Biologics License Application 761062
Romosozumab Injection

FDA Opening Remarks

Bone, Reproductive, and Urologic Drugs Advisory Committee Meeting

January 16, 2019

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Romosozumab

Mechanism: Monoclonal antibody that inhibits sclerostin, stimulating bone formation, and to a lesser extent, inhibiting bone resorption

Proposed Indication: Treatment of postmenopausal osteoporosis in women at high risk for fracture (Amgen is not seeking the broad treatment of postmenopausal osteoporosis indication)

Subcutaneous Injection: 120 mg once monthly, by healthcare provider

Treatment Duration: One year, then switch to antiresorptive therapy

Two Phase 3 Fracture Outcomes Trials

- **20070337** (N=7180): One year of double-blind romosozumab or placebo then one year of open-label denosumab

- **2011142** (N=4093): One year of double-blind romosozumab or alendronate then ≥1 year of open-label alendronate

Positive Fracture Outcomes Included in the Hierarchical Testing Strategy (Trial 337)

	Romosozumab Then Denosumab	Placebo Then Denosumab	Relative Risk Reduction (95% Confidence Interval)	p-value
Morphometric vertebral fracture, Month 12	0.5%	1.8%	73% (53, 84)	<0.001
Morphometric vertebral fracture, Month 24	0.6%	2.5%	75% (60, 84)	<0.001
Clinical fracture, Month 12	1.6%	2.5%	36% (11, 54)	<0.01

Clinical fracture = nonvertebral fracture plus symptomatic vertebral fracture

Positive Fracture Outcomes Included in the Hierarchical Testing Strategy (Trial 142)

	Romosozumab Then Alendronate	Alendronate	Relative Risk Reduction (95% Confidence Interval)	p-value
Morphometric vertebral fracture, Month 24	4.1%	8.0%	50% (34, 62)	<0.001
Clinical fracture, primary analysis timepoint	9.7%	13.0%	27% (12, 39)	<0.001
Nonvertebral fracture, primary analysis timepoint	8.7%	10.6%	19% (1, 34)	0.02

Clinical fracture = nonvertebral fracture plus symptomatic vertebral fracture

Primary analysis timepoint: after all subjects reached month 24 and had a prespecified event rate

Phase 3 Cardiovascular Assessment

- DCRI adjudicated cardiovascular serious adverse events
- TIMI performed a retrospective, second adjudication that included non-serious cardiovascular adverse events
- FDA's presentations focus on:
  - The DCRI adjudicated events (TIMI results were similar)
  - Major Adverse Cardiac Events (MACE)

DCRI = Duke Clinical Research Institute; TIMI = Thrombolysis in Myocardial Infarction

Cardiovascular Findings

One Year Double-Blind Treatment Period	337		142	
	Romosozumab	Placebo	Romosozumab	Alendronate
MACE	30 (0.8%)	29 (0.8%)	41 (2.0%)	22 (1.1%)
Hazard ratio (95% CI)	1.03 (0.62, 1.72)		1.87 (1.11, 3.14)	
Cardiovascular death	17 (0.5%)	15 (0.4%)	17 (0.8%)	12 (0.6%)
Hazard ratio (95% CI)	1.13 (0.56, 2.26)		1.42 (0.68, 2.97)	
Nonfatal myocardial infarction	9 (0.3%)	8 (0.2%)	16 (0.8%)	5 (0.2%)
Hazard ratio (95% CI)	1.12 (0.43, 2.91)		3.21 (1.18, 8.77)	
Nonfatal stroke	8 (0.2%)	10 (0.3%)	13 (0.6%)	7 (0.3%)
Hazard ratio (95% CI)	0.80 (0.32, 2.02)		1.86 (0.74, 4.67)	

The Conundrum

- Romosozumab is clearly efficacious, reducing the risk of fracture more than placebo and more than alendronate
- In one of two fracture outcomes trials, romosozumab increased the risk of major adverse cardiac events
  - True adverse effect of romosozumab or chance finding?
  - Cardioprotective effect of the alendronate comparator?
- Background cardiovascular risk increases after menopause; a true drug effect would further increase this risk

Discussion and Voting Questions

Discussion Question 1

Discuss whether the cardiovascular safety of romosozumab has been adequately characterized. If additional safety data are needed, discuss the type(s) of data that are needed and whether these data should be obtained pre-approval or post-approval.

Discussion Question 2

Amgen is seeking an indication for the treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

Discuss whether the benefit/risk profile of romosozumab could be improved by further narrowing the indicated population to patients at low cardiovascular risk, and if so, how to define the narrowed population.

Voting Question

Is the overall benefit/risk profile of romosozumab acceptable to support approval?

A. Yes, for Amgen's proposed indication (treatment of osteoporosis in postmenopausal women at high risk of fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy)

B. Yes, but for a different indication

C. No

Provide a rationale for your vote. If you voted for (B), describe the patient population in whom the benefits outweigh the risks.


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Clinical Efficacy and Safety Assessment

Romosozumab (BLA 761062)
Advisory Committee Meeting
January 16, 2019

Jacqueline Karp, M.D.
Division of Bone, Reproductive and Urologic Products

Objectives

- Key efficacy and safety findings of romosozumab postmenopausal osteoporosis fracture trials
  - Trial 20070337 (337)
  - Trial 20110142 (142)

- Cardiovascular safety concern

Romosozumab

- Immunoglobulin G2 (IgG2) monoclonal antibody against sclerostin
  - Sclerostin
    - Glycoprotein secreted by osteocytes
    - Acts through osteoblast receptors (lipoprotein receptor-related proteins 4, 5, and 6)
    - Inhibits Wnt signaling and bone formation
    - Increases bone resorption via effects on osteoclast mediators
- Increases bone formation, decreases bone resorption

Romosozumab Fracture Trials

	Trial 337	Trial 142
Design	Double-blind, placebo-controlled	Double-blind, active- controlled
Population	Women with osteoporosis aged 55-90 **(N=7180)**	Women with osteoporosis (+ prior fragility fracture) aged 55-90 **(N=4093)**
Treatment/Duration	- Randomized 1:1 to romosozumab or placebo x 12 months - Follow-on denosumab x 12 months	- Randomized 1:1 to romosozumab or alendronate x 12 months - Follow-on alendronate (variable, minimum 12 mos.)
Primary Endpoints	Morphometric (symptomatic + asymptomatic) vertebral fracture at month 12, month 24	Morphometric vertebral fracture at month 24, clinical fracture* at primary analysis**

* Composite of symptomatic vertebral fractures + nonvertebral fractures

** Event-driven; occurred when ≥ 330 subjects had clinical fracture and all completed 24-month visit

Trial 337: Primary Efficacy Endpoints

Endpoint	Subjects with Fracture, %		Absolute Risk Reduction (ARR), % (95% CI)	Relative Risk Reduction (RRR), % (95% CI)	P-value
	Placebo/ Denosumab	Romosozumab/ Denosumab			
Morphometric Vertebral Fracture Month 12	1.8	0.5	1.3 (0.8, 1.8)	73 (53, 84)	<0.001
Morphometric Vertebral Fracture Month 24	2.5	0.6	1.9 (1.3, 2.5)	75 (60, 84)	<0.001

Trial 337: Secondary Efficacy Endpoints

Endpoint	Subjects with Fracture, %		ARR, % (95% CI)	RRR, % (95% CI)	P-value
	Placebo/ Denosumab	Romosozumab/ Denosumab			
Clinical Fracture Month 12	2.5	1.6	1.2 (0.4, 1.9)	36 (11, 54)	0.008
Nonvertebral Fracture Month 12	2.1	1.6	0.8 (0.1, 1.4)	25 (-5, 47)	.096
Nonvertebral Fracture Month 24	3.6	2.7	1.0 (0.2, 1.9)	25 (3, 43)	Testing stopped
Hip Fracture* Month 12	0.4	0.2	0.2 (0.0, 0.6)	46 (-35, 78)	-
Hip Fracture* Month 24	0.6	0.3	0.4 (0.0, 0.7)	50 (-4, 76)	-

*Trial not powered to assess; only 33 occurred through month 24

Trial 337: Bone Mineral Density (BMD) Results

BMD, Mean Percent Change from Baseline, LOCF, ANCOVA

	Placebo/ Denosumab	Romosozumab/ Denosumab	LS Mean Difference (95% CI)
Month 12			
Lumbar Spine	0.4	13.1	12.7 (12.4, 12.9)
Total Hip	0.3	6.0	5.8 (5.6, 6.0)
Femoral Neck	0.3	5.5	5.2 (4.9, 5.4)
Month 24			
Lumbar Spine	5.5	16.6	11.1 (10.8, 11.4)
Total Hip	3.2	8.5	5.3 (5.1, 5.5)
Femoral Neck	2.3	7.3	4.9 (4.7, 5.2)

LOCF = last observation carried forward; ANCOVA = analysis of covariance; LS = least squares

Trial 142: Primary Efficacy Endpoints

Endpoint	Subjects with Fracture, %		Risk Reduction		P-value
	Alendronate/ Alendronate	Romosozumab/ Alendronate			
Morphometric Vertebral Fracture Month 24			ARR (95% CI)	RRR (95% CI)	
	8.0	4.1	4% (2.5, 5.6)	50% (34, 62)	<0.001
Clinical Fracture at Primary Analysis*			Hazard Ratio (HR) (95% CI)		
	13.0	9.7	0.73 (0.61, 0.88)		<0.001

*Based on 464 subjects with clinical fracture, median follow-up 33 months

Trial 142: Secondary Efficacy Endpoints

	Subjects with Fracture, %		HR (95% CI)	P-value
	Alendronate/ Alendronate	Romosozumab/ Alendronate		
Nonvertebral Fracture at Primary Analysis*	10.6	8.7	0.81 (0.66, 0.99)	0.019
Hip Fracture at Primary Analysis**	3.2	2.0	0.62 (0.42, 0.92)	-

* Based on 395 subjects with nonvertebral fracture
** Based on 107 subjects with hip fracture

Trial 142: BMD Results

BMD, Mean Percent Change from Baseline, LOCF, ANCOVA			
	Alendronate/ Alendronate	**Romosozumab/ Alendronate**	**LS Mean Difference (95% CI)**
Month 12			
Lumbar Spine	5.0	13.7	8.7 (8.3, 9.1)
Total Hip	2.8	6.2	3.3 (3.0, 3.6)
Femoral Neck	1.7	4.9	3.2 (2.9, 3.5)
Month 24			
Lumbar Spine	7.2	15.3	8.1 (7.6, 8.6)
Total Hip	3.5	7.2	3.8 (3.4, 4.1)
Femoral Neck	2.3	6.0	3.8 (3.4, 4.1)

LOCF = last observation carried forward; ANCOVA = analysis of covariance

Efficacy Summary (Trials 337 and 142)

- Significantly reduced risk of **morphometric vertebral fractures**
  - at **month 12** (romosozumab vs. placebo)
  - at **month 24** (romosozumab followed by denosumab vs. placebo followed by denosumab)
- Superiority of romosozumab followed by alendronate over alendronate alone in reducing
  - **morphometric vertebral fractures** at month 24
  - **clinical fractures** and **nonvertebral fractures** (median follow-up 33 months)
- Significantly higher **BMD** increases (all sites) vs. comparators

Romosozumab Safety
Trial 337 and Trial 142
12-month Double-Blind Treatment Periods

Treatment-emergent Adverse Events (AEs)

	Subject Incidence of Treatment-emergent AEs, 12-Month Double-Blind Treatment Period			
	Trial 337		Trial 142	
	Placebo	Romosozumab	Alendronate	Romosozumab
N	3591	3589	2047	2046
n, safety analysis	3576	3581	2014	2040
Age, mean years (SD)	71 (7)	71 (7)	74 (8)	74 (8)
Fatal AEs, n (%)	24 (0.7)	29 (0.8)	22 (1)	30 (1)
Serious AEs, n (%)	314 (9)	344 (10)	278 (14)	262 (13)
AEs leading to trial withdrawal, n (%)	50 (1)	45 (1)	27 (1)	28 (1)
AEs leading to study drug withdrawal, (%)	96 (3)	106 (3)	66 (3)	71 (4)
All AEs, (%)	2863 (80)	2812 (79)	1584 (79)	1543 (76)

Fatal AEs

- Balanced between treatment groups in both trials, with 2 exceptions
- **Trial 337**: deaths due to neoplasms
  - 3 (<0.1%) placebo vs. 8 (0.2%) romosozumab
  - due to malignant lung neoplasm (0 placebo, 4 romosozumab)
    - all smokers
    - short time to diagnosis (47-132 days after first dose)
    - overall fatal + nonfatal lung neoplasms balanced between treatment groups
- **Trial 142**: deaths due to cardiac disorders
  - 3 (0.1%) alendronate vs. 9 (0.4%) romosozumab

Serious Adverse Events (SAEs)

- **Trial 337:** 314 (9%) placebo vs. 344 (10%) romosozumab
- **Trial 142:** 278 (14%) alendronate vs. 262 (13%) romosozumab
- Event types balanced between treatment groups
- One notable imbalance (Trial 142)
  - higher incidence adjudicated positive cardiovascular (CV) SAEs in romosozumab vs. alendronate subjects

Adverse Events of Interest

Hypocalcemia

- AEs
  - **Trial 337:** 0 placebo, 1 (< 0.1%) romosozumab
  - **Trial 142:** 1 (< 0.1%) alendronate, 1 (< 0.1%) romosozumab
  - None serious
- Mild serum calcium decreases with romosozumab
  - Nadir at month 1
  - Normalization by month 12
  - Lowest: 1 subject with Grade 2 (7.0 to 8.0 mg/dL) in Trial 337

Injection Site Reactions

- **Trial 337:** 3% placebo, 5% romosozumab
- **Trial 142:** 3% alendronate, 4% romosozumab
- None of AEs serious
- Most common preferred terms (PTs): injection site pain, injection site erythema

Hypersensitivity

- **Trial 337:** 7% placebo, 7% romosozumab
  - SAEs: 0 placebo, 6 (0.2%) romosozumab
    - PTs: dermatitis allergic, alveolitis allergic, immune thrombocytopenic purpura (ITP), dermatitis, circulatory collapse, angioedema, dermatitis exfoliative, rash macular (1 subject experienced last 3)
- **Trial 142:** 6% alendronate, 6% romosozumab
  - SAEs: 2 (<0.1%) alendronate, 3 (0.1%) romosozumab
    - PTs: rash pruritic, dermatitis allergic, eczema, pruritus allergic, urticaria
- Most common PTs overall: rash, dermatitis allergic, eczema

Atypical Femoral Fractures and Osteonecrosis of the Jaw

	Trial 337		Trial 142	
	Placebo	Romosozumab	Alendronate	Romosozumab
Atypical Femoral Fractures (adjudicated positive), n	0	1	0	0
Osteonecrosis of the Jaw (adjudicated positive), n	0	1	0	0

Malignant or Unspecified Tumors

- Common pathway in sclerostin/tumor suppressor signaling (Wnt-beta-catenin)
- **Trial 337:** 2% placebo, 1% romosozumab
- **Trial 142:** 1% alendronate, 2% romosozumab
- Overall, data do not suggest safety signal
  - Balanced incidence
  - Confounders in neoplasm deaths in Trial 337

Immunogenicity

- **Trial 337:** 3575 romosozumab subjects with post-baseline results for anti-drug antibodies (ADAs)
    - 18% binding ADAs
    - 0.1% neutralizing ADAs
- **Trial 142:** 1955 romosozumab subjects with post-baseline results for ADAs
    - 15% binding ADAs
    - 0.6% neutralizing ADAs
- ADAs decreased serum romosozumab concentrations ~10%
- No effect on efficacy (BMD) or safety (overall AE reporting, hypersensitivity, injection site reactions, autoimmune disorders)

Cardiovascular Safety Assessment

Evaluation of CV SAEs

- Prespecified adjudication by Duke Clinical Research Institute (DCRI)
  - All deaths
  - All SAEs meeting prespecified “trigger” preferred terms
  - Additional SAEs identified during review of triggered events
  - Investigators also could flag potential CV SAEs

Positively Adjudicated CV SAEs

	12-Month Double-Blind Treatment Period			
	Trial 337		Trial 142	
	Placebo (N=3576)	Romosozumab (N=3581)	Alendronate (N=2014)	Romosozumab (N=2040)
Positively adjudicated CV SAEs*, n (%)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
CV death**	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Cardiac ischemic events	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Myocardial infarction	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Cerebrovascular events	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)

*Other CV SAEs included heart failure, noncoronary revascularization, and peripheral ischemic events not requiring revascularization

**Includes death of undetermined cause

Readjudication of CV Events

- Readjudication by Thrombolysis in Myocardial Infarction Study Group (TIMI) of all events previously adjudicated by DCRI (blinded to DCRI adjudication result)
- Posthoc review of all AE data, adjudication of all potential CV AEs (serious + nonserious) by TIMI
- DCRI and TIMI adjudication results similar
  - FDA presentation focuses on DCRI results

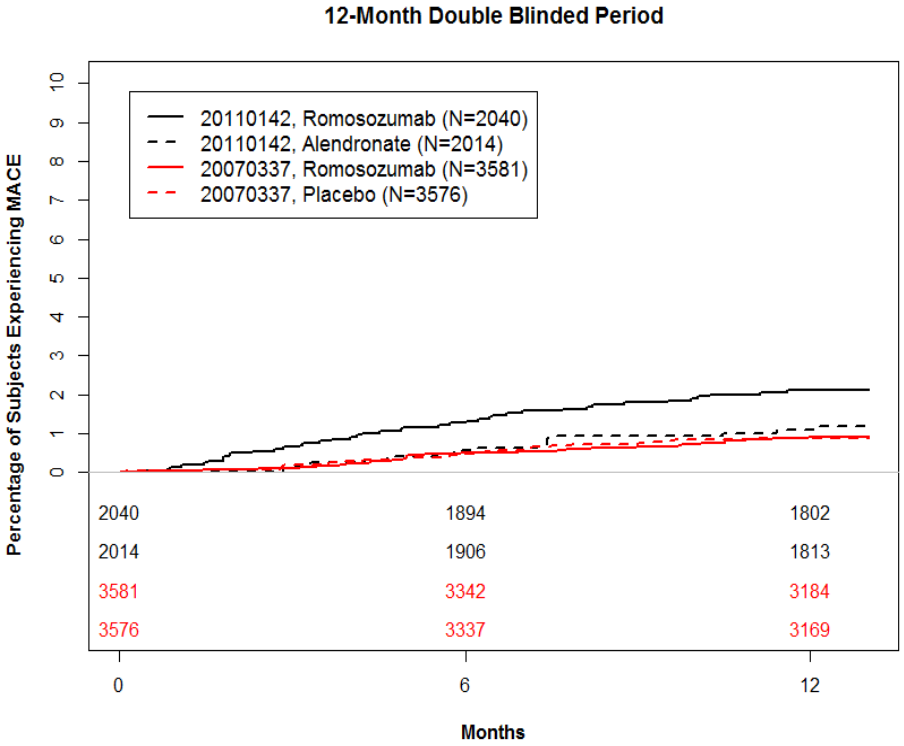
MACE (Major Adverse Cardiac Event): 12-Month Double-Blind Treatment Period

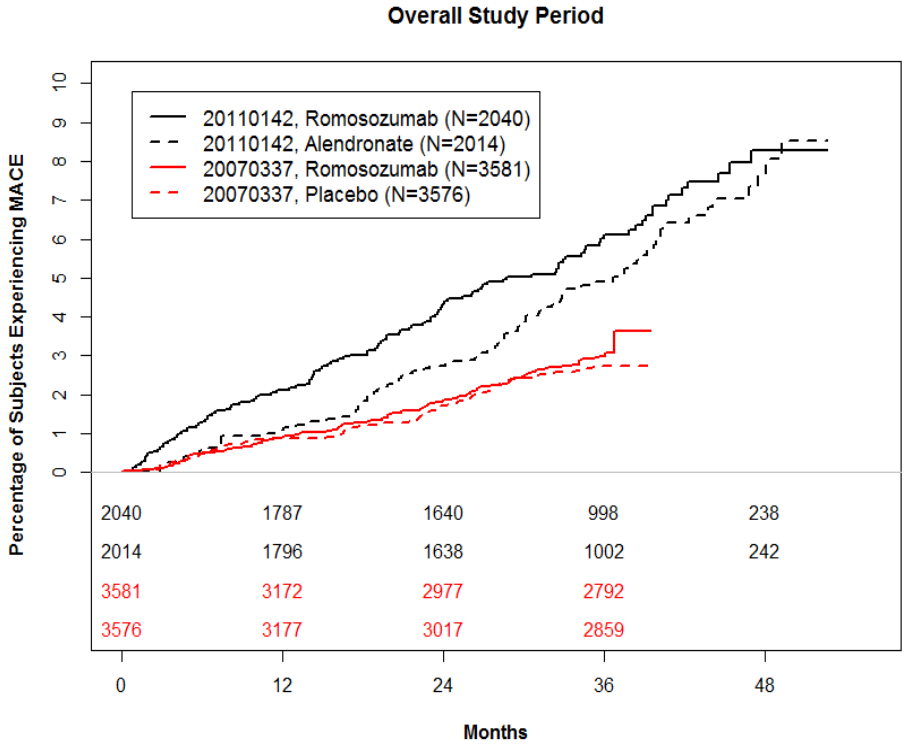
	Trial 337		Trial 142	
	Placebo (N=3576)	Romosozumab (N=3581)	Alendronate (N=2014)	Romosozumab (N=2040)
MACE, n (%)	29 (0.8)	30 (0.8)	22 (1.1)	41 (2.0)
CV death	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Nonfatal myocardial infarction	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Nonfatal stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)

MACE: Overall Study Period

	Trial 337 (24 months)		Trial 142 (24-55 months, median 33 months)	
	Placebo/ Denosumab (N=3576)	Romosozumab/ Denosumab (N=3581)	Alendronate/ Alendronate (N=2014)	Romosozumab/ Alendronate (N=2040)
MACE, n (%)	86 (2.4)	95 (2.7)	102 (5.1)	117 (5.7)
CV death	50 (1.4)	43 (1.2)	68 (3.4)	67 (3.3)
Nonfatal myocardial infarction	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Nonfatal stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)

Time to First MACE



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Cardiovascular Safety – Statistical Assessment

Romosozumab (BLA 761062)

Advisory Committee Meeting

January 16, 2019

Tae Hyun Jung, Ph.D.
Office of Biostatistics

FDA's Approach to Cardiovascular Safety Assessment

- Compare cardiovascular (CV) risk in romosozumab vs. comparator in women with postmenopausal osteoporosis
- Trials
  - Study 20070337 (337): romosozumab vs. placebo
  - Study 20110142 (142): romosozumab vs. alendronate

- **Objective**: to explore findings across trials

Traditional Meta-Analysis

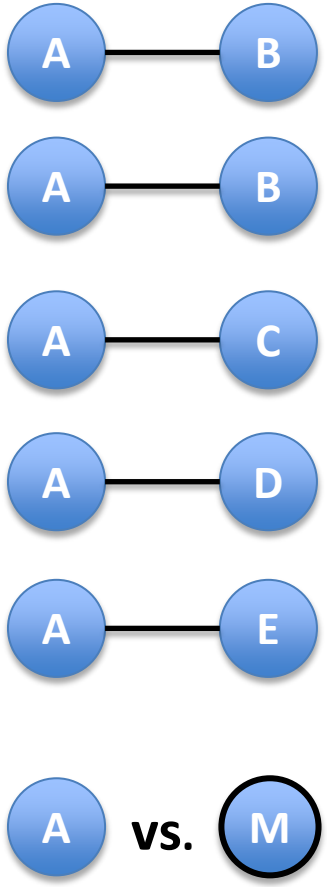
- Traditional meta-analysis combines evidence from relevant studies using appropriate statistical methods
- Inference could be limited
  - Alendronate and placebo treated as one comparator
  - No direct comparison of alendronate and placebo

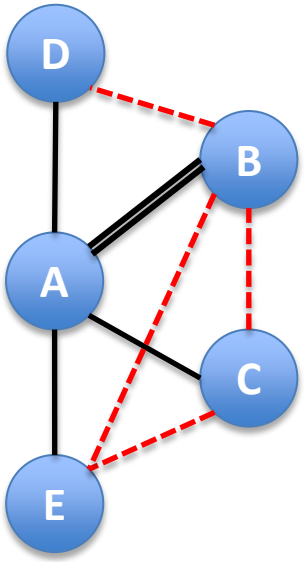
Network Meta-Analysis

- Extension of the traditional meta-analysis
- Network estimates are weighted sums of the observed estimates
- Compares multiple treatments simultaneously
- Preserves the within trial randomized comparison of each study
- Enables indirect comparisons of multiple interventions that have not been studied in head-to-head trials (alendronate vs. placebo)
- Assumes no effect modifiers

Network Meta-Analysis

Meta-Analysis





Network Meta-Analysis

Direct Estimate

Indirect Estimate

Network Meta-Analysis

- Steps of indirect effect estimation

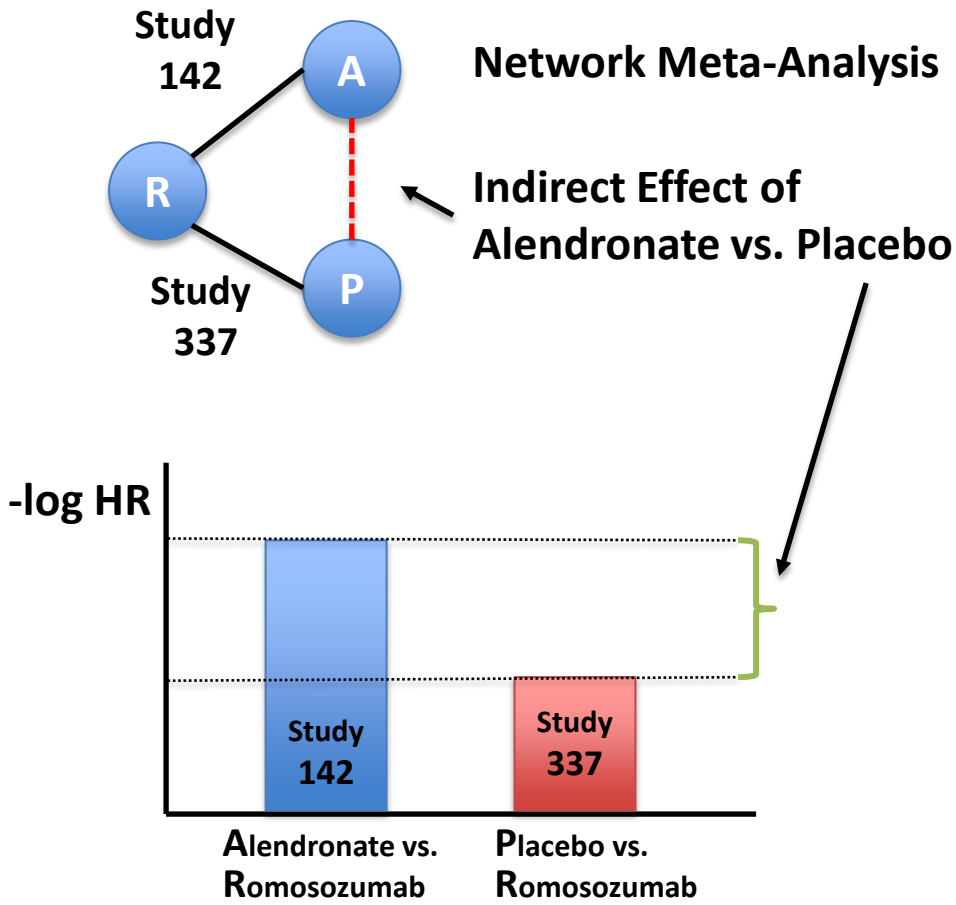
Step 1: Estimate direct effects of each study

Study 142: Hazard Ratio of MACE = 1.87 vs. alendronate
Study 337: Hazard Ratio of MACE = 1.03 vs. placebo

Step 2: Transform direct estimates using romosozumab as denominator

Study 142: Hazard Ratio of MACE = 1/1.87 = 0.53 = exp(-0.63)
Study 337: Hazard Ratio of MACE = 1/1.03 = 0.97 = exp(-0.03)

Step 3: Subtract transformed direct estimates (log scale) with weights applied



– Based on direct comparisons of 20110142 and 20070337, indirect comparison of alendronate and placebo can be estimated

Statistical Methods

- Network-meta analysis: fixed effects
- Primary safety outcome: time to DCRI adjudicated major adverse cardiac events (MACE)
- Analysis population: all randomized subjects who received at least one active dose in the 12-month double-blind study period
- α-level not adjusted for multiple testing

Study 337 Results

Comparison	Primary Endpoint (Components)	HR (95% CI) †
Romosozumab vs. Placebo	**MACE**	**1.03 (0.62 – 1.72)**
	(CV Death)	1.13 (0.56 – 2.26)
	(Nonfatal MI)	1.12 (0.43 –2.91)
	(Nonfatal Stroke)	0.80 (0.32 – 2.02)

†All hazard ratios are estimated based on 12-month double blind period

Study 142 Results

Comparison	Primary Endpoint (Components)	HR (95% CI) †
Romosozumab vs. Alendronate	**MACE**	**1.87 (1.11 – 3.14)**
	(CV Death)	1.42 (0.68 – 2.97)
	(Nonfatal MI)	3.21 (1.18 –8.77)
	(Nonfatal Stroke)	1.86 (0.74 – 4.67)

†All hazard ratios are estimated based on 12-month double blind period

Meta-Analysis Results

Analysis Model	Study	Comparison	Primary Endpoint	HR (95% CI) †
Meta-Anaylsis	337 & 142	Romosozumab vs. Comparator	MACE	1.38 (0.96 – 1.99)

Analysis Model	Study	Comparison	Primary Endpoint	HR (95% CI) †
Network Meta-Analysis	337	Romosozumab vs. Placebo (Direct)	MACE	1.03 (0.62 – 1.72)
	337 & 142	Alendronate vs. Placebo (Indirect)	MACE	0.55 (0.27 – 1.14)

†All hazard ratios are estimated based on 12-month double blind period

Summary

- In Study 142, the risk of MACE was higher with romosozumab than alendronate in the double blind period
- Meta-analysis was limited by treating alendronate and placebo as one single comparator
  - Romosozumab vs. Comparator: HR [95% CI] was **1.38 [0.96, 1.99]**
- Network meta-analysis explored the comparison of alendronate vs. placebo
  - Alendronate vs. Placebo: HR [95% CI] was **0.55 [0.27, 1.14]**

Limitations

- Study 142 included subjects with higher risk of fracture than Study 337. If there are effect modifiers related to the differences in the populations, this may explain the difference in results between the trials.
- Only two studies were included in the analysis
- Analyses are post-hoc and exploratory

Conclusion

- The estimated hazard of MACE is highest in the romosozumab group and lowest in the alendronate group
- Difficult to discern based on this analysis whether the increased risk in Study 142 is truly a drug effect, chance finding, or because of a reduced risk of MACE in the alendronate group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Cardiovascular Safety Summary

Theresa Kehoe, MD
Cross Discipline Team Leader
Division of Bone, Reproductive and Urologic Products

MACE Meta-Analyses

- Osteoporosis fracture trials 20070337 and 20110142
  - HR 1.38 (95% CI: 0.96, 1.99)

MACE: Major Adverse Cardiac Events
HR: Hazard Ratio

Evaluation of Plausibility

- Scant data available on the interplay of sclerostin and cardiovascular disease or cardiovascular risk factors
  - Sclerostin expressed in aorta, vascular/valvular calcification
    - role unknown
- Van Buchem disease/Sclerosteosis (sclerostin under expression)
  - Patients do not appear to have increased cardiac risk

MACE Results

- Conflicting Results in the Fracture Trials
  - Trial 20070337
    - HR 1.03 (95% CI: 0.62, 1.72)
  - Trial 20110142
    - HR 1.87 (95% CI: 1.11, 3.14)

Baseline Osteoporosis Characteristics

	Trial 20070337	Trial 20110142
Age, mean, years	**71**	**74**
Age > 75 years, n (%)	2240 (**31**)	2144 (**52**)
Lumbar spine T score, mean	**-2.72**	**-2.96**
T score ≤ -3.0, n (%)	2926 **(41)**	2021 **(49)**
Total hip T score, mean	**-2.47**	**-2.80**
T score ≤ -2.5, n (%)	3772 **(52)**	2740 **(67)**
Prevalent fracture, n (%)	1317 (**18**)	3933 (**96**)

MACE Subgroup Analysis, Month 12: Baseline Osteoporosis Characteristics

	Study 337			Study 142		
	Placebo (N=3576)	Romosozumab (N=3581)	HR (95% CI)	Alendronate (N=2014)	Romosozumab (N=2040)	HR (95% CI)
Age < 65 years	4/756 (0.5)	1/766 (0.1)	0.25 (0.03, 2.22)	1/237 (0.4)	3/237 (1.3)	3.03 (0.32, 29.12)
Age < 75 years	10/2461 (0.4)	9/2464 (0.4)	0.90 (0.37, 2.21)	8/965 (0.8)	14/970 (1.4)	1.76 (0.74, 4.20)
Age ≥ 75 years	19/1115 (1.7)	21/1117 (1.9)	1.10 (0.59, 2.05)	14/1049 (1.3)	27/1070 (2.5)	**1.93 (1.01, 3.67)**

MACE Subgroup Analysis, Month 12: Baseline Osteoporosis Characteristics

	Study 337			Study 142		
	Placebo (N=3576)	Romosozumab (N=3581)	HR (95% CI)	Alendronate (N=2014)	Romosozumab (N=2040)	HR (95% CI)
Lumbar spine BMD T score ≤ -3	11/1430 (0.8)	12/1492 (0.8)	1.04 (0.46, 2.36)	13/1011 (1.3)	17/996 (1.7)	1.35 (0.65, 2.78)
Lumbar spine BMD T score > -3	16/2040 (0.8)	18/2006 (0.9)	1.15 (0.58, 2.25)	8/910 (0.9)	21/952 (2.2)	**2.56 (1.13, 5.78)**

Baseline Cardiac Risk Characteristics

	Trial 20070337	Trial 20110142
Any CV-related disease, n (%)	5352 (**75**)	3221 (**79**)
Cardiovascular disease, n (%)	4658 (**65**)	2953 (**73**)
Hypertension, n (%)	3809 (**53**)	2475 (**61**)
Cerebrovascular disease, n (%)	377 (**5**)	335 (**8**)
Hyperlipidemia, n (%)	2787 (**39**)	1384 (**34**)
Diabetes, n (%)	924 (**13**)	521 (**13**)

MACE Subgroup Analysis, Month 12: Baseline Cardiac Risk Characteristic

	Study 337			Study 142		
	Placebo (N=3576)	**Romosozumab (N=3581)**	**HR (95% CI)**	**Alendronate (N=2014)**	**Romosozumab (N=2040)**	**HR (95% CI)**
Any Cardiovascular Risk Factor at Baseline	26/2703 (1.0)	26/2649 (1.0)	1.09 (0.59, 1.76)	20/1603 (1.2)	30/1618 (2.5)	**2.07 (1.19, 3.47)**
No Cardiovascular Risk Factor at Baseline	3/873 (0.3)	4/932 (0.4)	1.25 (0.28, 5.57)	2/411 (0.5)	1/422 (0.2)	0.49 (0.04, 5.38)

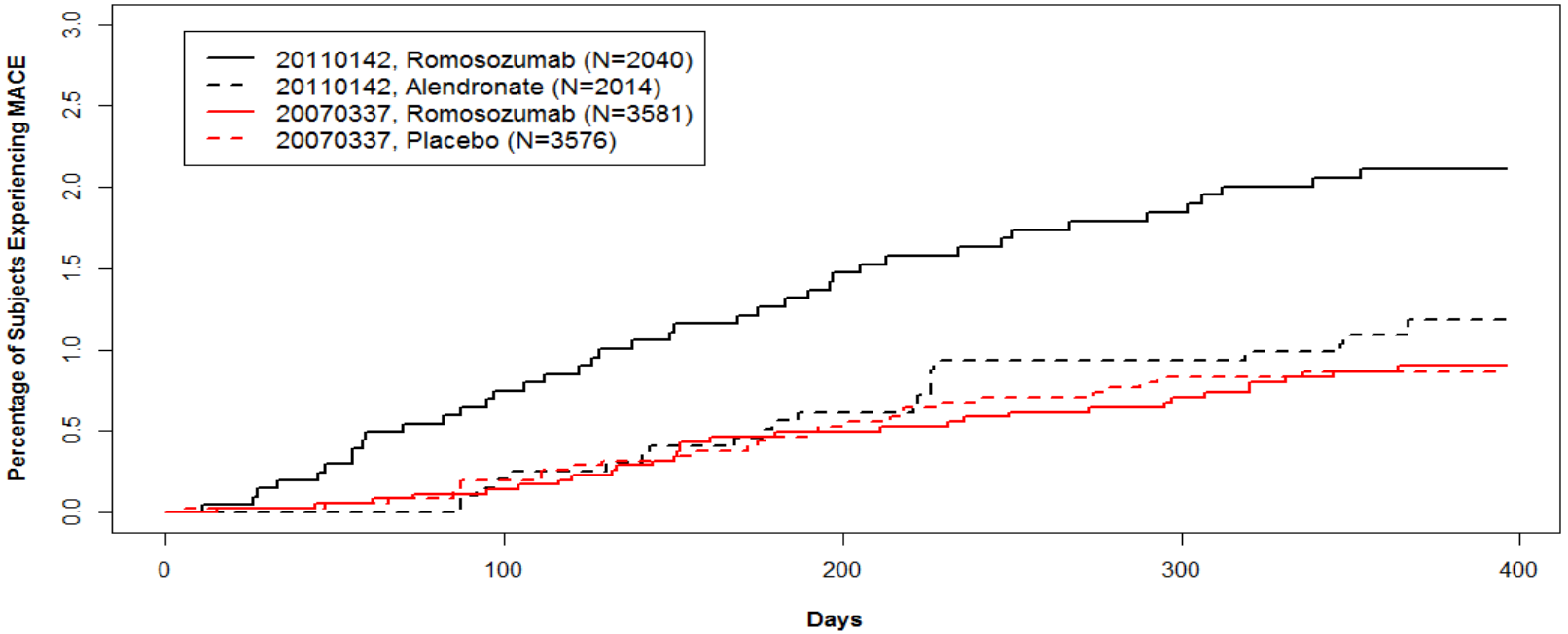
Subgroup Analyses

- FDA evaluated baseline risk characteristics for both osteoporosis and cardiovascular disease
- Subgroup analyses of trials 20070337 and 20110142 did not explain the trial differences in MACE

Comparator Differences

- One difference in the two fracture trials is the comparator group
  - Trial 20070337: placebo
  - Trial 20110142: alendronate
- Is there cardiovascular protection with alendronate use?
  - Potential biological plausibility
  - Alendronate has high specificity for bone
  - Study results to date are mixed

Time to First Occurrence of Adjudicated MACE through Month 12



Further Evaluations

- **Effect on Blood Pressure**
  - No effect on systolic or diastolic blood pressure evaluated at months 1, 6, and 12 in the fracture trials
  - Ambulatory blood pressure monitoring was not conducted
- **Effect on Vasoconstriction**
  - No effect on vascular tone as evaluated *in vitro* using human coronary artery rings
- **Effect on Platelet Aggregation**
  - No effect on platelet activation *in vitro* at concentrations up to 10x the intended human dose

Cardiovascular Safety Summary

- One of two large safety and efficacy trials of romosozumab for the treatment of osteoporosis in postmenopausal women has yielded a concerning cardiovascular safety signal
  - SOST is expressed in the cardiovascular system, nonclinical studies do not provide support for an association
  - Small number of MACE in both trials
  - Unclear if the population differences between the trials can explain the discrepant results

Romosozumab Benefit/Risk Profile

- **Benefit: Fracture Risk Reduction**
  - There is morbidity and mortality associated with fracture, most notably hip fractures
  - Osteoporosis and fracture risk increase in women after menopause
  - Romosozumab is efficacious in preventing fracture
- **Risk: Cardiovascular Safety**
  - There is morbidity and mortality associated with ischemic cardiovascular and cerebrovascular events
  - Cardiovascular risk increases in women after menopause
  - Does romosozumab cause increased risk for adverse CV outcomes?

Risk Difference at Month 12

Risk Difference per 1,000 patients (95% CI)	Trial 20070337 vs Placebo	Trial 20110142 vs Alendronate
Morphometric Vertebral fracture	-13 (-18, -8)	-18 (-32, -5)
Nonvertebral fracture	-8 (-14, -1)	-14 (-26, -1)
Hip fracture	-3 (-6, 0)	-3 (-9, 3)
MACE	0.3 (-4, 4)	9 (2, 17)

Next Steps

- Further Evaluation of the Cardiovascular Signal
  - Type of Trial/Study
    - Cardiovascular Outcomes trial
    - Observational study
  - Timing of the Trial/Study
    - Pre approval
    - Post approval

Cardiovascular Outcomes Trial

- Prospective, randomized, controlled trial
- Challenges
  - Very large sample size
  - Missing data
  - Generalizable?
- One year duration of therapy with romosozumab
- Early separation of the Kaplan Meier curves in trial 142 may indicate that one year duration may be sufficient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Feasibility of Using Observational Data to Assess Cardiovascular Risks Associated with Romosozumab

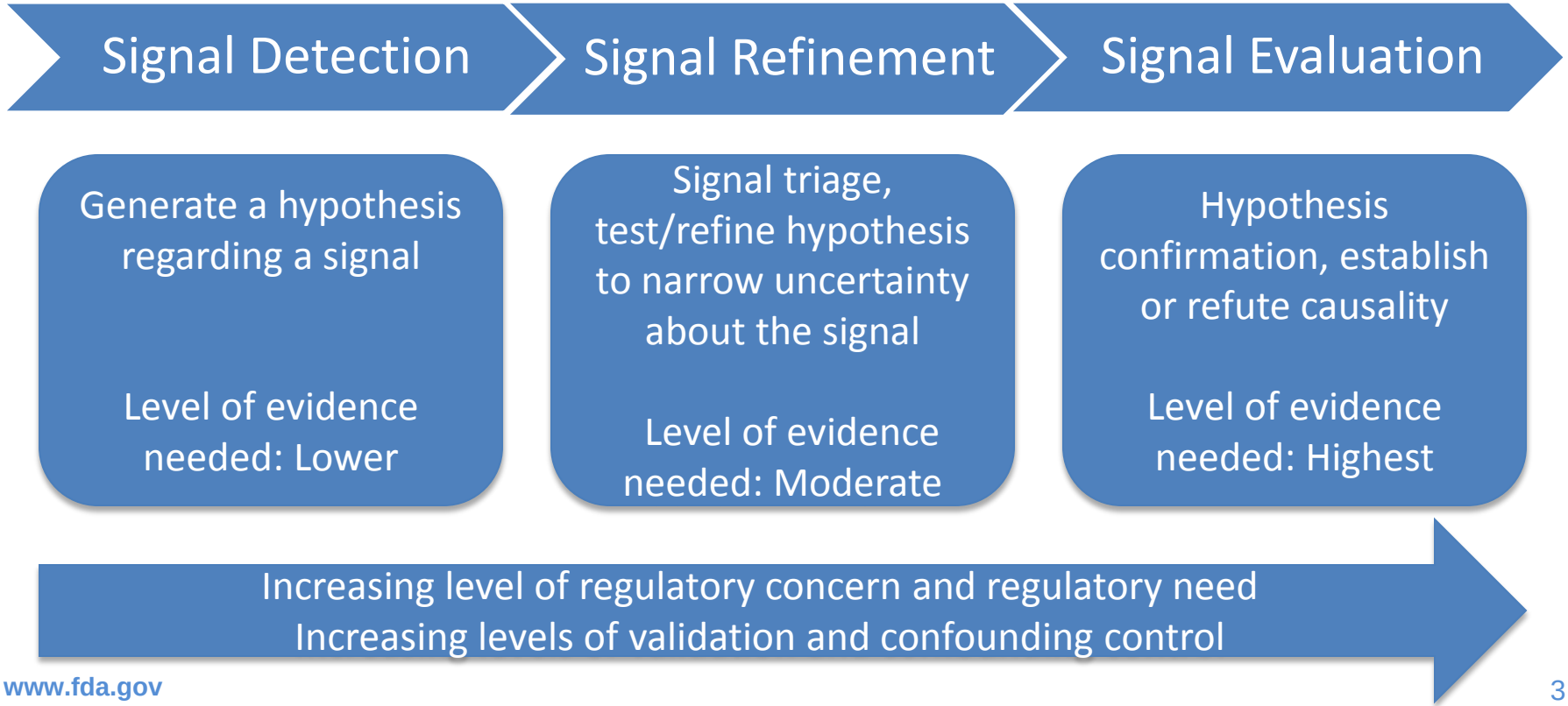
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
January 16, 2019

Wei Liu, PhD, MSc
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology

Outline

- Regulatory context for post-marketing surveillance
- Assessment of cardiovascular (CV) risks of romosozumab in the post-marketing setting
  - Randomized cardiovascular safety outcome trial
  - Observational studies
- Observational database study for romosozumab – strengths/limitations

Post-Marketing Signal Assessment



Study Question

- Whether romosozumab users are at a higher risk of CV events compared to users of other antiosteoporosis therapies?

Study Options

- Randomized cardiovascular safety outcome trials
- Observational studies
  - Primary data
  - Secondary data
    - Healthcare claims data
    - Electronic medical records (EMR)
    - Hybrids

Observational Studies to Assess Comparative CV Risks of Romosozumab

- Studies should be designed and conducted to resemble the "target trial"[1] that would answer the same study question
- May prove challenging, due to
  - Confounding by disease severity, residual confounding
  - Selection bias (post-index switching or discontinuation)
  - Measurement bias (uncertain validity of coding algorithms)

1. Hernan MA, Robins JM.AJE 2016; 183(8): 758-64

Confounding Concerns

- Confounding by disease severity
  - Romosozumab users may have been previously treated with other osteoporosis agents, or are at high risk for fracture
  - Severity of bone disease may influence cardiovascular risk
  - Severity of disease difficult to measure in database studies
- Unmeasured/residual confounding
  - Variables typically missing or incompletely captured in claims, e.g., smoking, body mass index, socioeconomic status
  - CV-risk factor may change over time
    - May occur in observational studies and trials

Confounding Control Approaches

- New-user/new-switcher design
- Active comparator
- Measure and control for disease severity, other time-varying characteristics
- Propensity score/disease risk score methods, instrumental variable analysis

Selection Bias Concerns

- Related to selection and retention of patients in the study
- Treatment switching and discontinuation during follow-up
  - Poor compliance due to lack of immediate benefits, occurrence of adverse events, costs, or inconvenience
  - Particular concern with intention-to-treat (ITT) designs
    - bias towards the null
- May occur in observational studies and clinical trials

Selection Bias Approaches

- Conduct analyses using both “as-treated” and “intention-to-treat” approaches
- Statistical adjustment method such as inverse probability of censoring weights
  - Relies on the untestable assumption of “no unmeasured confounders”

Measurement Bias Concerns

- Exposure misclassification
  - Claims: dispensing does not indicate real use of the drug
  - EMR: patient does not fill prescription; prescription from other healthcare setting not captured in EMR
- Misclassification of outcome and comorbidities
- Billing diagnosis and procedure codes with poor validity (e.g., obesity, smoking, immobility)

Reliability of Diagnosis Codes to Identify CV Outcomes in Claims Data

- Due to serious nature, hospitalization is expected for most nonfatal events (myocardial infarction, stroke, heart failure)
- Most claims data are not able to capture out-of-hospital CV deaths, unless linked to state or national death registries
- Nonfatal MI and stroke: positive predictive value (PPV) > 90% in Medicare data[1,2]
- PPV for the composite outcome of myocardial infarction, stroke, heart failure, coronary revascularization, all-cause mortality > 80%[3,4]

1. Kiyota Y, et al. *Am Heart J* 2004; 148(1): 99-104. 2. Kumamaru H, et al. *Circ Cardiovasc Qual Outcomes* 2014; 7(4): 611-19.
3. Zhang M, et al. *Circulation* 2018: 138(11): 1116-26. 4. Kim SC, et al. *J Am Coll Cardiol* 2018: 71(9): 994-1004.

Accounting for Measurement Bias

- Use validated outcomes with high positive predictive value and reasonable sensitivity
- Adjudicate outcomes, exposure and potential confounders using an independent panel
- Conduct sensitivity analyses to test the robustness of various case definitions

Observational Study vs. Trial

	Cardiovascular outcome trial	Observational database studies
Strengths	• Randomization reduces confounding • Outcome ascertainment via blinded adjudication	• Generalizability • Large sample size • Less resource intensive
Limitations	• Limited statistical power to evaluate small relative risk • No safety information in certain patient populations • Resource intensive	• Confounding and biases • Lack of information on key confounders (e.g., smoking, body mass index, family history of CV disease)

Conclusions

- A romosozumab CV safety study will be complicated by issues of confounding and bias
- Selection of study design and data source should be based on the study question and driven by the required level of evidence to address the specific regulatory need
- Study could be trial or observational, depending on level of evidence desired