, Intestinal malabsorption, upper gastrointestinal disorders)
Days [-365, 0]
EXCL: Nephrolithiasis or urolithiasis
Days [-365, 0]
EXCL: Poor treatment adherence (Alcohol/drug abuse)
Days [-365, 0]
EXCL: Prior use of Zoledronic Acid
Days [-365, 0]
EXCL: End-Stage Renal Disease, End-Stage Liver Disease
Days [-365, 0]
EXCL: Short life expectancy (CCI ≥ 10)
Days [-180, 0]
EXCL: Kyphoplasty or vertebroplasty
Days [-180, 0]
EXCL: Pregnancy
Days [-180, 0]
EXCL: Prior use of denosumab, romosozumab, oral bisphosphonates
Days [-180, 0]
EXCL: IV ibandronate, IV pamidronate
Days [-90, 0]
EXCL: Prior use of SERMs, Calcitonin, HRT
EXCL: Hypercalcemia and Hypocalcemia
Days [-30, 0]
PRIMARY OUTCOME:
New vertebral fractures
Covariate Assessment Window
Days [-365, 0]
Follow Up Window
Days [1, censor[a]]
Day 0
Time
[a] Censoring criteria:
• Occurrence of outcome
• Disenrollment
• Specific date reached
• Death
• Nursing home admission
• End of index exposure

5. Cohort Identification

5.1 Cohort Summary

This study will involve a new user, parallel group, propensity score-matched, retrospective cohort design comparing injectable subcutaneous teriparatide (20 μg daily) to oral risedronate (35 mg weekly). The patients will be required to have continuous enrollment during a baseline period of 365 days before initiation of teriparatide or oral risedronate. We will restrict the analyses to women older than 45 with osteoporosis and history of vertebral fractures.

5.2 Important steps for cohort formation

New use of teriparatide (exposure) is defined as no use of the exposure drug within the 730 days (2 years) prior to index date. This will emulate the trial requirement for which treatment with teriparatide was not allowed any time before randomization. New use of risedronate (comparator) is defined as no use of the comparator drug within the 180 days prior to index date. The shorter washout period for risedronate users, compared to teriparatide users, will emulate the trial requirement of discontinuation of risedronate at the beginning of the screening period. Differently from teriparatide, history of risedronate use was allowed in the trial. New users of teriparatide are not allowed to receive risedronate within the 180 days prior to index date, and new users of risedronate are not allowed to receive teriparatide within the 730 days (2 years) prior to index date.

5.2.1 Eligible cohort entry dates

Teriparatide indication for treatment of osteoporosis in postmenopausal women was approved by FDA on Nov 26, 2002 (the approval of risedronate for the same indication was antecedent to 2002). The initial eligible cohort entry date was the first date after Nov 26, 2002 commonly available in both the databases investigated (IBM® MarketScan®, Optum CDM). The last date eligible as cohort entry date was the end of available data for IBM® MarketScan®. For Optum CDM, we excluded the data cut that overlaps with the COVID-19 pandemic (range: April 1st - Jun 30th, 2020), since we assumed a higher proportion of drug discontinuation in that time period. The following eligible cohort entry dates were included:

- IBM® MarketScan®: Jan 1, 2004 (start of available data) – December 31, 2018 (end of available data)
- Optum CDM: Jan 1, 2004 (start of available data) – Mar 31, 2020

5.2.2 Specify inclusion/exclusion criteria for cohort entry and define the index date

Inclusion and exclusion criteria were adapted from the trial as closely as possible. Definitions for all inclusion/exclusion are provided in **Appendix A** and are summarized in the flowcharts below.

5.3 Flowchart of the study cohort assembly

For teriparatide vs. risedronate

	Optum CDM		IBM® MarketScan®	
	Excluded Patients	**Remaining Patients**	**Excluded Patients**	**Remaining Patients**
All patients		78202636		200203908
Did not meet cohort entry criteria	-77830806	371830	-199450502	753406
Excluded due to insufficient enrollment	-90897	280933	-176733	576673
Excluded due to prior use of referent	-199055	81878	-403827	172846
Excluded due to prior use of exposure	-19897	61981	-44254	128592
Excluded because patient qualified in >1 exposure category	0	61981	0	128592
Excluded based on Inclusion criteria #1 - Age >= 45	-1814	60167	-3865	124727
Excluded based on Inclusion criteria #2 - Female	-4439	55728	-9140	115587
Excluded based on Inclusion criteria #3.1 - History of vertebral fracture (including from inception to 90 days)	-48548	7180	-103348	12239
Excluded based on Inclusion criteria #3.2 - Vertebral fracture diagnosis excluded in the 90 days before cohort entry	-740	6440	-969	11270
Excluded based on Inclusion criteria #4 - Osteoporosis	-3	6437	-18	11252
Excluded based on Exclusion criteria #1 - Pregnancy	-1	6436	-1	11251
Excluded based on Exclusion criteria #2 - Paget's Disease	-5	6431	-9	11242
Excluded based on Exclusion criteria #3.1 - Renal Osteodystrophy	-2	6429	-1	11241
Excluded based on Exclusion criteria #3.2 - Osteomalacia	-11	6418	-12	11229
Excluded based on Exclusion criteria #3.3 - Cushing syndrome and other disorders of adrenal glands	-35	6383	-62	11167
Excluded based on Exclusion criteria #3.4 - Hyperparathyroidism and hypoparathyroidism	-60	6323	-86	11081
Excluded based on Exclusion criteria #3.5 - Intestinal malabsorption	-27	6296	-41	11040
Excluded based on Exclusion criteria #4 - Hypercalcemia and Hypocalcemia	-14	6282	-23	11017
Excluded based on Exclusion criteria #5 - Malignant neoplasm, excluding non-melanoma skin cancer	-500	5782	-936	10081
Excluded based on Exclusion criteria #6 - End-stage liver disease (ESLD)	-31	5751	-51	10030
Excluded based on Exclusion criteria #7 – End-stage renal disease (ESRD)	-6	5745	-14	10016
Excluded based on Exclusion criteria #8 - Nephrolithiasis or urolithiasis	-52	5693	-109	9907
Excluded based on Exclusion criteria #9 - Kyphoplasty or vertebroplasty	-17	5676	-47	9860

Excluded based on Exclusion criteria #10 - Osteonecrosis of the jaw	0	5676	-2	9858
Excluded based on Exclusion criteria #11 - Atypical subtrochanteric or diaphyseal femoral fractures	-28	5648	-55	9803
Excluded based on Exclusion criteria #12 - Upper gastrointestinal disorders	-170	5478	-221	9582
Excluded based on Exclusion criteria #13 - CCI (180 days)	-2	5476	-1	9581
Excluded based on Exclusion criteria #14 - Drug addiction or alcohol abuse or not compliant	-91	5385	-58	9523
Excluded based on Exclusion criteria #15 - Oral bisphosphonate use	-499	4886	-1024	8499
Excluded based on Exclusion criteria #16 - SERMs, Calcitonin, HRT	-101	4785	-321	8178
Excluded based on Exclusion criteria #17 - Zoledronic acid use	-2	4783	-7	8171
Excluded based on Exclusion criteria #18 - Intravenous ibandronate or pamidronate	-1	4782	-1	8170
Excluded based on Exclusion criteria #19 - Denosumab use	-10	4772	-4	8166
Excluded based on Exclusion criteria #20 - PTH or PTH analogue use	-44	4728	-137	8029
Excluded based on Exclusion criteria #21 - Romosozumab	0	4728	0	8029
Final cohort		**4728**		**8029**

6. Variables

6.1 Exposure-related variables:

Study drug:
New initiation of injectable subcutaneous teriparatide (20 µg daily). New initiation is defined as no use of teriparatide in the prior 730 days before treatment initiation (washout period). New users of teriparatide are not allowed to receive risedronate within the 180 days prior to treatment initiation.

Comparator agent:
New initiation of oral risedronate (35 mg weekly). New initiation is defined as no use of risedronate in the prior 180 days before treatment initiation (washout period). New users of risedronate are not allowed to receive teriparatide within the 730 days prior to treatment initiation.

6.2 Preliminary Covariates:

- Age
- Combined Comorbidity Index (CCI), measured over the baseline covariate assessment period, defined as 180 days prior to and

including index date.

Covariates listed above represent only a small subset of covariates that will ultimately be controlled for in the design and analysis. We use the covariates above only for initial feasibility analyses to judge whether there is likely to be sufficient overlap between treatment groups to proceed with the study. Remaining covariates are defined only after the study has passed the initial feasibility analysis and the initial power assessment and are listed in Table 1 (**Appendix B**). Gender is not included since the study is already restricted to female subjects.

6.3 Outcome variables and study follow-up:

6.3.1 Outcome variables

Effectiveness outcome variables of interest (definitions provided in **Appendix A**):

- **Primary outcome:** Vertebral fracture (algorithm adapted from Wright et al. 2019)
- **Secondary outcome**: Non-vertebral fracture

6.3.2 Study follow-up

As-treat (AT) analysis will be conducted with treatment defined as the index drug on the day of cohort entry. Similar to the trial, the patients will be followed for 24 months. A grace period and a risk exposure window of 60 days will be considered in the primary analysis.

The follow-up will start the day after drug initiation (i.e., cohort entry date), as described in the VERO trial, and will continue until the earliest date of the following events:

- The first occurrence of the outcome of interest,
- The date of end of continuous registration in the database,
- Discontinuation of the index drugs,
- Addition of the index drug from the other group or crossover,
- End of the study period,
- Measured death event occurs,
- Nursing home admission

- Nursing home admissions are considered a censoring event because the data sources utilized typically provide little to no data on a patient, particularly on drug utilization, after admission. We will utilize this as an exclusion reason for cohorts for the same reason.

A subgroup analysis will be performed by age categorized by tertiles () emulating one of the prespecified subgroup analyses of the VERO trial (Geusens P et al. 2018).

7. Initial Feasibility Analysis

Aetion report name:

For teriparatide vs. risedronate
Optum CDM - https://bwh-dope.aetion.com/projects/details/1640/results/66361/result/0
IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1641/results/66364/result/0

Date conducted: 02/25/2021

Complete Aetion feasibility analysis using age and CCI as the only covariates and the primary endpoint (Section 6.3.1) as the outcome. No measures of association will be computed nor will incidence rates stratified by treatment group.

- Report patient characteristics by treatment group
- Report summary parameters of study population **FEASIBILITY- FOR STUDY OUTCOME**
- Report reasons for censoring in the overall study population
- Report overall risk of the primary outcome.

8. Initial Power Assessment

Aetion report name:

For teriparatide vs. risedronate
Optum CDM - https://bwh-dope.aetion.com/projects/details/1640/results/66362/result/0
IBM® MarketScan®- https://bwh-dope.aetion.com/projects/details/1641/results/66363/result/0

Date conducted: 02/25/2021

In order to complete the initial power analysis, the dummy outcome of a 90-day gap in database enrollment will be used. This outcome is used to ensure that no information on the comparative risks of the outcomes of interest are available at this stage. Complete a 1:1 PS-matched comparative analysis using this outcome. PS should include only 2 covariates: age and combined comorbidity index. Power calculations are based on the formulas from Chow et al. (2008).

- Stop analyses until feasibility and power are reviewed by primary investigators and FDA. Reviewers evaluate the results of the analyses described above in Sections 7 and 8, including numbers of patients, patient characteristics, follow-up time, and reasons for censoring by treatment group, as well as overall rates of outcomes and study power. These parameters are re-evaluated and reported in the subsequent sections, after incorporating feedback and refining the protocol.

- Stop analyses until feasibility and power are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang Jessica Franklin	Date reviewed:	03/17/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	03/16/2021
Reasons for stopping analysis (if required):			

9. Balance Assessment

For teriparatide vs. risedronate
Optum CDM: https://bwh-dope.aetion.com/projects/details/1640/rwrs/67726
IBM® MarketScan®: https://bwh-dope.aetion.com/projects/details/1641/rwrs/67727

Date conducted: 03/29/21

After review of initial feasibility and power analyses, complete creation of the remaining covariates from Section 6.2. Again, using the dummy outcome of a 90-day gap in database enrollment, complete a 1:1 PS-matched analysis. The PS should include the complete list of covariates.

- Provide plot of PS distributions stratified by treatment group.

Note- Please refer to **Appendix B**.

- Report covariate balance after matching.

  Note- For Table 1, please refer to **Appendix B**.

- Report reasons for censoring by treatment group.

	Overall	**Referent**	**Exposure**
Dummy outcome	0 (0%)	0 (0%)	0 (0%)
Death	28 (0.65%)	9 (0.21%)	19 (0.44%)
End of patient enrollment	715 (16.5%)	300 (6.92%)	415 (9.58%)
End of index exposure	157 (3.62%)	70 (1.62%)	87 (2.01%)
Maximum follow-up time	442 (10.20%)	185 (4.27%)	257 (5.93%)
End of index exposure	2775 (64.03%)	1522 (35.12%)	1253 (28.91%)
Start of an additional exposure	37 (0.85%)	9 (0.21%)	28 (0.65%)
Nursing Home	180 (4.15%)	72 (1.66%)	108 (2.49%)

- Report follow-up time by treatment group.

Median Follow-Up Time (Days) [IQR]		
Patient Group	**Optum CDM**	**IBM® MarketScan®**
Overall Patient Population	163.5 [88 - 415]	190 [100 - 431.5]
Referent - Risedronate	148 [88 - 371]	148 [88 - 331]
Exposure - Teriparatide	192 [88 - 446]	234 [113 - 533]

- Report overall risk of the primary outcome.

	Optum CDM	IBM® MarketScan®	Pooled
Risk per 1,000 patients	15.9	18.9	17.8

10. Final Power Assessment

Date conducted:

- Re-calculate power in the appropriate excel table, using the revised number of matched patients from the PS-match in Section 9. All other parameters in the table should be the same as in Section 8.
    - Pooled

Superiority Analysis	
Number of patients matched	4,334
Reference	2,167
Exposed	2,167
Risk per 1,000 patients	17.80
Desired HR from RCT	0.44
Alpha (2-sided)	0.05
Number of events expected	77.1452
Power	0.950063363

    - Optum CDM

Superiority Analysis	
Number of patients matched	1,494
Reference	747
Exposed	747
Risk per 1,000 patients	15.90
Desired HR from RCT	0.44
Alpha (2-sided)	0.05
Number of events expected	23.7546
Power	0.516274582

- IBM® MarketScan®

Superiority Analysis	
Number of patients matched	2,840
Reference	1,420
Exposed	1,420
Risk per 1,000 patients	18.90
Desired HR from RCT	0.44
Alpha (2-sided)	0.05
Number of events expected	53.676
Power	0.852553869

- Stop analyses until balance and final power assessment are reviewed by primary investigators, FDA, and assigned members of advisory board.

Reviewed by PI:	Shirley Wang	Date reviewed:	04/16/2021
Reviewed by FDA:	Ken Quinto	Date reviewed:	04/15/2021
Reasons for stopping analysis (if required):			

11. Study Confidence and Concerns

Deadline for voting on study confidence and listing concerns:
Date votes and concerns are summarized:

- If final feasibility and power analyses are reviewed and approved, proceed to the remaining protocol steps.
- All study team and advisory board members that review this protocol should at this stage provide their level of confidence for the success of the RWD study in the Google Form. This form also provides space for reviewers to list any concerns that they feel may contribute to a failure to replicate the findings of the RCT, including differences in study populations, poor measurement of study variables, or residual confounding. All responses will be kept confidential and individual-level results will only be shared with the individual respondent.
- After the deadline for voting has passed, provide the distribution of responses and summarize all concerns here.

12. Register study protocol on clinicalTrials.gov

Date conducted: 04/30/2021

- Register the study on clinicalTrials.gov and upload this document.

13. Comparative Analyses

Aetion report name:
Date conducted:

13.1 For primary analysis:

13.2 For sensitivity analyses:

14. Requested Results

14.1 Table 1: Baseline characteristics before and after adjustment

Variable	Before adjustment			After adjustment		
	Referent	Exposure	Std. diff.	Referent	Exposure	Std. diff.
Number of patients			-			-
Age categories						
…						

14.2 Table 2: Follow-up time

Patient Group	Median Follow-Up Time (Days) [IQR]
Overall Patient Population	
Referent	
Exposure	

14.3 Table 3: Censoring events

	Overall	Referent	Exposure

Outcome			
Death			
Start of an additional exposure			
End of index exposure			
Specified date reached			
End of patient data			
End of patient enrollment			
…			

14.4 Table 4: Results from primary analyses;

Analysis	**No. exposed events**	**No. referent events**	**Exposed rate**	**Referent rate**	**HR (95% CI)**
Crude					
Analysis 1					
Analysis 2					
...					

HR, Hazard Ratio; CI, Confidence Interval.

14.5 Table 5: Results from secondary analyses.

15. References

Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, Bagur A, Malouf-Sierra J, Lakatos P, Fahrleitner-Pammer A, Lespessailles E, Minisola S, Body JJ, Geusens P, Möricke R, López-Romero P. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet*. 2018 Jan 20;391(10117):230-240. doi: 10.1016/S0140-6736(17)32137-2.

Wright NC, Daigle SG, Melton ME, Delzell ES, Balasubramanian A, Curtis JR. The Design and Validation of a New Algorithm to Identify Incident Fractures in Administrative Claims Data. *J Bone Miner Res.* 2019 Oct;34(10):1798-1807. doi: 10.1002/jbmr.3807.

Geusens P, Marin F, Kendler DL, Russo LA, Zerbini CA, Minisola S, Body JJ, Lespessailles E, Greenspan SL, Bagur A, Stepan JJ, Lakatos P, Casado E, Moericke R, López-Romero P, Fahrleitner-Pammer A. Effects of Teriparatide Compared with Risedronate on the Risk of Fractures in Subgroups of Postmenopausal Women with Severe Osteoporosis: The VERO Trial. *J Bone Miner Res.* 2018 May;33(5):783-794. doi: 10.1002/jbmr.3384.

Chow S, Shao J, Wang H. 2008. *Sample Size Calculations in Clinical Research*. 2nd Ed. Chapman & Hall/CRC Biostatistics Series. page 177.

Appendix A

#	VERO trial definitions	Implementation in routine care	Please see the following Google Drive for further details or any missing information: https://drive.google.com/drive/folders/1WD618wrywYjEaXzfLTcuK-VCcnb6b-gV?usp=sharing	
	Trial details - clinicaltrial.gov NCT01709110		**ICD-10 codes are not listed in this document because of excel cell size limitations and excessive number of ICD-10 codes. Full ICD-10 code lists will be available in the above Google Drive Folder (link above). ICD-9 to ICD-10 code conversions were completed using a SAS macro that implements forward/ backward mapping based on the CMS ICD-9 to ICD-10 mapping: https://www.nber.org/data/icd9-icd-10-cm-and-pcs-crosswalk-general-equivalence-mapping.html**	
	EXPOSURE vs. COMPARISON		References/Rationale	Color coding
E	Exposure: 20 µg of teriparatide once daily	Exposure: new use of **Teriparatide** (washout 730 days) **NDC Generic Name:** TERIPARATIDE **NDC codes:** 00002897101, 54868540600, 00002840001, 47781065289 **Brand names:** FORTEO **CPT/HCPCS Procedure Code:** J3110	Washout period - Criteria 20.1, 20.7	**Criteria**
C	Reference: 35 mg of oral risedronate once weekly Aim: To compare the anti-fracture efficacy of teriparatide with risedronate in patients with severe osteoporosis	Comparator: new-use of **Risedronate** (washout 180 days) **NDC Generic Name:** RISEDRONATE SODIUM, RISEDRONATE SODIUM/CALCIUM CARBONATE **NDC codes**: 00093309819, 00093309829, 00093309844, 00093309956, 00093310056, 00093550919, 00093550944, 00093777113, 00093777119, 00093777179, 00149047001, 00149047101, 00149047103, 00149047201, 00149047204, 00149047501, 00149047701, 00149047801, 00149047803, 00378404493, 00378411493, 00378415032, 00378415053, 00378471499, 00430047015, 00430047115, 00430047203, 00430047207, 00430047801, 00430047802, 00430097903, 00591204403, 00591204454, 00591207504, 00591207539, 00591210230, 00591210930, 00591387604, 16590072104, 16714087002, 23490924500, 33342010707, 33342010807, 33342010937, 33342010950, 47335066862, 47335066868, 47335092860, 47335092867, 49999044804, 54569546200, 54868438600, 54868467100, 54868551800, 54868606900, 59762040504, 59762040505, 59762040601, 59762040603, 59762040704, 60505309702, 60505309704, 60505316500, 63304044009, 63304044011, 65862051730, 65862051830, 65862051904, 65862051908, 65862087003, 65862087011, 68115068104 **Brand names:** ACTONEL, ATELVIA		**Adequate mapping in claims**
	PRIMARY OUTCOME			**Intermediate mapping in claims**
	New radiographic vertebral fractures during a 24-month study period. [Lateral spine radiographs were repeated at 12 and 24 months or early termination for new vertebral fractures. Additional unscheduled radiographs were done at any interim visit to detect new clinical vertebral fractures if the patient reported back pain clinically suggestive of a vertebral fracture.]	**Measured 1 day after drug initiation:** **Vertebral Fractures:** Algorithm include the following case-qualifyng (CQ): **CQ = 1 Inpatient claim with primary diagnosis code** ICD9 dx: 805.x, 806.x, 733.13 ICD10 dx: S12.0xxA,S12.0xxB-S12.6xxA, S12.6xxB, S12 S22.0xxA, S22.0xxB (excluding "traumatic" and "burst" fractures which are high-energy fractures), M48.50XA, M80.08XA (excluding "stress" and "fatigue" fractures which are fractures caused by abnormal stress on normal bones) **OR** **CQ = 2 Non-inpatient claim with any diagnosis code** [ICD9 dx: 805.x, 806.x, 733.13; ICD10 dx: S12.0xxA,S12.0xxB-S12.6xxA, S12.6xxB, S12 S22.0xxA, S22.0xxB (excluding "traumatic" and "burst" fractures), M48.50XA, M80.08XA (excluding "stress" and "fatigue" fractures)] **AND procedure code HCPCS** (22305, 22310, 22315, 22318, 22319, 22325-22328, 22510-22515, 22520-22525, 27200, 27202, 72291, 72292, 76012, 76013, 77082, 77085, 77086, S2360-S2363) **OR** **CQ = 3 Non-inpatient claim with diagnosis code** [ICD9 dx: 805.x, 806.x, 733.13; ICD10 dx: S12.0xxA,S12.0xxB-S12.6xxA, S12.6xxB, S12 S22.0xxA, S22.0xxB (excluding "traumatic" and "burst" fractures), M48.50XA, M80.08XA (excluding "stress" and "fatigue" fractures)] **AND Physician E&M codes** (HCPCS: 99024, 99058,99201-99215, 99241-99245, 99271-99285, 99301–99355, 99366, 99385–99387,99395–99404, 99429, 99499) **AND, up to 10 days earlier (or on the same day), Outpatient claim of spine imaging codes** (HCPCS: 72010-72159, 72240-72285, 72295) []	**Wright NC, Daigle SG, Melton ME, Delzell ES, Balasubramanian A, Curtis JR. The Design and Validation of a New Algorithm to Identify Incident Fractures in Administrative Claims Data. J Bone Miner Res. 2019 Oct;34(10):1798-1807. doi: 10.1002/jbmr.3807. Epub 2019 Aug 5. PMID: 31170317.**	**Poor mapping or cannot be measured in claims**
	INCLUSION CRITERIA			**Can't be measured in claims but not important for the analysis**
1	Postmenopausal women ≥ 45 years of age at the time of entry into the trial, whose last menstrual period occurred at least 2 years prior to entry into the trial, and are sufficiently mobile to complete study visits.	Female, ≥ 45 years of age at the time of drug initiation		
2	Women < 55 years of age in whom a bilateral oophorectomy cannot clearly be documented must have their postmenopausal status confirmed by a serum FSH level > 40 IU/L and serum estradiol level < 20 pg/mL or < 73 pmol/L.	**Measured 180 days prior to and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Excluded if patients had pregnancy codes Pregnancy (see "Pregnancy codes")		

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2	A minimum of 2 moderate (SQ2) or 1 severe (SQ3) vertebral fragility fractures [radiographic evidence of at least two moderate (ie, a reduction in vertebral body height of 26–40%) or one severe (more than 40% reduction) prevalent vertebral fragility fracture]	**Measured from enorlment to 90 days prior to the day of drug initiation in inpatient or outpatient care setting (any position):** Vertebral Fractures diagnosis: ICD9 diagnosis codes: 805.x, 806.x, 733.13 ICD10 diagnosis codes: M48.4, M48.5, M80.x, S12.x, S22.x, S32.x Vertebral fracture procedures: HCPCS codes: 22305, 22310, 22315, 22318, 22319, 22325-22328, 22510-22515, 22520-22525, 27200, 27202, 72291, 72292, 76012, 76013, 77082, 77085, 77086, S2360-S2363 ICD10 px: 0PQ3xx, 0PQ4xx, 0PR3xx, 0PR4xx, 0PS3xx, 0PS4xx ICD-9 px: 03.53	**NB. We excluded patients with diagnosis of vertebral fractures from 89 days prior to and including the day of drug initiation to increase the probability of measuring incident vertebral fractures and not prevalent vertebral fractures. The 90-day gap is described in: Wright NC, Daigle SG, Melton ME, Delzell ES, Balasubramanian A, Curtis JR. The Design and Validation of a New Algorithm to Identify Incident Fractures in Administrative Claims Data. J Bone Miner Res. 2019 Oct;34(10):1798-1807. doi: 10.1002/jbmr.3807.**
3	AP lumbar spine or total hip or femoral neck BMD ≥ 1.5 SD below the average BMD for young healthy, non-Hispanic, Caucasian women (T-score ≤ –1.5 SD).	**Measured start of all available data and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** **Osteoporosis diagnosis** ICD-9 diagnosis: 733.00, 733.01, 733.02, 733.03, 733.09, 733.13 ICD-10 diagnosis: M81.0, M81.6, M81.8, M80.88*, M80.00*, M80.01*, M80.02*, M80.03*, M80.04*, M80.05*, M80.06*, M80.07*, M80.08* OR **Osteoporosis treatments:** Alendronate, Ibandronate, Risedronate, Etidronate, Tiludronate, Denosumab, Calcitonin, Romosozumab, Raloxifene, ZA, Pamidronate (reported as osteoporosis drug in the VERO trial)	
4	Without language barrier, cooperative, able to come to the clinic for all follow-up visits; has given informed consent before entering the study and after being informed of the medications and procedures to be used in this study.	N/A	
5	In the opinion of the investigator, is willing to be trained and to use the pen injector daily, is able to satisfactorily use a pen-type injection delivery system, or is willing to receive daily subcutaneous injections from a caregiver who has been trained to use the pen injector.	N/A	
EXCLUSION CRITERIA			
1.1	Increased baseline risk of osteosarcoma. This includes patients with Paget's disease of the bone [..]. As elevation of serum alkaline phosphatase activity may indicate the presence of Paget's disease, an unexplained elevation of this enzyme activity will also be exclusionary.	**Measured 365 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** ICD-9 diagnosis: 731.0 Osteitis deformans without mention of bone tumor (Paget's Disease) ICD-10 diagnosis: M88.xxx Osteitis deformans [Paget's disease of bone] + Tiludronate (**exclusion criteria 21.1**)	
1.2	[...] previous primary skeletal malignancy, or skeletal exposure to therapeutic irradiation.	**Captured in criteria 13**	
2	History of unresolved skeletal diseases that affect bone metabolism, other than osteoporosis, including renal osteodystrophy, osteomalacia, hyperparathyroidism (uncorrected), hypoparathyroidism, and intestinal malabsorption.	**Measured 365 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Renal osteodystrophy ICD-9 diagnosis: 588.0 ICD-10 diagnosis: N25.0 Osteomalacia ICD-9 diagnosis: 268.2 ICD-10 diagnosis: M83.x Cushing syndrome and disorders of adrenal glands: ICD-9 diagnosis: 255.xx ICD-10 diagnosis: E24.x Hyperparathyroidism and hypoparathyroidism: ICD-9 diagnosis: 252.x, 588.81 ICD-10 diagnosis: E21.x, E20.x, N25.81 **Intestinal Malabsorption:** Celiac disease, Tropical sprue, Pancreatic steatorrhea, Non-celiac gluten sensitivity, Malabsorption due to intolerance elsewhere classified, Whipple's disease, Other intestinal malabsorption: ICD-9 diagnosis: 579.xx, 040.2 ICD-10 diagnosis: K90.xx	
3	Abnormally elevated values of serum albumin-corrected calcium levels at baseline, defined as ≥ 10.6 mg/dL (or ≥ 2.65 mmol/L). In cases with borderline non-eligible values (≥ 10.6 and ≤ 10.7 mg/dL), a re-test would be allowed during the screening period.	**Measured 30 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Hypercalcemia and Hypocalcemia: ICD-9 diagnosis: 275.41, 275.42 ICD-10 diagnosis: E83.51, E83.52	
4	Abnormally low values of serum albumin- corrected calcium levels at baseline, defined as < 8.0 mg/dL (or < 2.0 mmol/L). In cases with borderline non-eligible values (> 7.8 to < 8.0 mg/dL), a re-test would be allowed during the screening period to allow normalization with vitamin D and calcium supplements before the randomization visit.	**see Criteria 3**	

Appendix A

5	Abnormally elevated values of serum intact PTH(1-84) at baseline defined as > 72 pg/mL (or > 7.6 pmol/L). In cases with borderline non-eligible values (> 72 and < 79 pg/mL), a re-test would be allowed during the screening period to allow normalization with vitamin D and calcium supplements before the randomization visit.	**see Criteria 2, 3 and 6**	
6	Severe vitamin D deficiency at baseline defined as 25-hydroxy-vitamin D levels < 9.2 ng/mL (or < 23 nmol/L). In cases with borderline non-eligible values (> 8.0 and < 9.2 ng/mL), a re-test would be allowed during the screening period to allow normalization with vitamin D supplement before the randomization visit.	N/A	
7	Abnormal thyroid function not corrected by therapy. Patients with subclinical hyperthyroidism or hypothyroidism, defined as abnormally low or high TSH values respectively, with normal fT4 values are eligible to participate in the study.	N/A	
8	History of malignant neoplasms in the 5 years prior to Visit 2, with the exception of superficial basal cell or squamous cell carcinomas of the skin that have been definitively treated. Patients with carcinoma in situ of the uterine cervix treated definitively more than 1 year prior to entry into the study may be randomized. Patients with multiple myeloma or metastases to bone are excluded.	**Measured 1825 days (5 years) prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Malignant neoplasm: ICD-9 diagnosis: 140.xx-208.xx (except 173.xx, non-melanoma skin cancer) ICD-10 diagnosis: C00-C43, C45-C97, D45	
9	Active liver disease or clinical jaundice. Significantly impaired hepatic function, defined as aspartate aminotransferase (AST) > 75 U/L or alanine aminotransferase (ALT) > 75 U/L or gamma-glutamyl transpeptidase (GGT) > 300 U/L.	**Measured 365 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Cirrhosis: ICD-9 Diagnosis: 571.2, 571.5, 571.6 ICD-10 Diagnosis: K70.11, K70.2, K70.3x, K70.4x, K74.x Hepatic decompensation: ICD-9 Diagnosis: 456.0, 456.20, 456.1, 456.21, 789.5, 789.59, 572.2, 567.0, 567.2, 567.21, 567.22, 567.29, 567.8, 567.89, 567.9, 572.4 ICD-10 Diagnosis: R18.x, I85.x, K72.x, K65.x, K66.x, K67 HCC is already excluded with exclusion **criteria 13**	
10	Significantly impaired renal function as defined by a calculated endogenous creatinine clearance (ClCr) < 30 mL/min using the following Cockcroft-Gault formula for ClCr (Cockcroft and Gold 1976)	**Measured 365 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Chronic kidney disease stages IV-V, ESRD 2 codes for occurrence of ESRD/dialysis (either inpatient or outpatient), separated by at least 30 days: ICD-9 Diagnosis: 585.6, V45.1, V56.0, V56.8, 585.5 ICD-9 Procedure: 39.95, 54.98 ICD-10 Diagnosis: N18.5, N18.6, Z49.31, Z49.32, Z99.2 ICD-10 Procedure: 3E1M39Z, 5A1D60Z, 5A1D00Z, 3E1M39Z, 5A1D60Z, 5A1D00Z HCPCS/CPT codes: 50360, 50380, 90921, 90925, 90935, 90937, 90940, 90947, 90957, 90959, 90960, 90961, 90962, 90966, 90969, 90989, 99512, G0257, G0318, G0319, G0322, G0326, S9335, S9339, 50365, 90920, 90924, 90945, 90958, 90965, 90970, 90993, 90999, 99559, G0314, G0315, G0316, G0317, G0323, G0327 OR Kidney transplant: ICD-9 Diagnosis: 996.81, V42.0 ICD-9 Procedure: 55.6, 55.69 ICD-10 Diagnosis: T86.10, T86.13, T86.19, Z48.22, Z94.0, T86.11, T86.12 ICD-10 Procedure: 0TY00Z0, 0TY00Z2, 0TY10Z0, 0TY00Z1, 0TY10Z1, 0TY10Z2 HCPCS/CPT Code: 50360, 50365	
11	History of nephrolithiasis or urolithiasis within 1 year prior to Visit 2.	**Measured 365 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** ICD-9 Diagnosis: 592.xx, 274.11 ICD-10 Diagnosis: N20.xx-N23.xx ICD-9 Px: 57.0, 59.95, 56.0, 98.19, 98.51 ICD-10 Px: 0TCB7ZZ, 0TCB8ZZ, 0TFB0ZZ, 0TFB3ZZ, 0TFB4ZZ, 0TFB7ZZ, 0TFB8ZZ, 0TFC0ZZ, 0TFC3ZZ, 0TFC4ZZ, 0TFC7ZZ, 0TFC8ZZ, 0T9B7ZZ, 0T9B8ZZ, 0T9C7ZZ, 0T9C8ZZ, 0TCC7ZZ, 0TCC8ZZ, 0TC37ZZ, 0TC38ZZ, 0TC47ZZ, 0TC48ZZ, 0TC67ZZ, 0TC68ZZ, 0TC77ZZ, 0TC78ZZ, 0TC68ZZ, 0TC77ZZ, 0TC78ZZ, 0T768DZ, 0T778DZ, 0T788DZ, 0TF38ZZ, 0TF48ZZ, 0TF68ZZ, 0TF78ZZ CPT: 52005, 52310, 52332, 52352, 52353, 52356, 52317, 52318	
12	Considered imminent candidates for kyphoplasty or vertebroplasty before Visit 2.	N/A	
13	Patients who have been treated with kyphoplasty or vertebroplasty at 3 or more levels before Visit 2, regardless of the time since the last procedure.	**see Criteria 14**	
14	Patients who have been treated with kyphoplasty or vertebroplasty within the last 6 months before Visit 2.	**Measured 180 days prior to and including the day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** ICD-9 Procedure: Kyphoplasty: 81.66 Vertebroplasty: 81.65 ICD-10 Procedure: Kyphoplasty 0PS33ZZ, OPU33JZ, OPS43ZZ, OPU43JZ, OQS03ZZ, OQU03JZ, 0QS13ZZ, QS13JZ0, 0QSS3ZZ, 0QUS3JZ Vertebroplasty 0PU33JZ, 0PU34JZ, 0PU43JZ, 0PU44JZ, 0QU03JZ, 0QU04JZ, 0QU13JZ, 0QU14JZ CPT: 22514, 22515, 22520, 22521, 22522, 22523, 22524, 22525, 0200T, C9718, C9719, S2362, S2363	

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15	Patients with history of osteonecrosis of the jaw or who are, according to the clinical judgment of the investigator, at high risk to develop osteonecrosis of the jaw, including poor oral hygiene, scheduled invasive dental procedures, high doses of bisphosphonates and/or chemotherapy to treat malignancy.	**Measured start of all available data and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** History of osteonecrosis of the jaw: ICD-9 diagnosis: 733.45 ICD-10 diagnosis: M87.180	
16	Patients with history of atypical subtrochanteric or diaphyseal femoral fractures, according to the diagnostic criteria of the American Society for Bone and Mineral Research Task Force (Shane et al. 2010).	**Measured start of all available data and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** ICD-9 diagnosis: 733.15, 821.0x, 821.1x ICD-10 diagnosis: M84.75, S72.3x	
17	Active or recent history of significant upper gastrointestinal disorders, such as esophageal disorders which delay esophageal transit or emptying (e.g. stricture or achalasia).	**Measured 365 days prior to and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** ICD-9 diagnosis: 530.x ICD-10 diagnosis: K22.x	
18	Unable to stand or sit in the upright position for at least 30 minutes.	N/A	
19	Poor medical or psychiatric condition for participating in a clinical study, in the opinion of the investigator.	**Measured on the day of drug initiation:** CCI >=10 (life expectancy less than the expected duration of the trial)	
20	History of excessive consumption of alcohol or abuse of drugs in the 1 year prior to Visit 2, in the opinion of the investigator.	**Measured 365 days prior to and including day of drug initiation in inpatient or outpatient care setting (any diagnosis position):** Alcohol Abuse or Dependence ICD-9 diagnosis: 291.xx, 303.xx, 305.0x, 571.0x, 571.1x, 571.2x, 571.3x, 357.5x, 425.5x, E860.0x (CMS has not released mapping for new ICD10 for this code), V11.3x ICD-10 diagnosis: F10.x, K70.x, G62.1, I42.6, 099.31x OR Drug Abuse or Dependence ICD-9 diagnosis: 292.xx, 304.xx, 305.2x-305.9x, 648.3x ICD-10 diagnosis: F11.x, F12.x, F13.x, F14.x, F15.x, F16.x, F17.2x, F18.x, F19.x, F55.2, G62.0, 099.32x OR Non-compliance: ICD-9 diagnosis: V45.12, V15.81 ICD-10 diagnosis: Z91.19, Z91.15	**Patorno, Elisabetta et al. "Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study." BMJ 2018;360:k119 http://dx.doi.org/10.1136/bmj.k119** **Patorno, Elisabetta et al. "Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care: A First Analysis from the Empagliflozin Comparative Effectiveness and Safety (EMPRISE) Study." Circulation. 2019 Apr 8. doi: 10.1161/CIRCULATIONAHA.118.039177**
21.1	Previous treatment with the following bone active drugs is allowed but treatment must be discontinued at Visit 1 or at the time indicated below: 1. Oral bisphosphonates (including alendronate, risedronate, ibandronate, etidronate).	**Measured 180 days prior to and 1 day before the day of drug initiation:** Generic names: Alendronate, Ibandronate, Risedronate, Etidronate, Tiludronate	
21.2	2. SERMs, calcitonin, estrogen (oral, transdermal, or injectable), progestin, estrogen analog, estrogen agonist, estrogen antagonist or tibolone, androgens, strontium ranelate, or active vitamin D3 analogues.	**Measured 30 days prior to and 1 day before the day of drug initiation:** Generic names: SERMs: OSPEMIFENE, RALOXIFENE HCL, ESTROGENS, CONJUGATED/BAZEDOXIFENE ACETATE Calcitonin HRT: estrogens, progestins, androgens	**Strontium not approved in USA for treatment of osteoporosis.** **Vitamin D3 analogues over the counter**
21.3	Intravenous zoledronate, if the last dose was administered at least 12 months before Visit 1.	**Measured 365 days prior to and 1 day before the day of drug initiation:** Generic name: Zoledronic Acid	
21.4	Intravenous ibandronate or pamidronate, if the last dose was administered at least 3 months before Visit 1.	**Measured 90 days prior to and 1 day before the day of drug initiation:** Generic name: Ibandronate or pamidronate CPT codes: C9229, J1740, C9411, J2430	
21.5	Subcutaneous denosumab, if the last dose was administered at least 6 months before Visit 1.	**Measured 180 days prior to and 1 day before the day of drug initiation:** Generic name: Denosumab	
21.6	Fluoride unless given at therapeutic doses (> 20 mg/day) for more than 3 months in the 2 years prior to Visit 1, or for more than a total of 2 years, or at any dosages within the 6 months prior to Visit 2 (previous or current use of fluoridated water or topical dental fluoride treatment is permitted).	N/A	**Sodium Fluoride is not used to treat the osteoporosiss since 2001/2002 when a RCT and sub meta-analysis showed an increased of risk of fractures in the exp arm**
21.7	Prior treatment with PTH, teriparatide, or other PTH analogs; or prior participation in any other clinical trial studying PTH, teriparatide, or other PTH analogs.	**Measured 730 days (2 years) prior to and 1 day before the day of drug initiation:** Generic names: parathyroid hormone , teriparatide, abaloparatide Brand names: Natpara® (parathyroid hormone), Forteo® Reprity (teriparatide), Tymlos® (abaloparatide)	
22	Known hypersensitivity to teriparatide or risedronate, or to any diluents or excipients of teriparatide or risedronate 35 mg/week oral tablet.	N/A	

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23	Currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving an investigational product or non-approved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.	N/A	
24	Site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.	N/A	
25	Lilly employees or employees of third-party organizations (TPOs) involved in study who require exclusion of their employees.	N/A	
26	Romosozumab	**Measured 180 days prior to and 1 day before the day of drug initiation:** Generic name: Romosozumab	

Appendix A

Pregnancy
Dx codes
650 NORMAL DELIVERY
660 OBSTRUCTED LABOR
661 ABNORMALITY OF FORCES OF LABOR
662 LONG LABOR
663 UMBILICAL CORD COMPLICATIONS DURING LABOR AND DELIVERY
664 TRAUMA TO PERINEUM AND VULVA DURING DELIVERY
665 OTHER OBSTETRICAL TRAUMA
667 RETAINED PLACENTA OR MEMBRANES WITHOUT HEMORRHAGE
668 COMPLICATIONS OF THE ADMINISTRATION OF ANESTHETIC OR OTHER SEDATION IN LABOR AND DELIVERY
669.94 UNSPECIFIED COMPLICATION OF LABOR AND DELIVERY POSTPARTUM CONDITION OR COMPLICATION
V24 POSTPARTUM CARE AND EXAMINATION
V24.0 POSTPARTUM CARE AND EXAMINATION IMMEDIATELY AFTER DELIVERY
V24.1 POSTPARTUM CARE AND EXAMINATION OF LACTATING MOTHER
V24.2 ROUTINE POSTPARTUM FOLLOW
V27 OUTCOME OF DELIVERY
V27.0 MOTHER WITH SINGLE LIVEBORN
V27.1 MOTHER WITH SINGLE STILLBORN
V27.2 MOTHER WITH TWINS BOTH LIVEBORN
V27.3 MOTHER WITH TWINS ONE LIVEBORN AND ONE STILLBORN
V27.4 MOTHER WITH TWINS BOTH STILLBORN
V27.5 MOTHER WITH OTHER MULTIPLE BIRTH ALL LIVEBORN
V27.6 MOTHER WITH OTHER MULTIPLE BIRTH SOME LIVEBORN
V27.7 MOTHER WITH OTHER MULTIPLE BIRTH ALL STILLBORN
V27.9 MOTHER WITH UNSPECIFIED OUTCOME OF DELIVERY
Procedure codes
72.0 LOW FORCEPS OPERATION
72.1 LOW FORCEPS OPERATION WITH EPISIOTOMY
72.2 MID FORCEPS OPERATION
72.21 MID FORCEPS OPERATION WITH EPISIOTOMY
72.29 OTHER MID FORCEPS OPERATION
72.3 HIGH FORCEPS OPERATION
72.31 HIGH FORCEPS OPERATION WITH EPISIOTOMY
72.39 OTHER HIGH FORCEPS OPERATION
72.4 FORCEPS ROTATION OF FETAL HEAD
72.5 BREECH EXTRACTION
72.51 PARTIAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD
72.52 OTHER PARTIAL BREECH EXTRACTION
72.53 TOTAL BREECH EXTRACTION WITH FORCEPS TO AFTERCOMING HEAD

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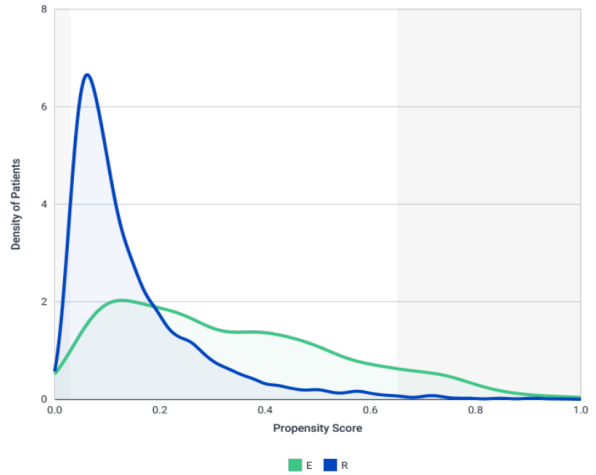
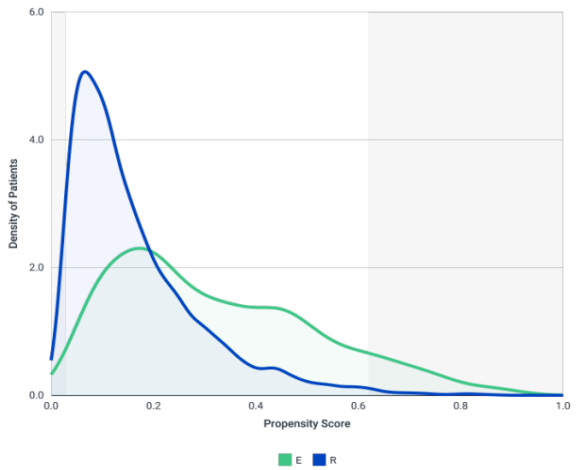
72.54 OTHER TOTAL BREECH EXTRACTION
72.6 FORCEPS APPLICATION TO AFTERCOMING HEAD
72.7 VACUUM EXTRACTION
72.71 VACUUM EXTRACTION WITH EPISIOTOMY
72.79 OTHER VACUUM EXTRACTION
72.8 OTHER SPECIFIED INSTRUMENTAL DELIVERY
72.9 UNSPECIFIED INSTRUMENTAL DELIVERY
73.0 ARTIFICIAL RUPTURE OF MEMBRANES
73.01 INDUCTION OF LABOR BY ARTIFICIAL RUPTURE OF MEMBRANES
73.09 OTHER ARTIFICIAL RUPTURE OF MEMBRANES
73.1 OTHER SURGICAL INDUCTION OF LABOR
73.2 INTERNAL AND COMBINED VERSION AND EXTRACTION
73.21 INTERNAL AND COMBINED VERSION WITHOUT EXTRACTION
73.22 INTERNAL AND COMBINED VERSION WITH EXTRACTION
73.3 FAILED FORCEPS
73.4 MEDICAL INDUCTION OF LABOR
73.5 MANUALLY ASSISTED DELIVERY
73.51 MANUAL ROTATION OF FETAL HEAD
73.59 OTHER MANUALLY ASSISTED DELIVERY
73.6 EPISIOTOMY
73.8 OPERATIONS ON FETUS TO FACILITATE DELIVERY
73.9 OTHER OPERATIONS ASSISTING DELIVERY
73.91 EXTERNAL VERSION ASSISTING DELIVERY
73.92 REPLACEMENT OF PROLAPSED UMBILICAL CORD
73.93 INCISION OF CERVIX TO ASSIST DELIVERY
73.94 PUBIOTOMY TO ASSIST DELIVERY
73.99 OTHER OPERATIONS ASSISTING DELIVERY
74.0 CLASSICAL CESAREAN SECTION
74.1 LOW CERVICAL CESAREAN SECTION
74.2 EXTRAPERITONEAL CESAREAN SECTION
74.3 REMOVAL OF EXTRATUBAL ECTOPIC PREGNANCY
74.4 CESAREAN SECTION OF OTHER SPECIFIED TYPE
74.9 CESAREAN SECTION OF UNSPECIFIED TYPE
74.91 HYSTEROTOMY TO TERMINATE PREGNANCY
74.99 OTHER CESAREAN SECTION OF UNSPECIFIED TYPE
75.4 MANUAL REMOVAL OF RETAINED PLACENTA
75.5 REPAIR OF CURRENT OBSTETRIC LACERATION OF UTERUS
75.6 REPAIR OF OTHER CURRENT OBSTETRIC LACERATION
75.7 MANUAL EXPLORATION OF UTERINE CAVITY, POSTPARTUM
75.9 OTHER OBSTETRIC OPERATIONS

Appendix B

Optum	MarketScan

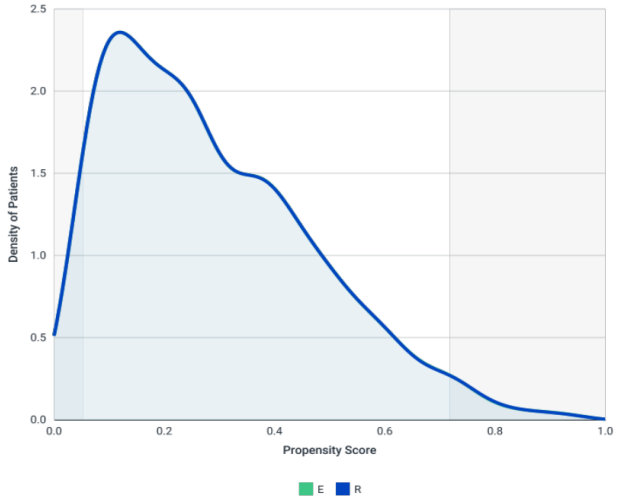
BEFORE PS MATCHING

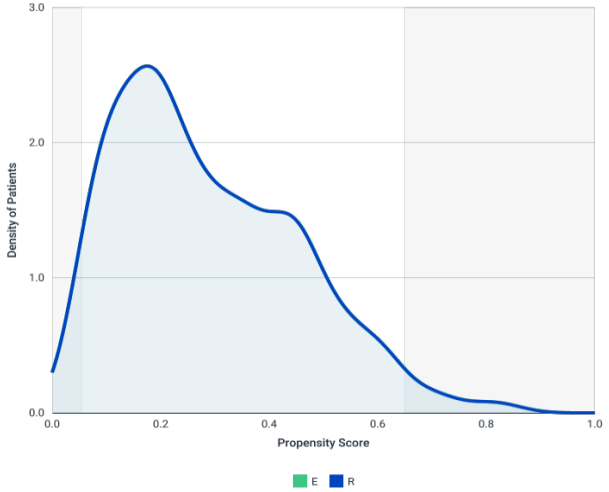




The c-statistics for the propensity score model, pre-matching was 0.781. The post-matching c-statistic was 0.578.	The c-statistics for the propensity score model, pre-matching was 0.758. The post-matching c-statistic was 0.554.

AFTER PS MATCHING





Appendix B

	Unmatched								
	Optum			Marketscan			POOLED		
Variable	**Risedronate**	**Teriparatide**	**St. Diff.**	**Risedronate**	**Teriparatide**	**St. Diff.**	**Risedronate**	**Teriparatide**	**St. Diff.**
Number of patients	**3,875**	**853**		**6,464**	**1,565**		**10,339**	**2,418**	
Demographic characteristics									
Age									
...mean (sd)	72.33 (10.26)	71.04 (10.08)	0.127	70.65 (12.30)	70.66 (11.23)	-0.001	71.28 (11.58)	70.79 (10.84)	0.044
...median [IQR]	74.00 [65.00, 81.00]	72.00 [63.00, 79.50]	0.197	71.00 [60.00, 81.00]	71.00 [62.00, 80.00]	0.000	72.12 (11.58)	71.35 (10.84)	0.069
Age categories									
...< 50; n (%)	46 (1.2%)	12 (1.4%)	-0.018	138 (2.1%)	24 (1.5%)	0.045	184 (1.8%)	036 (1.5%)	0.024
...50 - 64; n (%)	906 (23.4%)	250 (29.3%)	-0.134	2,387 (36.9%)	526 (33.6%)	0.069	3,293 (31.9%)	776 (32.1%)	-0.004
...65 - 79; n (%)	1,787 (46.1%)	378 (44.3%)	0.036	2,013 (31.1%)	616 (39.4%)	-0.174	3,800 (36.8%)	994 (41.1%)	-0.088
...>= 80; n (%)	1,136 (29.3%)	213 (25.0%)	0.097	1,926 (29.8%)	399 (25.5%)	0.096	3,062 (29.6%)	612 (25.3%)	0.096
Region									
...Northeast; n (%)	352 (9.1%)	78 (9.1%)	0.000	1,422 (22.0%)	260 (16.6%)	0.137	1,774 (17.2%)	338 (14.0%)	0.088
...Midwest; n (%)	580 (15.0%)	149 (17.5%)	-0.068	1,712 (26.5%)	475 (30.4%)	-0.087	2,292 (22.2%)	624 (25.8%)	-0.084
...South; n (%)	1,522 (39.3%)	350 (41.0%)	-0.035	2,085 (32.3%)	593 (37.9%)	-0.118	3,607 (34.9%)	943 (39.0%)	-0.085
...West; n (%)	1,421 (36.7%)	276 (32.4%)	0.091	1,245 (19.3%)	237 (15.1%)	0.111	2,666 (25.8%)	513 (21.2%)	0.109
Calendar Time year of initiation									
...Jan 2004 - Dec 2006; n (%)	288 (7.4%)	44 (5.2%)	0.091	1,402 (21.7%)	150 (9.6%)	0.338	1,690 (16.3%)	194 (8.0%)	0.256
...Jan 2007 - Dec 2009; n (%)	1,164 (30.0%)	126 (14.8%)	0.371	1,880 (29.1%)	301 (19.2%)	0.233	3,044 (29.4%)	427 (17.7%)	0.278
...Jan 2010 - Dec 2012; n (%)	1,142 (29.5%)	157 (18.4%)	0.262	1,629 (25.2%)	416 (26.6%)	-0.032	2,771 (26.8%)	573 (23.7%)	0.071
...Jan 2013 - Dec 2015; n (%)	658 (17.0%)	232 (27.2%)	-0.248	1,014 (15.7%)	416 (26.6%)	-0.269	1,672 (16.2%)	648 (26.8%)	-0.260
...Jan 2016 - Mar 2020; n (%) #	623 (16.1%)	294 (34.5%)	-0.433	539 (8.3%)	282 (18.0%)	-0.027	1,162 (11.2%)	576 (23.8%)	-0.336
Race									
...White; n (%)	2,764 (71.3%)	640 (75.0%)	-0.084	NA	NA	NA	2,764 (71.3%)	640 (75.0%)	-0.084
...Black or African American; n (%)	216 (5.6%)	44 (5.2%)	0.018	NA	NA	NA	216 (5.6%)	44 (5.2%)	0.018
...Asian; n (%)	185 (4.8%)	31 (3.6%)	0.060	NA	NA	NA	185 (4.8%)	31 (3.6%)	0.060
...Others; n (%)	710 (18.3%)	138 (16.2%)	0.056	NA	NA	NA	710 (18.3%)	138 (16.2%)	0.056
Metropolitan Statistical Area									
...Urban; n (%)	NA	NA	NA	4,979 (77.0%)	1,173 (75.0%)	0.047	4,979 (77.0%)	1,173 (75.0%)	0.047
...Rural; n (%)	NA	NA	NA	37 (0.6%)	41 (2.6%)	-0.160	37 (0.6%)	41 (2.6%)	-0.160
...Unknown/Missing; n (%)	NA	NA	NA	1,448 (22.4%)	351 (22.4%)	0.000	1,448 (22.4%)	351 (22.4%)	0.000
General Health Related Measures									
Smoking; n (%)	355 (9.2%)	123 (14.4%)	-0.162	290 (4.5%)	108 (6.9%)	-0.104	645 (6.2%)	231 (9.6%)	-0.126
Obesity or Overweight; n (%)	259 (6.7%)	85 (10.0%)	-0.120	222 (3.4%)	88 (5.6%)	-0.106	481 (4.7%)	173 (7.2%)	-0.106
Obesity; n (%)	175 (4.5%)	57 (6.7%)	-0.096	174 (2.7%)	64 (4.1%)	-0.077	349 (3.4%)	121 (5.0%)	-0.080
Overweight; n (%)	97 (2.5%)	33 (3.9%)	-0.080	58 (0.9%)	28 (1.8%)	-0.078	155 (1.5%)	061 (2.5%)	-0.071
Cardiovascular Measures									
Hypertension; n (%)	2,391 (61.7%)	503 (59.0%)	0.055	2,945 (45.6%)	744 (47.5%)	-0.038	5,336 (51.6%)	1,247 (51.6%)	0.000
Hyperlipidemia; n (%)	2,236 (57.7%)	439 (51.5%)	0.125	2,462 (38.1%)	620 (39.6%)	-0.031	4,698 (45.4%)	1,059 (43.8%)	0.032
Coronary artery disease (MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease); n (%)	669 (17.3%)	126 (14.8%)	0.068	897 (13.9%)	262 (16.7%)	-0.078	1,566 (15.1%)	388 (16.0%)	-0.025
Old MI; n (%)	103 (2.7%)	21 (2.5%)	0.013	62 (1.0%)	20 (1.3%)	-0.028	165 (1.6%)	041 (1.7%)	-0.008
Acute MI; n (%)	48 (1.2%)	6 (0.7%)	0.052	65 (1.0%)	18 (1.2%)	-0.019	113 (1.1%)	024 (1.0%)	0.010
ACS/unstable angina; n (%)	63 (1.6%)	10 (1.2%)	0.034	90 (1.4%)	25 (1.6%)	-0.016	153 (1.5%)	035 (1.4%)	0.008
Stable angina; n (%)	119 (3.1%)	18 (2.1%)	0.063	145 (2.2%)	37 (2.4%)	-0.013	264 (2.6%)	055 (2.3%)	0.019
Coronary atherosclerosis and other CHD; n (%)	576 (14.9%)	107 (12.5%)	0.070	800 (12.4%)	232 (14.8%)	-0.070	1,376 (13.3%)	339 (14.0%)	-0.020
History of CABG or PTCA; n (%)	104 (2.7%)	19 (2.2%)	0.032	57 (0.9%)	24 (1.5%)	-0.055	161 (1.6%)	043 (1.8%)	-0.015
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)	290 (7.5%)	61 (7.2%)	0.011	415 (6.4%)	94 (6.0%)	0.017	705 (6.8%)	155 (6.4%)	0.016
Stroke (Ischemic or hemorrhagic); n (%)	160 (4.1%)	39 (4.6%)	-0.025	260 (4.0%)	54 (3.5%)	0.026	420 (4.1%)	093 (3.8%)	0.015
TIA; n (%)	126 (3.3%)	20 (2.3%)	0.061	187 (2.9%)	47 (3.0%)	-0.006	313 (3.0%)	067 (2.8%)	0.012
Late effects of cerebrovascular disease; n (%)	95 (2.5%)	27 (3.2%)	-0.042	92 (1.4%)	20 (1.3%)	0.009	187 (1.8%)	047 (1.9%)	-0.007
Heart Failure; n (%)	279 (7.2%)	44 (5.2%)	0.083	466 (7.2%)	128 (8.2%)	-0.038	745 (7.2%)	172 (7.1%)	0.004
Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)	310 (8.0%)	73 (8.6%)	-0.022	393 (6.1%)	102 (6.5%)	-0.016	703 (6.8%)	175 (7.2%)	-0.016
Atrial fibrillation and Other cardiac dysrhythmia; n (%)	593 (15.3%)	154 (18.1%)	-0.075	906 (14.0%)	259 (16.5%)	-0.070	1,499 (14.5%)	413 (17.1%)	-0.071
Atrial fibrillation; n (%)	323 (8.3%)	81 (9.5%)	-0.042	492 (7.6%)	153 (9.8%)	-0.078	815 (7.9%)	234 (9.7%)	-0.064
Other cardiac dysrhythmia; n (%)	416 (10.7%)	121 (14.2%)	-0.106	602 (9.3%)	175 (11.2%)	-0.063	1,018 (9.8%)	296 (12.2%)	-0.077
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)	763 (19.7%)	175 (20.5%)	-0.020	1,010 (15.6%)	277 (17.7%)	-0.056	1,773 (17.1%)	452 (18.7%)	-0.042
Diabetes mellitus without mention of complications; n (%)	689 (17.8%)	151 (17.7%)	0.003	891 (13.8%)	236 (15.1%)	-0.037	1,580 (15.3%)	387 (16.0%)	-0.019
Diabetes with specified complications; n (%)	248 (6.4%)	61 (7.2%)	-0.032	292 (4.5%)	101 (6.5%)	-0.088	540 (5.2%)	162 (6.7%)	-0.063
Diabetes with unspecified complications; n (%)	34 (0.9%)	6 (0.7%)	0.022	41 (0.6%)	14 (0.9%)	-0.035	075 (0.7%)	020 (0.8%)	-0.012
Hypoglycemia; n (%)	54 (1.4%)	17 (2.0%)	-0.046	56 (0.9%)	24 (1.5%)	-0.055	110 (1.1%)	041 (1.7%)	-0.051
GI Conditions									
Upper GI (Diseases of esophagus, stomach and duodenum); n (%)	852 (22.0%)	254 (29.8%)	-0.179	861 (13.3%)	334 (21.3%)	-0.213	1,713 (16.6%)	588 (24.3%)	-0.192
GI bleeding; n (%)	167 (4.3%)	30 (3.5%)	0.041	269 (4.2%)	54 (3.5%)	0.036	436 (4.2%)	084 (3.5%)	0.036

Appendix B

Eating disorders, Non-infective enteritis and colitis, postoperative disorders of the digestive system; n (%)	616 (15.9%)	165 (19.3%)	-0.089	794 (12.3%)	238 (15.2%)	-0.084	1,410 (13.6%)	403 (16.7%)	-0.087
Eating disorders (Anorexia and Bulimia); n (%)	238 (6.1%)	68 (8.0%)	-0.074	190 (2.9%)	74 (4.7%)	-0.094	428 (4.1%)	142 (5.9%)	-0.083
Non-infective enteritis and colitis; n (%)	323 (8.3%)	85 (10.0%)	-0.059	469 (7.3%)	143 (9.1%)	-0.066	792 (7.7%)	228 (9.4%)	-0.061
Intraoperative and postprocedural complications and disorders of digestive system; n (%)	158 (4.1%)	38 (4.5%)	-0.020	257 (4.0%)	55 (3.5%)	0.026	415 (4.0%)	093 (3.8%)	0.010
Disorders of gallbladder, biliary tract and pancreas; n (%)	100 (2.6%)	40 (4.7%)	-0.112	188 (2.9%)	57 (3.6%)	-0.039	288 (2.8%)	097 (4.0%)	-0.066
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)	317 (8.2%)	116 (13.6%)	-0.174	426 (6.6%)	184 (11.8%)	-0.181	743 (7.2%)	300 (12.4%)	-0.176
Osteoarthrosis; n (%)	1,276 (32.9%)	347 (40.7%)	-0.162	1,580 (24.4%)	528 (33.7%)	-0.206	2,856 (27.6%)	875 (36.2%)	-0.185
Other rheumatic disorders (including gout); n (%)	2,635 (68.0%)	630 (73.9%)	-0.130	4,107 (63.5%)	1,129 (72.1%)	-0.185	6,742 (65.2%)	1,759 (72.7%)	-0.163
Gout and other crystal arthropathies; n (%)	80 (2.1%)	15 (1.8%)	0.022	68 (1.1%)	29 (1.9%)	-0.066	148 (1.4%)	044 (1.8%)	-0.032
Other rheumatic disorders; n (%)	2,620 (67.6%)	628 (73.6%)	-0.132	4,090 (63.3%)	1,123 (71.8%)	-0.182	6,710 (64.9%)	1,751 (72.4%)	-0.162
Neuro Conditions									
Parkinson's disease; n (%)	10 (0.3%)	1 (0.1%)	0.045	8 (0.1%)	2 (0.1%)	0.000	018 (0.2%)	003 (0.1%)	0.026
Alzheimer and other Dementia Disease ; n (%)	373 (9.6%)	62 (7.3%)	0.083	462 (7.1%)	100 (6.4%)	0.028	835 (8.1%)	162 (6.7%)	0.054
Seizure disorders (epilepsy); n (%)	61 (1.6%)	21 (2.5%)	-0.064	73 (1.1%)	31 (2.0%)	-0.073	134 (1.3%)	052 (2.2%)	-0.069
Delirium/Psychosis; n (%)	148 (3.8%)	33 (3.9%)	-0.005	192 (3.0%)	62 (4.0%)	-0.054	340 (3.3%)	095 (3.9%)	-0.032
Other Conditions									
Vitamin D deficiency; n (%)	633 (16.3%)	250 (29.3%)	-0.314	546 (8.4%)	263 (16.8%)	-0.255	1,179 (11.4%)	513 (21.2%)	-0.268
Liver disease; n (%)	128 (3.3%)	37 (4.3%)	-0.052	194 (3.0%)	56 (3.6%)	-0.034	322 (3.1%)	093 (3.8%)	-0.038
Chronic kidney disease stages I-III; n (%)	414 (10.7%)	81 (9.5%)	0.040	181 (2.8%)	72 (4.6%)	-0.095	595 (5.8%)	153 (6.3%)	-0.021
Chronic kidney disease stages IV-V, ESRD; n (%)	130 (3.4%)	18 (2.1%)	0.080	60 (0.9%)	27 (1.7%)	-0.071	190 (1.8%)	045 (1.9%)	-0.007
Premature menopause; n (%)	5 (0.1%)	3 (0.4%)	-0.060	9 (0.1%)	1 (0.1%)	0.000	014 (0.1%)	004 (0.2%)	-0.026
Oophorectomy; n (%)	5 (0.1%)	0 (0.0%)	0.045	1 (0.0%)	1 (0.1%)	-0.045	006 (0.1%)	001 (0.0%)	0.045
COPD; n (%)	623 (16.1%)	142 (16.6%)	-0.014	798 (12.3%)	244 (15.6%)	-0.095	1,421 (13.7%)	386 (16.0%)	-0.065
Asthma; n (%)	384 (9.9%)	102 (12.0%)	-0.067	484 (7.5%)	147 (9.4%)	-0.068	868 (8.4%)	249 (10.3%)	-0.065
Obstructive sleep apnea; n (%)	151 (3.9%)	60 (7.0%)	-0.137	143 (2.2%)	62 (4.0%)	-0.104	294 (2.8%)	122 (5.0%)	-0.114
Syncope; n (%)	215 (5.5%)	49 (5.7%)	-0.009	343 (5.3%)	89 (5.7%)	-0.018	558 (5.4%)	138 (5.7%)	-0.013
Falls; n (%)	499 (12.9%)	180 (21.1%)	-0.220	173 (2.7%)	128 (8.2%)	-0.244	672 (6.5%)	308 (12.7%)	-0.212
VTE; n (%)	142 (3.7%)	36 (4.2%)	-0.026	203 (3.1%)	58 (3.7%)	-0.033	345 (3.3%)	094 (3.9%)	-0.032
Gait abnormality; n (%)	498 (12.9%)	179 (21.0%)	-0.217	578 (8.9%)	202 (12.9%)	-0.129	1,076 (10.4%)	381 (15.8%)	-0.161
Osteopenia; n (%)	1,260 (32.5%)	279 (32.7%)	-0.004	1,720 (26.6%)	344 (22.0%)	0.107	2,980 (28.8%)	623 (25.8%)	0.067
History of hip and femur fractures; n (%)	162 (4.2%)	66 (7.7%)	-0.148	280 (4.3%)	141 (9.0%)	-0.189	442 (4.3%)	207 (8.6%)	-0.176
Other Fractures ; n (%)	267 (6.9%)	123 (14.4%)	-0.245	425 (6.6%)	199 (12.7%)	-0.208	692 (6.7%)	322 (13.3%)	-0.221
Glucocorticoid-Induced Osteoporosis; n (%)	4 (0.1%)	3 (0.4%)	-0.060	1 (0.0%)	2 (0.1%)	-0.045	005 (0.0%)	005 (0.2%)	-0.063
Combined comorbidity score									
...mean (sd)	1.03 (2.10)	1.28 (2.22)	-0.116	0.66 (1.57)	0.92 (1.78)	-0.155	0.80 (1.79)	1.05 (1.95)	-0.134
...median [IQR]	0.00 [0.00, 2.00]	1.00 [0.00, 2.00]	-0.463	0.00 [0.00, 1.00]	0.00 [0.00, 1.00]	0.000	0.00 (1.79)	0.35 (1.95)	-0.187
Frailty Score: Empirical Version 365 days as Categories									
...< 0.12908; n (%)	1,600 (41.3%)	372 (43.6%)	-0.047	2,630 (40.7%)	507 (32.4%)	0.173	4,230 (40.9%)	879 (36.4%)	0.093
...0.12908 - 0.1631167; n (%)	852 (22.0%)	173 (20.3%)	0.042	1,510 (23.4%)	342 (21.9%)	0.036	2,362 (22.8%)	515 (21.3%)	0.036
...>= 0.1631167; n (%)	1,423 (36.7%)	308 (36.1%)	0.012	2,324 (36.0%)	716 (45.8%)	-0.200	3,747 (36.2%)	1,024 (42.3%)	-0.125
Medication Use									
Use of oral corticosteroids; n (%)	1,089 (28.1%)	314 (36.8%)	-0.187	1,859 (28.8%)	572 (36.5%)	-0.165	2,948 (28.5%)	886 (36.6%)	-0.174
Use of antidepressants; n (%)	1,247 (32.2%)	327 (38.3%)	-0.128	2,143 (33.2%)	654 (41.8%)	-0.178	3,390 (32.8%)	981 (40.6%)	-0.162
Use of anticonvulsants; n (%)	565 (14.6%)	180 (21.1%)	-0.170	904 (14.0%)	376 (24.0%)	-0.257	1,469 (14.2%)	556 (23.0%)	-0.228
Use of beta blocker OR calcium channel blocker; n (%)	1,270 (32.8%)	270 (31.7%)	0.024	2,060 (31.9%)	537 (34.3%)	-0.051	3,330 (32.2%)	807 (33.4%)	-0.026
Use of PPIs; n (%)	965 (24.9%)	254 (29.8%)	-0.110	1,761 (27.2%)	569 (36.4%)	-0.199	2,726 (26.4%)	823 (34.0%)	-0.166
Use of opioids; n (%)	1,674 (43.2%)	488 (57.2%)	-0.283	2,972 (46.0%)	976 (62.4%)	-0.334	4,646 (44.9%)	1,464 (60.5%)	-0.316
Use of antipsychotics; n (%)	108 (2.8%)	28 (3.3%)	-0.029	230 (3.6%)	61 (3.9%)	-0.016	338 (3.3%)	089 (3.7%)	-0.022
Use of anxiolytics/hypnotics; n (%)	435 (11.2%)	91 (10.7%)	0.016	816 (12.6%)	255 (16.3%)	-0.105	1,251 (12.1%)	346 (14.3%)	-0.065
Use of dementia meds; n (%)	219 (5.7%)	34 (4.0%)	0.079	349 (5.4%)	77 (4.9%)	0.023	568 (5.5%)	111 (4.6%)	0.041
Use of antiparkinsonian meds; n (%)	127 (3.3%)	33 (3.9%)	-0.032	226 (3.5%)	67 (4.3%)	-0.041	353 (3.4%)	100 (4.1%)	-0.037
Use of Benzodiazepine; n (%)	568 (14.7%)	200 (23.4%)	-0.223	1,491 (23.1%)	433 (27.7%)	-0.106	2,059 (19.9%)	633 (26.2%)	-0.150
All antidiabetic medications; n (%)	439 (11.3%)	82 (9.6%)	0.056	670 (10.4%)	188 (12.0%)	-0.051	1,109 (10.7%)	270 (11.2%)	-0.016
ACEI/ARB; n (%)	1,555 (40.1%)	280 (32.8%)	0.152	2,234 (34.6%)	527 (33.7%)	0.019	3,789 (36.6%)	807 (33.4%)	0.067
Use of Anticoagulants; n (%)	301 (7.8%)	81 (9.5%)	-0.061	548 (8.5%)	176 (11.2%)	-0.091	849 (8.2%)	257 (10.6%)	-0.082
Use of Amiodarone; n (%)	36 (0.9%)	10 (1.2%)	-0.029	81 (1.3%)	26 (1.7%)	-0.033	117 (1.1%)	036 (1.5%)	-0.035
Digoxin; n (%)	92 (2.4%)	17 (2.0%)	0.027	233 (3.6%)	45 (2.9%)	0.039	325 (3.1%)	062 (2.6%)	0.030
Use of Diuretics; n (%)	1,273 (32.9%)	251 (29.4%)	0.076	2,096 (32.4%)	515 (32.9%)	-0.011	3,369 (32.6%)	766 (31.7%)	0.019
Use of Aspirin; n (%)	24 (0.6%)	6 (0.7%)	-0.012	90 (1.4%)	25 (1.6%)	-0.016	114 (1.1%)	031 (1.3%)	-0.018
NSAIDs (NOT including aspirin); n (%)	807 (20.8%)	218 (25.6%)	-0.114	1,496 (23.1%)	365 (23.3%)	-0.005	2,303 (22.3%)	583 (24.1%)	-0.043
HRT (Use of estrogens, progestins, androgens); n (%)	240 (6.2%)	50 (5.9%)	0.013	445 (6.9%)	102 (6.5%)	0.016	685 (6.6%)	152 (6.3%)	0.012
Other Pressors; n (%)	24 (0.6%)	5 (0.6%)	0.000	38 (0.6%)	24 (1.5%)	-0.088	062 (0.6%)	029 (1.2%)	-0.064
Use of Statins ; n (%)	1,599 (41.3%)	276 (32.4%)	0.185	2,393 (37.0%)	568 (36.3%)	0.015	3,992 (38.6%)	844 (34.9%)	0.077
Selective Estrogen Receptor Modulators (SERMs); n (%)	61 (1.6%)	19 (2.2%)	-0.044	128 (2.0%)	39 (2.5%)	-0.034	189 (1.8%)	058 (2.4%)	-0.042

Appendix B

Healthcare Utilization Measures									
Use of any drugs claims									
...mean (sd)	21.89 (16.94)	25.76 (18.99)	-0.215	20.60 (16.91)	26.58 (19.21)	-0.330	21.08 (16.92)	26.29 (19.13)	-0.289
Number of office visits									
...mean (sd)	8.64 (6.54)	12.05 (7.91)	-0.470	9.37 (7.10)	12.43 (8.14)	-0.401	9.10 (6.90)	12.30 (8.06)	-0.427
Number of ED visits									
...mean (sd)	0.59 (1.17)	0.77 (1.14)	-0.156	0.49 (1.14)	0.65 (1.25)	-0.134	0.53 (1.15)	0.69 (1.21)	-0.136
Number of Hospitalizations									
...mean (sd)	0.32 (0.86)	0.48 (1.01)	-0.171	1.83 (6.41)	2.30 (5.88)	-0.076	1.26 (5.10)	1.66 (4.77)	-0.081
Recent hospitalization (-30 days to Index Rx date); n (%)	55 (1.4%)	21 (2.5%)	-0.080	125 (1.9%)	37 (2.4%)	-0.034	180 (1.7%)	058 (2.4%)	-0.049
Old hospitalizations (-450 to -31 days); n (%)	579 (14.9%)	200 (23.4%)	-0.217	1,301 (20.1%)	420 (26.8%)	-0.159	1,880 (18.2%)	620 (25.6%)	-0.180
Number of Endocrinologist visits									
...mean (sd)	0.14 (0.67)	0.52 (1.28)	-0.372	1.52 (2.62)	1.77 (2.97)	-0.089	1.00 (2.11)	1.33 (2.51)	-0.142
Number of DXA test performed									
...mean (sd)	0.57 (0.57)	0.74 (0.56)	-0.301	0.41 (0.51)	0.50 (0.53)	-0.173	0.47 (0.53)	0.58 (0.54)	-0.206
Number of hospital days									
...mean (sd)	3.68 (14.88)	5.21 (17.30)	-0.095	1.83 (6.41)	2.30 (5.88)	-0.076	2.52 (10.42)	3.33 (11.31)	-0.074
Occurrence of basic or comprehensive blood chemistry test; n (%)	2,611 (67.4%)	660 (77.4%)	-0.012	2,508 (38.8%)	720 (46.0%)	-0.146	5,119 (49.5%)	1,380 (57.1%)	-0.153
Number of HbA1C test ordered									
...mean (sd)	0.55 (1.14)	0.53 (1.13)	0.018	0.28 (0.84)	0.27 (0.79)	0.012	0.38 (0.96)	0.36 (0.92)	0.021
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)	305 (7.9%)	77 (9.0%)	-0.040	649 (10.0%)	146 (9.3%)	0.024	954 (9.2%)	223 (9.2%)	0.000
Number of Mammograms (Breast cancer screening); n (%)	1,955 (50.5%)	408 (47.8%)	0.054	3,028 (46.8%)	583 (37.3%)	0.193	4,983 (48.2%)	991 (41.0%)	0.145
Number of Pap smear (Cervical cancer screening); n (%)	873 (22.5%)	153 (17.9%)	0.115	1,683 (26.0%)	279 (17.8%)	0.199	2,556 (24.7%)	432 (17.9%)	0.167
Flu vaccine; n (%)	1,331 (34.3%)	318 (37.3%)	-0.063	1,329 (20.6%)	349 (22.3%)	-0.041	2,660 (25.7%)	667 (27.6%)	-0.043
Pneumococcal vaccine; n (%)	493 (12.7%)	168 (19.7%)	-0.191	417 (6.5%)	155 (9.9%)	-0.124	910 (8.8%)	323 (13.4%)	-0.147
Copay for pharmacy cost (charges in U.S. $)									
...mean (sd)	32.47 (33.44)	39.58 (80.44)	-0.115	24.71 (28.10)	21.31 (23.34)	0.132	27.62 (30.21)	27.76 (51.33)	-0.003
...median [IQR]	24.33 [13.75, 40.90]	25.00 [12.09, 41.51]	-0.011	18.73 [8.26, 32.00]	16.84 [7.92, 28.17]	0.073	20.83 (30.21)	19.72 (51.33)	0.026
...Missing; n (%)	0 (0.0%)	1 (0.1%)	-0.018	0 (0.0%)	5 (0.3%)	-0.078	000 (0.0%)	006 (0.2%)	-0.063
Business Type									
...Commercial; n (%)	1,313 (33.9%)	344 (40.3%)	-0.133	NA	NA	NA	1,313 (33.9%)	344 (40.3%)	-0.133
...Medicare; n (%)	2,562 (66.1%)	509 (59.7%)	0.133	NA	NA	NA	2,562 (66.1%)	509 (59.7%)	0.133
Insurance Plan Type									
...Comprehensive; n (%)	NA	NA	NA	1,771 (27.4%)	476 (30.4%)	-0.066	1,771 (27.4%)	476 (30.4%)	-0.066
...HMO; n (%)	NA	NA	NA	922 (14.3%)	109 (7.0%)	0.238	922 (14.3%)	109 (7.0%)	0.238
...PPO; n (%)	NA	NA	NA	3,087 (47.8%)	780 (49.8%)	-0.040	3,087 (47.8%)	780 (49.8%)	-0.040
...Others; n (%)	NA	NA	NA	684 (10.6%)	200 (12.8%)	-0.068	684 (10.6%)	200 (12.8%)	-0.068

Aetion link to Optum results: https://bwh-dope.aetion.com/projects/details/1640/rwrs/67726
Aetion link to Marketscan results: https://bwh-dope.aetion.com/projects/details/1641/rwrs/67727

#The last cohort entry date in Optum is Mar 31, 2020 and in Marketscan is Dec 31, 2018

Appendix B

PS-matched									
	Optum			Marketscan			POOLED		
Variable	**Risedronate**	**Teriparatide**	**St. Diff.**	**Risedronate**	**Teriparatide**	**St. Diff.**	**Risedronate**	**Teriparatide**	**St. Diff.**
Number of patients	**747**	**747**		**1,420**	**1,420**		**2,167**	**2,167**	
Demographic characteristics									
Age									
...mean (sd)	71.16 (10.45)	71.32 (10.12)	-0.016	70.57 (11.42)	70.82 (11.22)	-0.022	70.77 (11.10)	70.99 (10.85)	-0.020
...median [IQR]	73.00 [63.00, 79.00]	72.00 [63.00, 80.00]	0.097	71.00 [61.00, 79.00]	71.00 [62.00, 80.00]	0.000	71.69 (11.10)	71.34 (10.85)	0.032
Age categories*									
...< 50; n (%)	8 (1.1%)	12 (1.6%)	-0.043	22 (1.5%)	23 (1.6%)	-0.008	030 (1.4%)	035 (1.6%)	-0.016
...50 - 64; n (%)	207 (27.7%)	208 (27.8%)	-0.002	478 (33.7%)	472 (33.2%)	0.011	685 (31.6%)	680 (31.4%)	0.004
...65 - 79; n (%)	350 (46.9%)	333 (44.6%)	0.046	571 (40.2%)	551 (38.8%)	0.029	921 (42.5%)	884 (40.8%)	0.034
...>= 80; n (%)	182 (24.4%)	194 (26.0%)	-0.037	349 (24.6%)	374 (26.3%)	-0.039	531 (24.5%)	568 (26.2%)	-0.039
Region*									
...Northeast; n (%)	73 (9.8%)	69 (9.2%)	0.020	267 (18.8%)	250 (17.6%)	0.031	340 (15.7%)	319 (14.7%)	0.028
...Midwest; n (%)	117 (15.7%)	125 (16.7%)	-0.027	402 (28.3%)	419 (29.5%)	-0.026	519 (24.0%)	544 (25.1%)	-0.026
...South; n (%)	317 (42.4%)	302 (40.4%)	0.041	545 (38.4%)	530 (37.3%)	0.023	862 (39.8%)	832 (38.4%)	0.029
...West; n (%)	240 (32.1%)	251 (33.6%)	-0.032	206 (14.5%)	221 (15.6%)	-0.031	446 (20.6%)	472 (21.8%)	-0.029
Calendar Time year of initiation*									
...Jan 2004 - Dec 2006; n (%)	44 (5.9%)	43 (5.8%)	0.004	150 (10.6%)	149 (10.5%)	0.003	194 (9.0%)	192 (8.9%)	0.004
...Jan 2007 - Dec 2009; n (%)	122 (16.3%)	123 (16.5%)	-0.005	297 (20.9%)	292 (20.6%)	0.007	419 (19.3%)	415 (19.2%)	0.003
...Jan 2010 - Dec 2012; n (%)	158 (21.2%)	153 (20.5%)	0.017	402 (28.3%)	397 (28.0%)	0.007	560 (25.8%)	550 (25.4%)	0.009
...Jan 2013 - Dec 2015; n (%)	190 (25.4%)	200 (26.8%)	-0.032	369 (26.0%)	361 (25.4%)	0.014	559 (25.8%)	561 (25.9%)	-0.002
...Jan 2016 - Mar 2020; n (%) #	233 (31.2%)	228 (30.5%)	0.015	202 (14.2%)	221 (15.6%)	-0.039	435 (20.1%)	449 (20.7%)	-0.015
Race*									
...White; n (%)	562 (75.2%)	556 (74.4%)	0.018	NA	NA	NA	562 (75.2%)	556 (74.4%)	0.018
...Black or African American; n (%)	43 (5.8%)	40 (5.4%)	0.017	NA	NA	NA	43 (5.8%)	40 (5.4%)	0.017
...Asian; n (%)	29 (3.9%)	30 (4.0%)	-0.005	NA	NA	NA	29 (3.9%)	30 (4.0%)	-0.005
...Others; n (%)	113 (15.1%)	121 (16.2%)	-0.030	NA	NA	NA	113 (15.1%)	121 (16.2%)	-0.030
Metropolitan Statistical Area*									
...Urban; n (%)	NA	NA	NA	1,089 (76.7%)	1,069 (75.3%)	0.033	1,089 (76.7%)	1,069 (75.3%)	0.033
...Rural; n (%)	NA	NA	NA	25 (1.8%)	28 (2.0%)	-0.015	25 (1.8%)	28 (2.0%)	-0.015
...Unknown/Missing; n (%)	NA	NA	NA	306 (21.5%)	323 (22.7%)	-0.029	306 (21.5%)	323 (22.7%)	-0.029
General Health Related Measures									
Smoking; n (%)*	100 (13.4%)	93 (12.4%)	0.030	82 (5.8%)	91 (6.4%)	-0.025	182 (8.4%)	184 (8.5%)	-0.004
Obesity or Overweight; n (%)*	61 (8.2%)	68 (9.1%)	-0.032	68 (4.8%)	76 (5.4%)	-0.027	129 (6.0%)	144 (6.6%)	-0.025
Obesity; n (%)	44 (5.9%)	45 (6.0%)	-0.004	51 (3.6%)	54 (3.8%)	-0.011	095 (4.4%)	099 (4.6%)	-0.010
Overweight; n (%)	22 (2.9%)	27 (3.6%)	-0.039	22 (1.5%)	26 (1.8%)	-0.024	044 (2.0%)	053 (2.4%)	-0.027
Cardiovascular Measures									
Hypertension; n (%)*	452 (60.5%)	446 (59.7%)	0.016	636 (44.8%)	663 (46.7%)	-0.038	1,088 (50.2%)	1,109 (51.2%)	-0.020
Hyperlipidemia; n (%)*	413 (55.3%)	403 (53.9%)	0.028	544 (38.3%)	551 (38.8%)	-0.010	957 (44.2%)	954 (44.0%)	0.004
Coronary artery disease (MI, angina, Coronary atherosclerosis and other forms of chronic ischemic heart disease); n (%)*	117 (15.7%)	111 (14.9%)	0.022	212 (14.9%)	222 (15.6%)	-0.019	329 (15.2%)	333 (15.4%)	-0.006
Old MI; n (%)	14 (1.9%)	20 (2.7%)	-0.053	18 (1.3%)	17 (1.2%)	0.009	032 (1.5%)	037 (1.7%)	-0.016
Acute MI; n (%)	7 (0.9%)	6 (0.8%)	0.011	16 (1.1%)	15 (1.1%)	0.000	023 (1.1%)	021 (1.0%)	0.010
ACS/unstable angina; n (%)	12 (1.6%)	9 (1.2%)	0.034	16 (1.1%)	23 (1.6%)	-0.043	028 (1.3%)	032 (1.5%)	-0.017
Stable angina; n (%)	24 (3.2%)	14 (1.9%)	0.083	33 (2.3%)	32 (2.3%)	0.000	057 (2.6%)	046 (2.1%)	0.033
Coronary atherosclerosis and other CHD; n (%)	103 (13.8%)	94 (12.6%)	0.035	190 (13.4%)	195 (13.7%)	-0.009	293 (13.5%)	289 (13.3%)	0.006
History of CABG or PTCA; n (%)	17 (2.3%)	16 (2.1%)	0.014	12 (0.8%)	18 (1.3%)	-0.049	029 (1.3%)	034 (1.6%)	-0.025
Cerebrovascular disease (Stroke, TIA, Late effects); n (%)*	39 (5.2%)	56 (7.5%)	-0.094	79 (5.6%)	88 (6.2%)	-0.025	118 (5.4%)	144 (6.6%)	-0.051
Stroke (Ischemic or hemorrhagic); n (%)	23 (3.1%)	36 (4.8%)	-0.087	48 (3.4%)	50 (3.5%)	-0.005	071 (3.3%)	086 (4.0%)	-0.037
TIA; n (%)	19 (2.5%)	18 (2.4%)	0.006	36 (2.5%)	45 (3.2%)	-0.042	055 (2.5%)	063 (2.9%)	-0.025
Late effects of cerebrovascular disease; n (%)	12 (1.6%)	24 (3.2%)	-0.105	17 (1.2%)	19 (1.3%)	-0.009	029 (1.3%)	043 (2.0%)	-0.055
Heart Failure; n (%)*	36 (4.8%)	41 (5.5%)	-0.032	99 (7.0%)	115 (8.1%)	-0.042	135 (6.2%)	156 (7.2%)	-0.040
Peripheral Vascular Disease (PVD) or PVD Surgery; n (%)*	64 (8.6%)	62 (8.3%)	0.011	98 (6.9%)	88 (6.2%)	0.028	162 (7.5%)	150 (6.9%)	0.023
Atrial fibrillation and Other cardiac dysrhythmia; n (%)*	138 (18.5%)	132 (17.7%)	0.021	237 (16.7%)	226 (15.9%)	0.022	375 (17.3%)	358 (16.5%)	0.021
Atrial fibrillation; n (%)	76 (10.2%)	70 (9.4%)	0.027	128 (9.0%)	131 (9.2%)	-0.007	204 (9.4%)	201 (9.3%)	0.003
Other cardiac dysrhythmia; n (%)	111 (14.9%)	101 (13.5%)	0.040	164 (11.5%)	152 (10.7%)	0.025	275 (12.7%)	253 (11.7%)	0.031
Diabetes Related Measures									
Diabetes with or w/o complications; n (%)*	161 (21.6%)	149 (19.9%)	0.042	255 (18.0%)	240 (16.9%)	0.029	416 (19.2%)	389 (18.0%)	0.031
Diabetes mellitus without mention of complications; n (%)	143 (19.1%)	133 (17.8%)	0.034	220 (15.5%)	206 (14.5%)	0.028	363 (16.8%)	339 (15.6%)	0.033
Diabetes with specified complications; n (%)	59 (7.9%)	48 (6.4%)	0.058	89 (6.3%)	86 (6.1%)	0.008	148 (6.8%)	134 (6.2%)	0.024
Diabetes with unspecified complications; n (%)	7 (0.9%)	5 (0.7%)	0.022	11 (0.8%)	11 (0.8%)	0.000	018 (0.8%)	016 (0.7%)	0.012

Appendix B

Hypoglycemia; n (%)*	9 (1.2%)	15 (2.0%)	-0.064	17 (1.2%)	22 (1.5%)	-0.026	026 (1.2%)	037 (1.7%)	-0.042
GI Conditions									
Upper GI (Diseases of esophagus, stomach and duodenum); n (%)*	211 (28.2%)	217 (29.0%)	-0.018	269 (18.9%)	275 (19.4%)	-0.013	480 (22.2%)	492 (22.7%)	-0.012
GI bleeding; n (%)*	26 (3.5%)	27 (3.6%)	-0.005	58 (4.1%)	51 (3.6%)	0.026	084 (3.9%)	078 (3.6%)	0.016
Eating disorders, Non-infective enteritis and colitis, postoperative disorders of the digestive system; n (%)*	145 (19.4%)	146 (19.5%)	-0.003	206 (14.5%)	203 (14.3%)	0.006	351 (16.2%)	349 (16.1%)	0.003
Eating disorders (Anorexia and Bulimia); n (%)	63 (8.4%)	60 (8.0%)	0.015	50 (3.5%)	62 (4.4%)	-0.046	113 (5.2%)	122 (5.6%)	-0.018
Non-infective enteritis and colitis; n (%)	69 (9.2%)	75 (10.0%)	-0.027	133 (9.4%)	124 (8.7%)	0.024	202 (9.3%)	199 (9.2%)	0.003
Intraoperative and postprocedural complications and disorders of digestive system; n (%)	34 (4.6%)	34 (4.6%)	0.000	58 (4.1%)	46 (3.2%)	0.048	092 (4.2%)	080 (3.7%)	0.026
Disorders of gallbladder, biliary tract and pancreas; n (%)*	33 (4.4%)	35 (4.7%)	-0.014	57 (4.0%)	52 (3.7%)	0.016	090 (4.2%)	087 (4.0%)	0.010
Rheumatic Conditions									
Rheumatoid arthritis and other inflammatory polyarthropathies; n (%)*	95 (12.7%)	97 (13.0%)	-0.009	163 (11.5%)	150 (10.6%)	0.029	258 (11.9%)	247 (11.4%)	0.016
Osteoarthrosis; n (%)*	283 (37.9%)	298 (39.9%)	-0.041	445 (31.3%)	456 (32.1%)	-0.017	728 (33.6%)	754 (34.8%)	-0.025
Other rheumatic disorders (including gout); n (%)*	550 (73.6%)	548 (73.4%)	0.005	997 (70.2%)	1,005 (70.8%)	-0.013	1,547 (71.4%)	1,553 (71.7%)	-0.007
Gout and other crystal arthropathies; n (%)	21 (2.8%)	15 (2.0%)	0.052	25 (1.8%)	25 (1.8%)	0.000	046 (2.1%)	040 (1.8%)	0.022
Other rheumatic disorders; n (%)*	547 (73.2%)	546 (73.1%)	0.002	991 (69.8%)	1,000 (70.4%)	-0.013	1,538 (71.0%)	1,546 (71.3%)	-0.007
Neuro Conditions									
Parkinson's disease; n (%)	1 (0.1%)	0 (0.0%)	0.045	3 (0.2%)	1 (0.1%)	0.026	004 (0.2%)	001 (0.0%)	0.063
Alzheimer and other Dementia Disease ; n (%)*	49 (6.6%)	56 (7.5%)	-0.035	71 (5.0%)	86 (6.1%)	-0.048	120 (5.5%)	142 (6.6%)	-0.046
Seizure disorders (epilepsy); n (%)	17 (2.3%)	13 (1.7%)	0.043	26 (1.8%)	27 (1.9%)	-0.007	043 (2.0%)	040 (1.8%)	0.015
Delirium/Psychosis; n (%)	30 (4.0%)	31 (4.1%)	-0.005	35 (2.5%)	57 (4.0%)	-0.085	065 (3.0%)	088 (4.1%)	-0.059
Other Conditions									
Vitamin D deficiency; n (%)*	212 (28.4%)	206 (27.6%)	0.018	218 (15.4%)	217 (15.3%)	0.003	430 (19.8%)	423 (19.5%)	0.008
Liver disease; n (%)*	26 (3.5%)	33 (4.4%)	-0.046	49 (3.5%)	47 (3.3%)	0.011	075 (3.5%)	080 (3.7%)	-0.011
Chronic kidney disease stages I-III; n (%)*	70 (9.4%)	74 (9.9%)	-0.017	65 (4.6%)	59 (4.2%)	0.020	135 (6.2%)	133 (6.1%)	0.004
Chronic kidney disease stages IV-V, ESRD; n (%)	21 (2.8%)	17 (2.3%)	0.032	18 (1.3%)	21 (1.5%)	-0.017	039 (1.8%)	038 (1.8%)	0.000
Premature menopause; n (%)	1 (0.1%)	3 (0.4%)	-0.060	1 (0.1%)	1 (0.1%)	0.000	002 (0.1%)	004 (0.2%)	-0.026
Oophorectomy; n (%)	1 (0.1%)	0 (0.0%)	0.045	0 (0.0%)	1 (0.1%)	-0.045	001 (0.0%)	001 (0.0%)	0.000
COPD; n (%)*	123 (16.5%)	130 (17.4%)	-0.024	214 (15.1%)	207 (14.6%)	0.014	337 (15.6%)	337 (15.6%)	0.000
Asthma; n (%)*	80 (10.7%)	88 (11.8%)	-0.035	132 (9.3%)	135 (9.5%)	-0.007	212 (9.8%)	223 (10.3%)	-0.017
Obstructive sleep apnea; n (%)*	49 (6.6%)	48 (6.4%)	0.008	56 (3.9%)	50 (3.5%)	0.021	105 (4.8%)	098 (4.5%)	0.014
Syncope; n (%)*	39 (5.2%)	45 (6.0%)	-0.035	77 (5.4%)	85 (6.0%)	-0.026	116 (5.4%)	130 (6.0%)	-0.026
Falls; n (%)*	134 (17.9%)	142 (19.0%)	-0.028	79 (5.6%)	81 (5.7%)	-0.004	213 (9.8%)	223 (10.3%)	-0.017
VTE; n (%)	33 (4.4%)	32 (4.3%)	0.005	49 (3.5%)	47 (3.3%)	0.011	082 (3.8%)	079 (3.6%)	0.011
Gait abnormality; n (%)*	141 (18.9%)	140 (18.7%)	0.005	167 (11.8%)	166 (11.7%)	0.003	308 (14.2%)	306 (14.1%)	0.003
Osteopenia; n (%)*	256 (34.3%)	247 (33.1%)	0.025	316 (22.3%)	315 (22.2%)	0.002	572 (26.4%)	562 (25.9%)	0.011
History of hip and femur fractures; n (%)*	41 (5.5%)	45 (6.0%)	-0.021	105 (7.4%)	102 (7.2%)	0.008	146 (6.7%)	147 (6.8%)	-0.004
Other Fractures ; n (%)*	90 (12.0%)	95 (12.7%)	-0.021	170 (12.0%)	160 (11.3%)	0.022	260 (12.0%)	255 (11.8%)	0.006
Glucocorticoid-Induced Osteoporosis; n (%)*	2 (0.3%)	2 (0.3%)	0.000	1 (0.1%)	2 (0.1%)	0.000	003 (0.1%)	004 (0.2%)	-0.026
Combined comorbidity score									
...mean (sd)	1.20 (2.17)	1.25 (2.25)	-0.023	0.90 (1.71)	0.86 (1.72)	0.023	1.00 (1.88)	0.99 (1.92)	0.005
...median [IQR]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	0.000	0.00 [0.00, 2.00]	0.00 [0.00, 1.00]	0.000	0.34 (1.88)	0.34 (1.92)	0.000
Frailty Score: Empirical Version 365 days as Categories									
...< 0.12908; n (%)	317 (42.4%)	318 (42.6%)	-0.004	476 (33.5%)	472 (33.2%)	0.006	793 (36.6%)	790 (36.5%)	0.002
...0.12908 - 0.1631167; n (%)	158 (21.2%)	155 (20.7%)	0.012	309 (21.8%)	318 (22.4%)	-0.014	467 (21.6%)	473 (21.8%)	-0.005
...>= 0.1631167; n (%)	272 (36.4%)	274 (36.7%)	-0.006	635 (44.7%)	630 (44.4%)	0.006	907 (41.9%)	904 (41.7%)	0.004
Medication Use									
Use of oral corticosteroids; n (%)*	268 (35.9%)	266 (35.6%)	0.006	498 (35.1%)	506 (35.6%)	-0.010	766 (35.3%)	772 (35.6%)	-0.006
Use of antidepressants; n (%)*	256 (34.3%)	275 (36.8%)	-0.052	606 (42.7%)	576 (40.6%)	0.043	862 (39.8%)	851 (39.3%)	0.010
Use of anticonvulsants; n (%)*	159 (21.3%)	149 (19.9%)	0.035	323 (22.7%)	311 (21.9%)	0.019	482 (22.2%)	460 (21.2%)	0.024
Use of beta blocker OR calcium channel blocker; n (%)*	250 (33.5%)	235 (31.5%)	0.043	471 (33.2%)	478 (33.7%)	-0.011	721 (33.3%)	713 (32.9%)	0.009
Use of PPIs; n (%)*	222 (29.7%)	219 (29.3%)	0.009	488 (34.4%)	501 (35.3%)	-0.019	710 (32.8%)	720 (33.2%)	-0.009
Use of opioids; n (%)*	419 (56.1%)	420 (56.2%)	-0.002	848 (59.7%)	853 (60.1%)	-0.008	1,267 (58.5%)	1,273 (58.7%)	-0.004
Use of antipsychotics; n (%)*	21 (2.8%)	24 (3.2%)	-0.023	53 (3.7%)	54 (3.8%)	-0.005	074 (3.4%)	078 (3.6%)	-0.011
Use of anxiolytics/hypnotics; n (%)*	74 (9.9%)	88 (11.8%)	-0.061	249 (17.5%)	228 (16.1%)	0.037	323 (14.9%)	316 (14.6%)	0.008
Use of dementia meds; n (%)*	34 (4.6%)	32 (4.3%)	0.015	73 (5.1%)	69 (4.9%)	0.009	107 (4.9%)	101 (4.7%)	0.009
Use of antiparkinsonian meds; n (%)*	21 (2.8%)	26 (3.5%)	-0.040	58 (4.1%)	64 (4.5%)	-0.020	079 (3.6%)	090 (4.2%)	-0.031
Use of Benzodiazepine; n (%)*	146 (19.5%)	162 (21.7%)	-0.054	404 (28.5%)	382 (26.9%)	0.036	550 (25.4%)	544 (25.1%)	0.007
All antidiabetic medications; n (%)*	78 (10.4%)	73 (9.8%)	0.020	162 (11.4%)	166 (11.7%)	-0.009	240 (11.1%)	239 (11.0%)	0.003
ACEI/ARB; n (%)*	261 (34.9%)	256 (34.3%)	0.013	470 (33.1%)	475 (33.5%)	-0.008	731 (33.7%)	731 (33.7%)	0.000
Use of Anticoagulants; n (%)*	71 (9.5%)	72 (9.6%)	-0.003	158 (11.1%)	148 (10.4%)	0.023	229 (10.6%)	220 (10.2%)	0.013
Use of Amiodarone; n (%)	9 (1.2%)	8 (1.1%)	0.009	19 (1.3%)	23 (1.6%)	-0.025	028 (1.3%)	031 (1.4%)	-0.009

Appendix B

Digoxin; n (%)	18 (2.4%)	14 (1.9%)	0.034	45 (3.2%)	38 (2.7%)	0.030	063 (2.9%)	052 (2.4%)	0.031
Use of Diuretics; n (%)*	205 (27.4%)	220 (29.5%)	-0.047	466 (32.8%)	466 (32.8%)	0.000	671 (31.0%)	686 (31.7%)	-0.015
Use of Aspirin; n (%)	5 (0.7%)	5 (0.7%)	0.000	25 (1.8%)	24 (1.7%)	0.008	030 (1.4%)	029 (1.3%)	0.009
NSAIDs (NOT including aspirin); n (%)	203 (27.2%)	188 (25.2%)	0.045	377 (26.5%)	318 (22.4%)	0.096	580 (26.8%)	506 (23.4%)	0.078
HRT (Use of estrogens, progestins, androgens); n (%)*	47 (6.3%)	44 (5.9%)	0.017	84 (5.9%)	93 (6.5%)	-0.025	131 (6.0%)	137 (6.3%)	-0.012
Other Pressors; n (%)	5 (0.7%)	5 (0.7%)	0.000	8 (0.6%)	20 (1.4%)	-0.080	013 (0.6%)	025 (1.2%)	-0.064
Use of Statins ; n (%)*	258 (34.5%)	252 (33.7%)	0.017	521 (36.7%)	523 (36.8%)	-0.002	779 (35.9%)	775 (35.8%)	0.002
Selective Estrogen Receptor Modulators (SERMs); n (%)*	7 (0.9%)	19 (2.5%)	-0.124	31 (2.2%)	38 (2.7%)	-0.032	038 (1.8%)	057 (2.6%)	-0.055
Healthcare Utilization Measures									
Use of any drugs claims*									
...mean (sd)	24.76 (18.01)	24.95 (18.56)	-0.010	25.89 (19.03)	25.43 (18.22)	0.025	25.50 (18.68)	25.26 (18.34)	0.013
Number of office visits*									
...mean (sd)	11.57 (7.84)	11.48 (7.34)	0.012	11.99 (8.51)	11.90 (7.78)	0.011	11.85 (8.29)	11.76 (7.63)	0.011
Number of ED visits*									
...mean (sd)	0.69 (1.22)	0.76 (1.17)	-0.059	0.59 (1.19)	0.60 (1.22)	-0.008	0.62 (1.20)	0.66 (1.20)	-0.033
Number of Hospitalizations*									
...mean (sd)	0.46 (1.02)	0.46 (1.02)	0.000	2.09 (5.83)	2.09 (5.52)	0.000	1.53 (4.76)	1.53 (4.51)	0.000
Recent hospitalization (-30 days to Index Rx date); n (%)	14 (1.9%)	19 (2.5%)	-0.041	28 (2.0%)	29 (2.0%)	0.000	042 (1.9%)	048 (2.2%)	-0.021
Old hospitalizations (-450 to -31 days); n (%)	163 (21.8%)	167 (22.4%)	-0.014	356 (25.1%)	360 (25.4%)	-0.007	519 (24.0%)	527 (24.3%)	-0.007
Number of Endocrinologist visits*									
...mean (sd)	0.41 (1.19)	0.43 (1.11)	-0.017	1.75 (2.89)	1.73 (2.94)	0.007	1.29 (2.44)	1.28 (2.47)	0.004
Number of DXA test performed*									
...mean (sd)	0.73 (0.63)	0.73 (0.54)	0.000	0.49 (0.52)	0.49 (0.52)	0.000	0.57 (0.56)	0.57 (0.53)	0.000
Number of hospital days*									
...mean (sd)	5.18 (17.50)	4.98 (17.59)	0.011	2.09 (5.83)	2.09 (5.52)	0.000	3.16 (11.30)	3.09 (11.25)	0.006
Occurrence of basic or comprehensive blood chemistry test; n (%)*	577 (77.2%)	573 (76.7%)	0.012	626 (44.1%)	615 (43.3%)	0.016	1,203 (55.5%)	1,188 (54.8%)	0.014
Number of HbA1C test ordered*									
...mean (sd)	0.55 (1.09)	0.54 (1.15)	0.009	0.27 (0.78)	0.26 (0.79)	0.013	0.37 (0.90)	0.36 (0.93)	0.011
Flexible Sigmoidoscopy or colonoscopy or CT virtual colonoscopy; n (%)*	64 (8.6%)	68 (9.1%)	-0.018	142 (10.0%)	138 (9.7%)	0.010	206 (9.5%)	206 (9.5%)	0.000
Number of Mammograms (Breast cancer screening); n (%)*	352 (47.1%)	359 (48.1%)	-0.020	547 (38.5%)	545 (38.4%)	0.002	899 (41.5%)	904 (41.7%)	-0.004
Number of Pap smear (Cervical cancer screening); n (%)*	144 (19.3%)	138 (18.5%)	0.020	264 (18.6%)	265 (18.7%)	-0.003	408 (18.8%)	403 (18.6%)	0.005
Flu vaccine; n (%)*	278 (37.2%)	273 (36.5%)	0.015	312 (22.0%)	314 (22.1%)	-0.002	590 (27.2%)	587 (27.1%)	0.002
Pneumococcal vaccine; n (%)*	132 (17.7%)	135 (18.1%)	-0.010	125 (8.8%)	134 (9.4%)	-0.021	257 (11.9%)	269 (12.4%)	-0.015
Copay for pharmacy cost (charges in U.S. $)*									
...mean (sd)	36.14 (46.87)	34.80 (42.78)	0.030	21.56 (22.23)	21.55 (23.62)	0.000	26.59 (32.88)	26.12 (31.56)	0.015
...median [IQR]	23.44 [13.37, 42.35]	25.00 [11.82, 41.43]	-0.035	17.18 [7.87, 29.33]	17.29 [8.09, 28.68]	-0.005	19.34 (32.88)	19.95 (31.56)	-0.019
...Missing; n (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Business Type*									
...Commercial; n (%)	291 (39.0%)	291 (39.0%)	0.000	NA	NA	NA	291 (39.0%)	291 (39.0%)	0.000
...Medicare; n (%)	456 (61.0%)	456 (61.0%)	0.000	NA	NA	NA	456 (61.0%)	456 (61.0%)	0.000
Insurance Plan Type*									
...Comprehensive; n (%)	NA	NA	NA	413 (29.1%)	431 (30.4%)	-0.028	413 (29.1%)	431 (30.4%)	-0.028
...HMO; n (%)	NA	NA	NA	97 (6.8%)	104 (7.3%)	-0.020	97 (6.8%)	104 (7.3%)	-0.020
...PPO; n (%)	NA	NA	NA	731 (51.5%)	705 (49.6%)	0.038	731 (51.5%)	705 (49.6%)	0.038
...Others; n (%)	NA	NA	NA	179 (12.6%)	180 (12.7%)	-0.003	179 (12.6%)	180 (12.7%)	-0.003

***Included in the 1:1 PS matching model**