Anabolic Therapies for Osteoporosis in Postmenopausal Women: Effectiveness and Value

Public Meeting – June 30, 2017

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI: TCEGuest

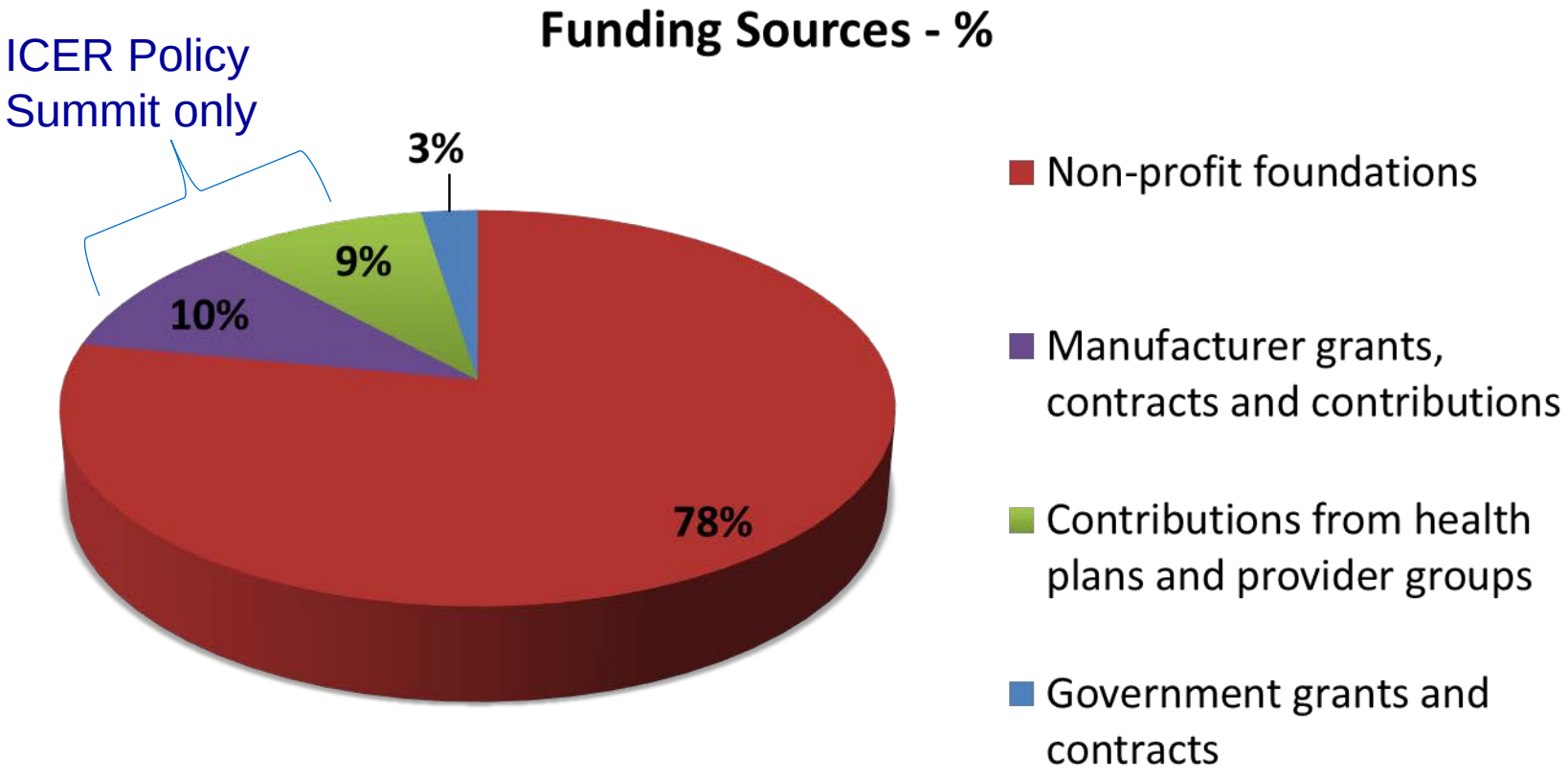
Welcome and Introduction

- California Technology Assessment Forum (CTAF)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2017

ICER Policy Summit only



Welcome and Introduction

- **Why are we here today?**
  - Innovation promising substantial benefits to patients and their families

- "At times, and especially after a hip fracture, long-term care services are required for intensive rehabilitation. A good number of these patients are no longer able to live independently and need to move in with a family member, move to an assisted living or custodial care facility. This is an added concern for families who need to make and pay for these arrangements, or provide this care directly."

  --National Osteoporosis Foundation

- "I became unsure of myself. I was afraid to lift my own granddaughter, to do the DIY projects that I always do, for fear of fracturing. I was afraid to trust the BODY that I live in and that, beyond all else, was the worst of it!"

  -- Patient with osteoporosis

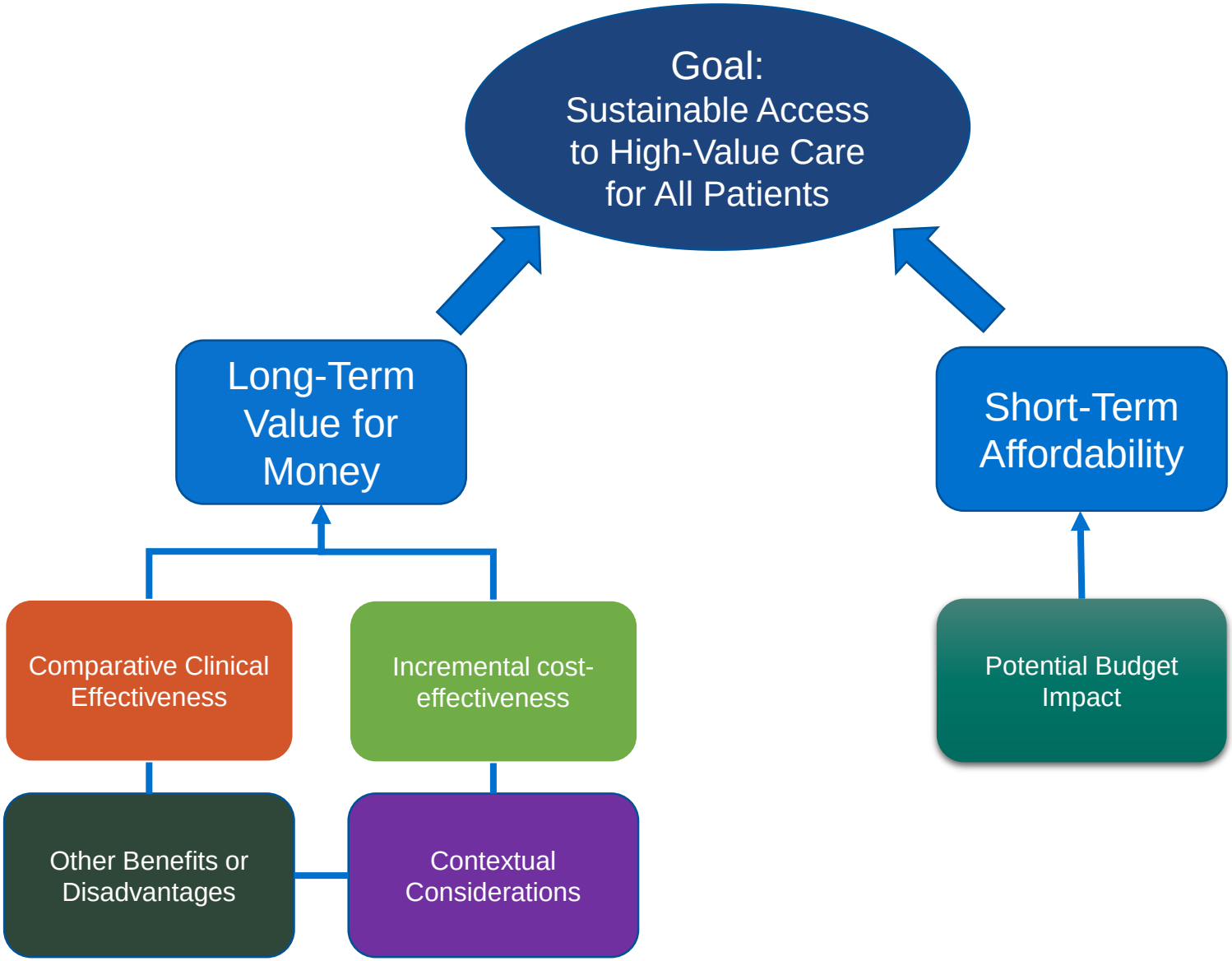
Welcome and Introduction

- **Why are we here today?**
  - Increasing health care costs affecting individuals, state and federal budgets
  - New mechanisms of action often raise questions about appropriate use, cost
  - Patients can have difficulty accessing drugs
    - Step therapy protocols
    - Requirements to switch drugs with new insurance
    - High out-of-pocket costs
  - Need for objective evaluation and public discussion of the evidence on effectiveness and value

Welcome and Introduction

How was the ICER report on anabolic therapies for osteoporosis developed?

- Scoping with guidance from patient groups, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Washington cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
  - Douglas Bauer, MD
  - Teresa Fama, MD
  - Anna Tosteson, ScD
- How is the evidence report structured to support CTAF voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental cost-effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

10:00am: Welcome and Opening Remarks

10:05 am: Presentation of the Evidence

Evidence Review: Jeff Tice, MD

Cost Effectiveness: Lotte Steuten, MSc, PhD, University of Washington

10:55 am: Manufacturer Public Comment and Discussion

11:40 pm: Public Comments and Discussion

12:00 pm: Lunch

12:45 pm: CTAF Deliberation and Votes

1:45 pm: Break

2:00 pm: Policy Roundtable

3:30 pm: Reflections and Wrap Up

4:00 pm: Meeting Adjourned

Evidence Review

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Key review team members:

Patricia Synnott, MALD, MS

Disclosures:

We have no conflicts of interest relevant to this report.

Topic in Context

- Weakening of the bone through loss of mineral content and quality that increases the risk for fracture
- 2-3 million fractures annually in US
- Cost: $20-$25 billion
- Underdiagnosed and undertreated
  - Women with fracture or BMD<-2.5: only 20-30% are evaluated and treated
  - 12 months after hip fracture: 2% had DXA, 15% treated with appropriate drug

Effect on Lives Can Be Profound

- Osteoporosis itself: silent
- Hip fracture
  - Hospitalization, skilled nursing facility for rehabilitation
  - Loss of independence
  - Mortality
- Vertebral fractures
  - Loss of height, kyphosis
  - Decreased respiratory function
  - Pain

Management

- Adequate calcium and vitamin D intake
- Weight bearing exercise
- Fall prevention
- T-score < -2.5 or prior vertebral/hip fracture
  - Oral bisphosphonate
  - Intolerant of oral bisphosphonate
    - Zoledronic acid
    - Denosumab

Harms of Therapies: Anti-Resorptive Drugs

- Bisphosphonates, denosumab
  - Osteonecrosis of the jaw
    - 96% in cancer treatment
  - Atypical femoral fractures
    - 1 per 110 hip fractures prevented
- Oral bisphosphonates: daily or weekly pill
  - Pill esophagitis
- Zoledronic acid: annual infusion
  - Infusion reaction: flu-like symptoms
    - 30% first infusion
    - 5% subsequent infusion

Scope of the Review

- Anabolic agents
  - Drugs that stimulate bone formation: teriparatide, abaloparatide, romosozumab
  - Population: postmenopausal women with osteoporosis
  - Comparator: zoledronic acid
- **Caveat**: Romosozumab consideration by the FDA delayed beyond 2017
  - Not included in comparative effectiveness
    - Not in network meta-analysis
    - Not in cost-effectiveness, budget impact models

Anabolic Therapies

- Teriparatide 20 mcg: FDA approval 11/26/2002
  - PTH analog
  - Given once daily via subcutaneous (SC) injection (pen)
- Abaloparatide 80 mcg: FDA approval 4/28/2017
  - PTHrP analog
  - Given once daily via SC injection (pen)
- Romosozumab 210 mg: FDA consideration delayed
  - Monoclonal antibody to sclerostin
  - Both anabolic and anti-resorptive
  - Given once monthly via SC injection

Fracture Outcomes

- Fragility: low impact fractures
- Morphometric Vertebral fractures
  - Compare lateral spine x-rays before and during therapy
  - Semiquantitative (SQ): radiologist using Genant scale
  - Quantitative (QM): place six points: 20% loss of height and 4 mm
  - Combination: SQ confirmed SQ, QM confirmed SQ, other
- Clinical vertebral fracture
  - ~35% of morphometric fractures
- Non-vertebral fragility fractures
  - **Hip**, forearm, humerus, pelvis
  - Exclude: skull, face, fingers, toes, pathologic fractures

Insights from Discussions with Patients

- NOF Survey Top Two Patient Concerns
  - Loss of independence
  - Loss of mobility
- Top caregiver concern
  - No longer being able to care for loved-one
- Why not taking prescribed medication
  - Concern about side effects
- Use of needles, need for refrigeration matter
- Insurance barriers are confusing
- Clinical trials don’t measure outcomes that matter to patients

Issues of Focus

Key Clinical Trials

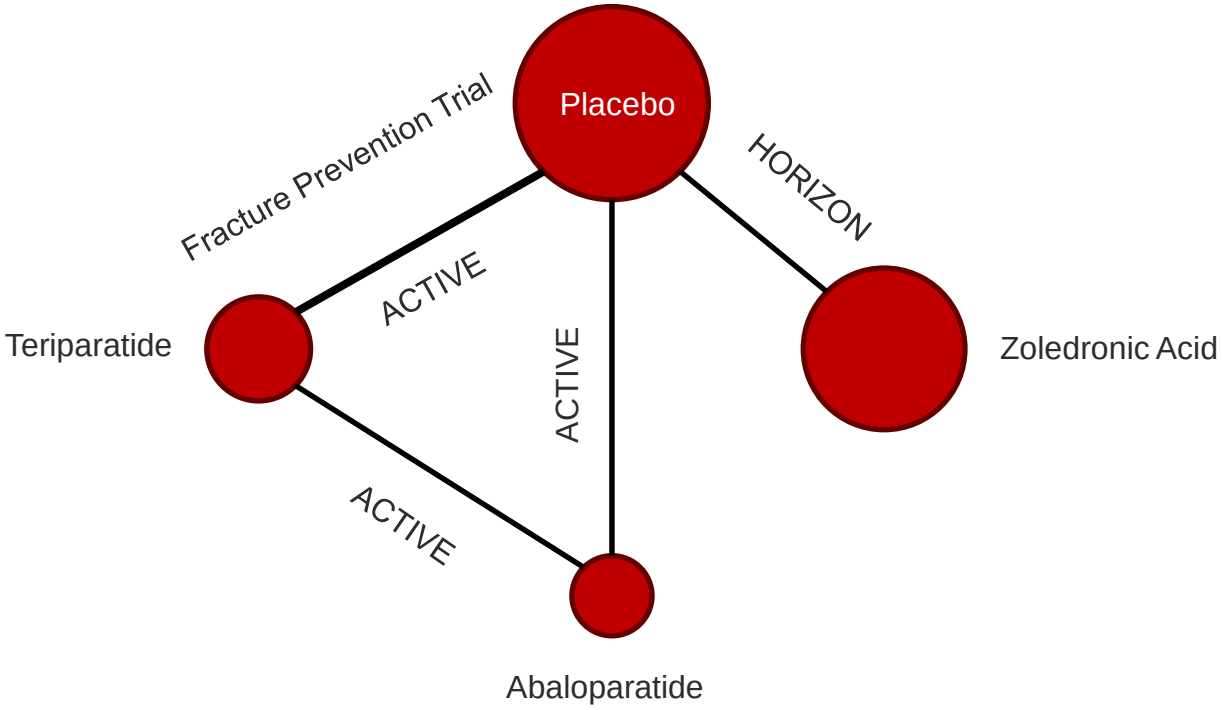
Reference	Study	Group	N	F/U, months	Age, years	BMI, kg/m²	Prior Fracture
Neer 2001 **Prevrhal 2009**	Fracture Prevention Trial	Teriparatide Placebo	541 544	21 21	69 69	26.8 26.7	100% V
Miller 2016	ACTIVE	Abaloparatide Teriparatide* Placebo	824 818 821	18 18	69 69	25.0 25.2 25.1	24% V 63% any
Cosman 2016	FRAME	Romosozumab Placebo	3589 3591	12 12	71 71	24.7 24.7	18% V 22% non-V
Black 2007	HORIZON	Zoledronic acid Placebo	3889 3876	36 36	73 73	25.1 25.4	63% V

Non-V: non-vertebral fracture, V: vertebral fracture

*Teriparatide was open label; fracture adjudication was done by central committee blinded to allocation status

Major difference between trials is prevalence of vertebral fractures at baseline

Network Diagram



Relative Risk for Vertebral fractures

Abaloparatide (80 mcg)			
0.76 (0.20 – 2.26)	**Teriparatide (20 mcg)**		
0.44 (0.12 – 1.15)	0.57 (0.30 – 1.02)	**Zoledronic Acid (5 mg)**	
0.13 (0.03 – 0.33)	**0.17 (0.09 – 0.29)**	**0.30 (0.24 – 0.37)**	**Placebo**

Caveats with NMA

- Fixed effects model: standard when few trials
  - Random effects model results wildly improbable
- Slightly different outcome measures
  - See next slide
- Teriparatide open-label in ACTIVE trial
- Different prevalence of vertebral fractures at baseline
  - Patients with prior fracture at higher risk for subsequent fracture
  - No effect modification by vertebral fracture status or other measures of risk for future fracture

Vertebral Fractures: NMA Versus Trials

Drug	NMA Estimate	RCT Estimates
Abaloparatide	0.13 (0.03-0.33)	0.14 (0.05-0.39)[1]
Teriparatide	0.17 (0.09-0.29)	0.16 (0.08-0.33)[2] 0.20 (0.08-0.47)[3]
Zoledronic acid	0.30 (0.24-0.37)	0.30 (0.24-0.38)[4]

[1] ACTIVE Trial: SQ, confirmed with SQ
[2] Fracture Prevention Trial: SQ alone originally (RR 0.35, 95% CI 0.22-0.55); SQ + QM Prevrhal 2009 used in NMA and presented in this table).
[3] ACTIVE Trial: SQ, confirmed with SQ
[4] Horizon Trial: QM, confirmed with SQ

Non-Vertebral Fractures: NMA

Abaloparatide (80 mcg)			
0.83 (0.46 – 1.46)	**Teriparatide (20 mcg)**		
0.69 (0.38 – 1.16)	0.82 (0.54 – 1.22)	**Zoledronic Acid (5 mg)**	
0.51 (0.28 – 0.85)	**0.61 (0.41 – 0.88)**	**0.75 (0.64 – 0.87)**	**Placebo**

Non-Vertebral Fractures: NMA Versus Trials

Drug	NMA Estimate	RCT Estimates
Abaloparatide	0.51 (0.28-0.85)	0.57 (0.32-1.00)
Teriparatide	0.61 (0.41-0.88)	0.47 (0.25-0.88) 0.72 (0.42-1.22)
Zoledronic acid	0.75 (0.64-0.87)	0.75 (0.64-0.87)

Hip Fractures

- Zoledronic acid: relative risk (RR) 0.59 (0.42-0.83)
- Insufficient data for teriparatide and abaloparatide
  - Observational data for teriparatide comparing patients adherent for 2 years to those adherent less than 3 months
    - RR 0.55 (0.42-0.74)

Patient-Reported Outcomes

- No trial reports on loss of independence, activities of daily living (ADLs), instrumental ADLs, mobility, caregiver burden, or quality of life

Harms

- No differences from placebo in serious adverse events
- No differences from placebo in discontinuation due to adverse events except for abaloparatide more than teriparatide and placebo in ACTIVE trial (10% vs. 7% vs. 6%)
- More hypercalcemia with abaloparatide and teriparatide
- More injection site reactions with abaloparatide

Unpublished Studies

- VERO trial: 2 years teriparatide versus risedronate
  - 1360 women with prior vertebral fractures and T ≤ -1.5
  - V Fx: 5.4% versus 12.0%, HR 0.44, p<0.001
  - Non-V Fx: 4.0% versus 6.1%, HR 0.66, p=0.1
- ARCH trial: 1 year romosozumab then 1 year alendronate versus 2 years alendronate
  - 4093 women with hip T-score ≤ -2.5 and a vertebral fracture or hip T-score ≤ -2.0 and hip fracture or 2 vertebral fractures
  - V Fx: HR 0.50
  - Non-V Fx: HR 0.81
  - Increase in serious CVD events (2.5% versus 1.9%)

Other Benefits or Disadvantages and Contextual Considerations

- Both abaloparatide and teriparatide require daily SC injections vs. annual 15-minute infusion for zoledronic acid
- Burden for caregiver if they need to give daily injections
- Teriparatide requires refrigeration, abaloparatide does not require refrigeration after first dose per pen
- No other factors that differ between drugs

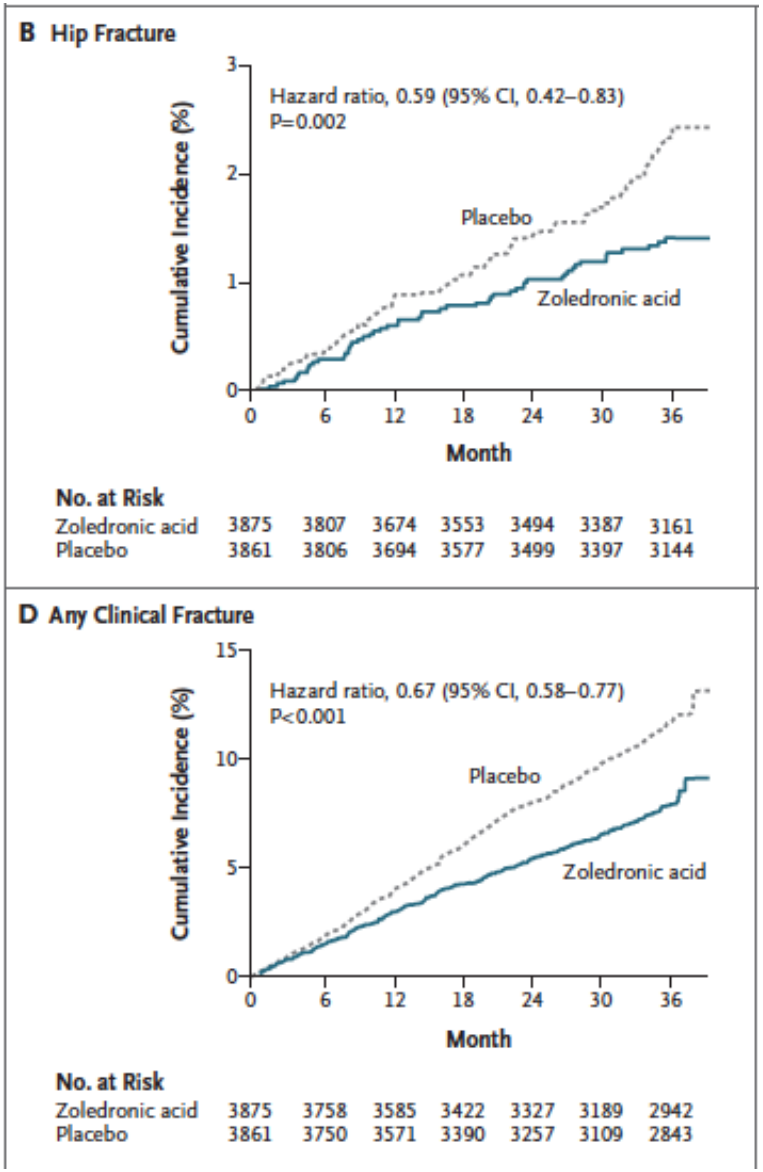
Controversies and Uncertainties

- No randomized-controlled trial data on hip fractures for abaloparatide or teriparatide: American College of Physicians (ACP) 2017 guidelines
- Lack of data on patient centered outcomes: independence and quality of life
- Primary outcome in trials: morphometric fractures – majority asymptomatic. Least relevant to patients.
- Heterogeneity of definitions for incident vertebral fractures
- Appropriate sequencing of therapy
- Definition of highest-risk population who should start with therapy other than oral bisphosphonate

Public Comments Received

- Heterogeneity of trial populations: is it appropriate to combine them in NMA?
  - Yes: there is no effect modification
- Anabolics work faster: shorter trials
  - Zoledronic significant reduction at 1 year ($p<0.001$)
  - See KM for zoledronic acid next slide
  - Need RCTs with fracture outcomes
- Zoledronic acid is inappropriate comparator
  - Parenteral, for highest-risk women. Feedback.
- Certain subgroups should receive anabolics
  - No clear evidence: Policy roundtable?

Horizon Trial: Zoledronic Acid Versus Placebo



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Summary

- NMA: abaloparatide and teriparatide reduce vertebral and non-vertebral fractures compared to placebo
- No significant differences from each other or zoledronic acid
- Minimal harms: more injection site reactions and hypercalcemia with abaloparatide
- Extensive real-world experience with teriparatide that supports RCT findings
- Both require daily SC injection

ICER Evidence Ratings for Abaloparatide and Teriparatide

- The evidence is promising, but inconclusive (P/I) for the net health benefit comparing abaloparatide and teriparatide to zoledronic acid
- There is moderate certainty that the drugs provide small or substantial net health benefit compared to no therapy (B+)
- There is insufficient evidence (I) for the two drugs compared to each other

Appendix Slides

NMA Sensitivity Analyses: Morphometric Vertebral Fracture Comparisons to Placebo

Drug	Study Publication RR (95% CrI)	Fixed Effects RR (95% CrI)	Random Effects, Vague Priors RR (95% CrI)	Random Effects, Informative Priors RR (95% CrI)	Frequentist Approach, Random Effects RR (95% CI)	Sensitivity Analysis Excluding Teriparatide Arm of ACTIVE Trial, Fixed Effects RR (95% CrI)	Sensitivity Analysis Using Neer 2001 Teriparatide Data, Fixed Effects, RR (95% CrI)
Abaloparatide (80 mcg)	**0.14 (0.05 – 0.39)**	**0.13 (0.03 – 0.33)**	**0.13 (0.01 – 0.95)**	**0.13 (0.03 – 0.38)**	**0.13 (0.05 – 0.38)**	**0.13 (0.04 – 0.34)**	**0.14 (0.04 – 0.35)**
Teriparatide* (20 mcg)	**0.16 (0.08 – 0.33)**	**0.17 (0.09 – 0.29)**	**0.17 (0.03 – 0.75)**	**0.17 (0.09 – 0.34)**	**0.17 (0.10 – 0.30)**	**0.15 (0.07 – 0.28)**	**0.30 (0.19 – 0.45)**
Zoledronic Acid (5 mg)	**0.30 (0.24 – 0.38)**	**0.30 (0.24 – 0.37)**	0.30 (0.03 – 1.94)	**0.30 (0.15 – 0.55)**	**0.30 (0.24 – 0.38)**	**0.30 (0.24 – 0.37)**	**0.30 (0.24 – 0.38)**

CI: confidence interval, CrI: credible interval, RR: relative risk

*Teriparatide results were calculated using Prevrhal, 2009 with the exception of the final column, which used data from Neer, 2001.

Estimates in bold signify that the 95% credible interval does not contain 1.

NMA Sensitivity Analyses: Non-Vertebral Fracture Comparisons to Placebo

Drug	Study Publication RR (95% CrI)	Fixed Effects RR (95% CrI)	Random Effects, Vague Priors RR (95% CrI)	Random Effects, Informative Priors RR (95% CrI)	Frequentist Approach, Random Effects RR (95% CI)	Sensitivity Analysis Excluding Teriparatide Arm of ACTIVE Trial, Fixed Effects RR (95% CrI)
Abaloparatide (80 mcg)	0.57* (0.32 – 1.00)	**0.51 (0.28 – 0.85)**	0.50 (0.07 – 2.80)	0.50 (0.23 – 1.04)	**0.50 (0.28 – 0.91)**	**0.55 (0.31 – 0.95)**
Teriparatide (20 mcg)	**0.47 (0.25 – 0.88)**	0.61 (0.41 – 0.88)	0.60 (0.13 – 2.32)	0.60 (0.34 – 1.04)	**0.61 (0.39 – 0.94)**	**0.45 (0.23 – 0.81)**
Zoledronic Acid (5 mg)	**0.75* (0.64 – 0.87)**	**0.75 (0.64 – 0.87)**	0.75 (0.10 – 4.08)	0.75 (0.40 – 1.36)	**0.75 (0.58 – 0.97)**	**0.75 (0.64 – 0.86)**

CI: confidence interval, CrI: credible interval, NR: not reported, RR: relative risk

*Denotes use of hazard ratios instead of relative risks; RRs were not reported in the trial publication.

Estimates in bold signify that the 95% credible interval does not contain 1.

Cost Effectiveness

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Disclosures:

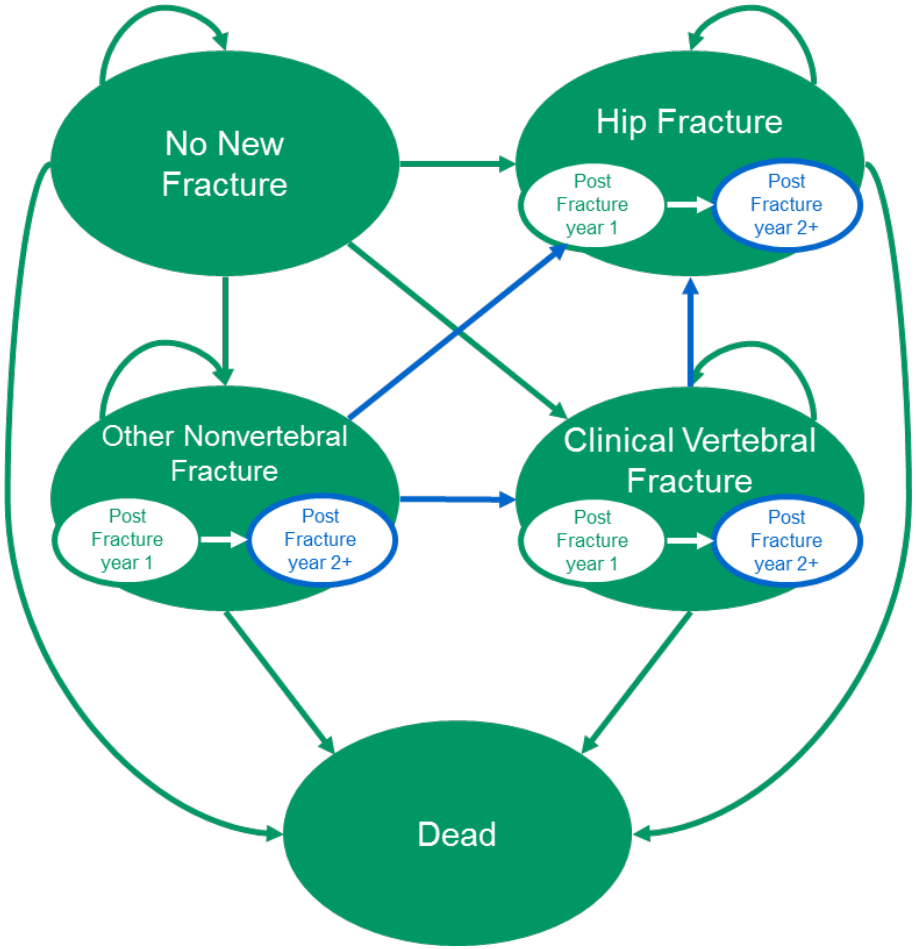
We have no conflicts of interest relevant to this report.

Objective

Estimate the cost-effectiveness of abaloparatide and teriparatide, each followed by treatment with a bisphosphonate (zoledronic acid) compared to treatment with zoledronic acid alone.

Methods in Brief

Overall Approach

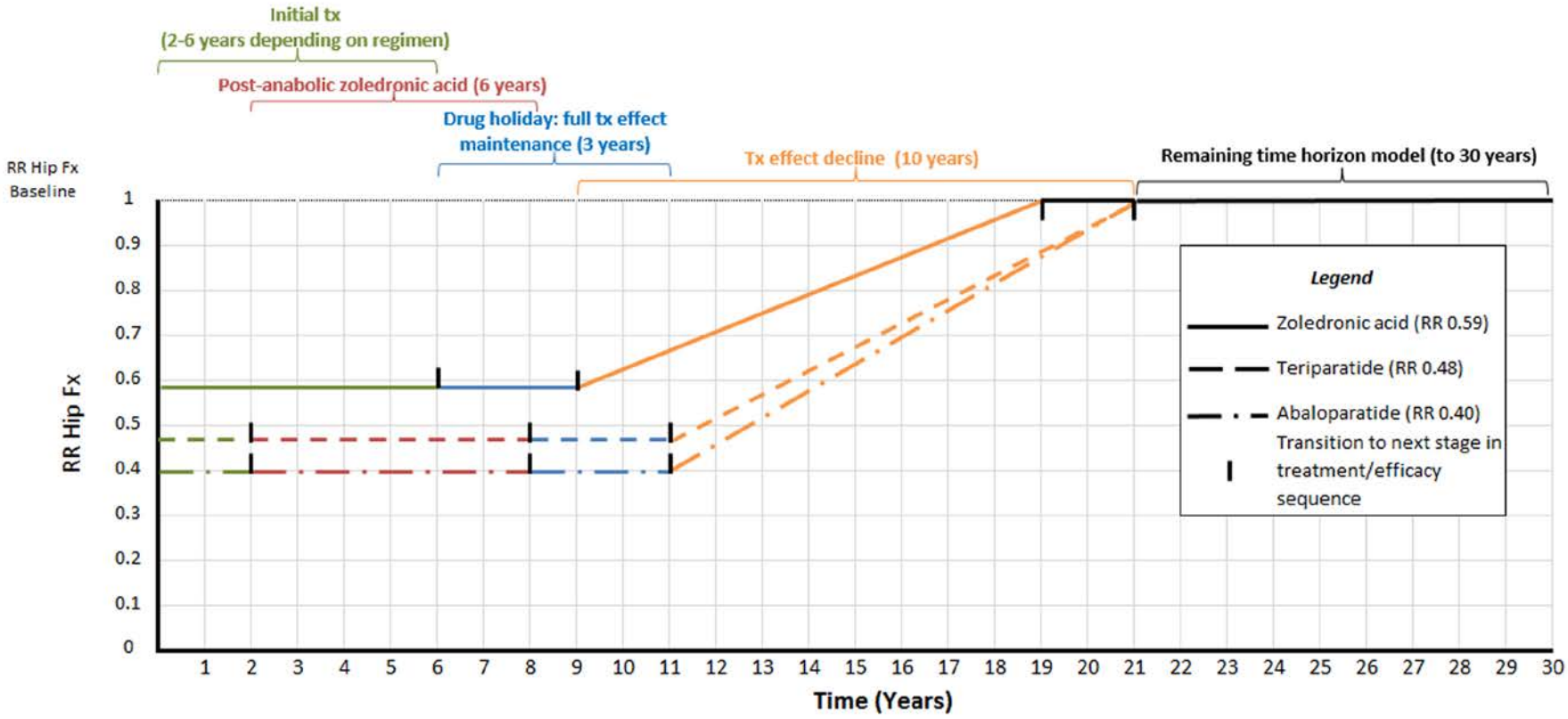


- Target population: 70-year-old postmenopausal women
  - Fracture incidence similar to that observed in anabolic drug trials
- Lifelong time horizon summing:
  - Time in health states adjusted for quality of life (QoL) &
  - Costs associated with each health state

Key Model Assumptions

- From a post-fracture state, patients can transition to same or worse fracture state only (or death).
  - Fracture hierarchy: hip > clinical vertebral > other non-vertebral.
- Subject to the fracture hierarchy, patients may have an unlimited number of fractures.
- No serious adverse events modelled in base-case analysis.
  - Scenario analysis for IV infusion reactions of zoledronic acid
- All comparators' adherence rates were 100% in base-case analysis

Treatment Sequence and Effect Over Time



Clinical Inputs – Fracture Relative Risks

- Annual RRs of fracture for each drug derived from:
  1. NMA: vertebral and non-vertebral fractures
  2. HORIZON and NMA: hip fractures
     - Zoledronic acid: RR from HORIZON trial
     - Anabolic agents: multiplied non-vertebral RR from NMA by ratio of hip to non-vertebral fracture RRs from HORIZON
- NMA RR estimates for vertebral fracture include both clinical and morphometric vertebral fractures:
  - Based on retrospective cohort analysis, we modelled a 35% proportion of overall vertebral fractures to be clinical vertebral fractures

Clinical Inputs – Baseline Fracture Risks

- Applied relative risk estimates from NMA to age-stratified baseline (placebo) estimates of annual probability of fracture to derive each comparator's annual fracture probabilities.
- Age-stratified baseline annual fracture probabilities derived by calculating fracture risks of an average 70-year old patient
  - Using pooled data placebo arms of Fracture Prevention, ACTIVE, FRAME, and HORIZON trials.
- To model increasing fracture risk as patients age, we extrapolated pooled estimates from Melton et al.
  - Calibrated 10-year cumulative incidence of hip fracture to match the FRAX 10-year probability of hip fracture (9.5%)

Clinical Inputs – Post-Fracture Excess Mortality

- Excess mortality rate after hip fractures. When controlled for underlying health status, roughly 50% lower than studies that adjusted for age and gender only (Tosteson 2007).
  - Fracture-related excess mortality applied only to hip fractures in base case
  - Scenario analysis using 50% multiplier to excess mortality rates for vertebral and other fractures.

Clinical Inputs – Post-Fracture Disutility

- Age-stratified baseline utility estimates for patients with no new fracture based on study including non-institutionalized US adult population (Hanmer, 2006)
- EQ-5D utility multipliers applied to baseline estimates for each fracture and post-fracture health state.
- Utility multipliers derived from publicly-available literature and/or manufacturer-submitted data*
  - Utility multipliers for vertebral fracture applied to 35% of patients with clinical vertebral fracture
  - Non-clinical vertebral fractures had no utility multiplier applied in the base case analysis; explored in scenario analysis

*Hanmer, 2006; Kanis, 2004, Oleksik, 2000; Peasgood, 2009; Burstrom, 2006.

Economic Inputs – Drug Costs

Zoledronic acid: average generic wholesale acquisition cost (WAC) of $306 (Redbook Online, 2017)

Teriparatide:

- Net price of $1,866.34 per pen (represents 38% discount from WAC).
- 28 doses per pen; approximately 13 pens / year.

Abaloparatide:

- Used list price of $1,625 per pen; applied 27% discount
- Net price of $1,186.25
- 30 doses per pen; approximately 12 pens / year

Economic Inputs – Fracture, Other Costs

- Derived from publicly available US cohort studies in representative populations.
- Specific estimates for fracture and post-fracture health states.
  - Costs for vertebral fracture applied to 35% of patients, reflecting proportion of clinical vertebral fractures
  - Non-clinical vertebral fractures had no fracture-related costs applied
- Included IV administration cost for zoledronic acid ($168); no administration cost for anabolic drugs
- Assumed supportive care costs to be similar among comparators

Results

Base-Case Results

Regimen	Cost	QALYs	Life Years
Zoledronic acid	$25,465	8.933	12.188
Teriparatide	$68,905	8.979	12.193
Abaloparatide	$47,525	8.999	12.195

QALY: quality-adjusted life year

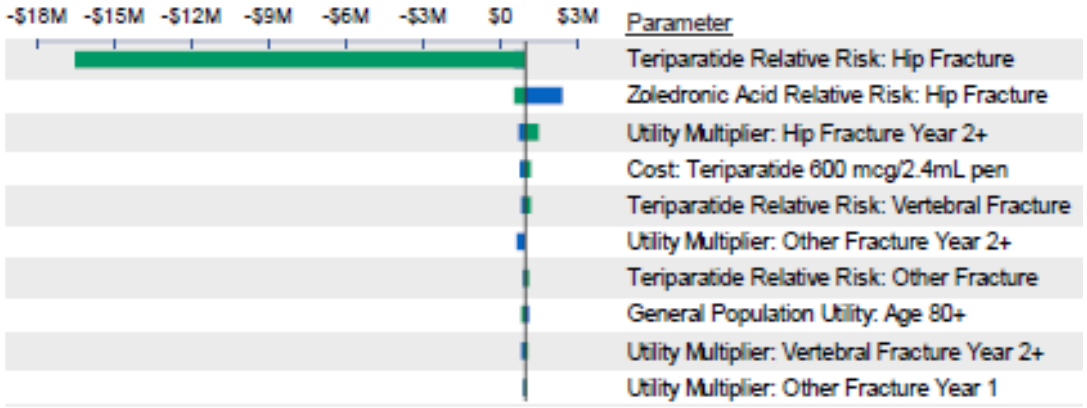
Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. Zoledronic Acid
Teriparatide	$43,440	0.046	0.005	$941,537
Abaloparatide	$22,061	0.066	0.007	$333,892

ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year

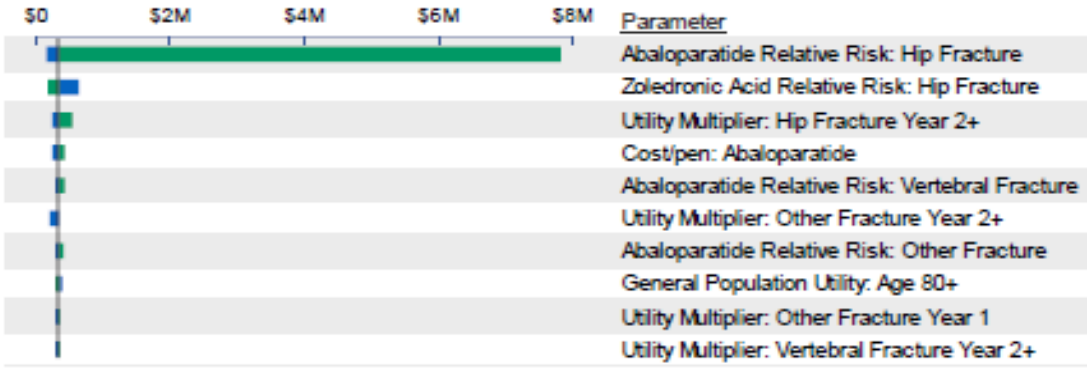
Lifetime Cumulative Fracture Probabilities	Zoledronic Acid	Teriparatide	Abaloparatide
Hip	0.24	0.21	0.19
Non-Vertebral	0.18	0.14	0.13
Other Non-Vertebral	0.54	0.50	0.46

One-Way Sensitivity Analyses

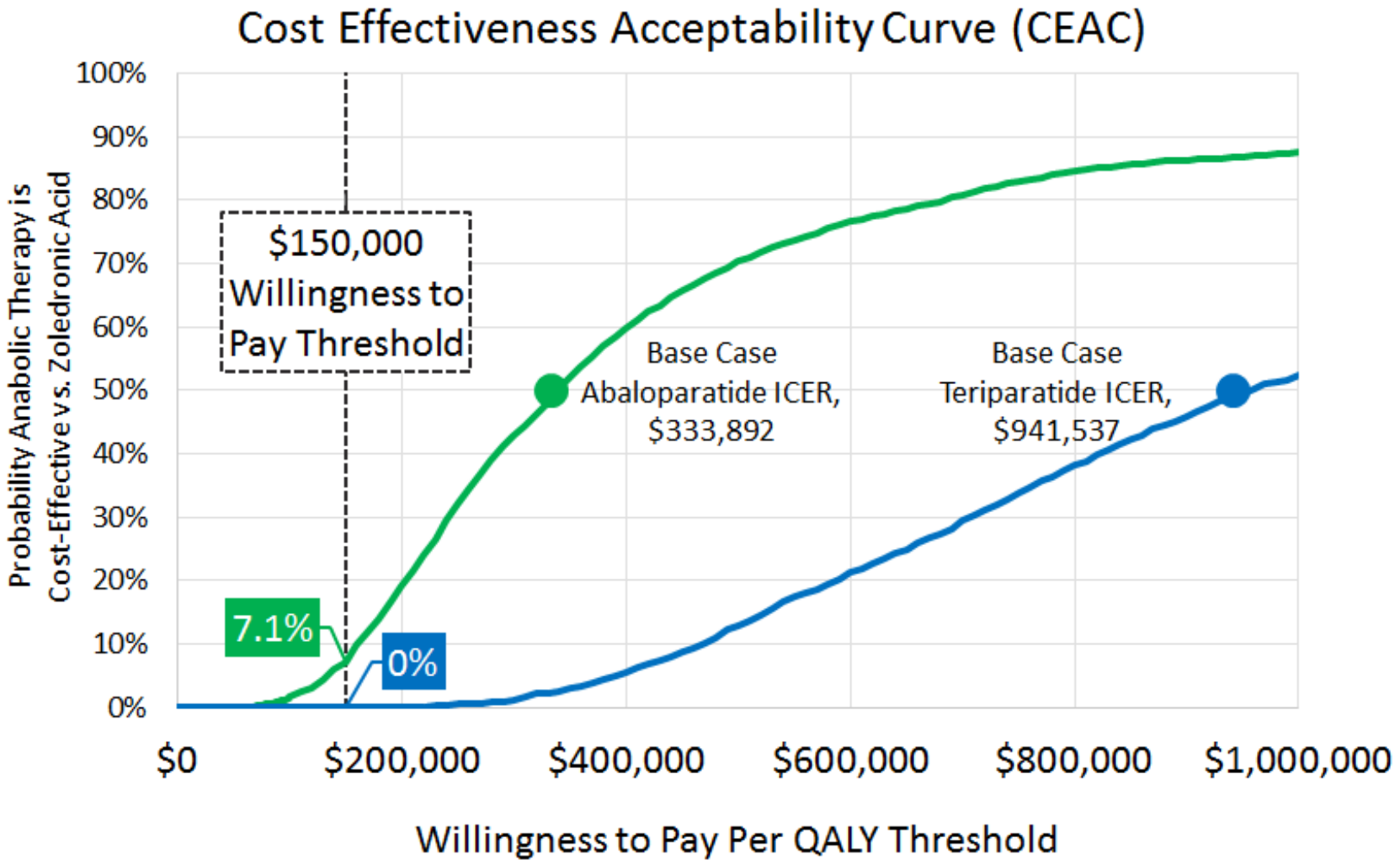
Teriparatide versus Zoledronic Acid



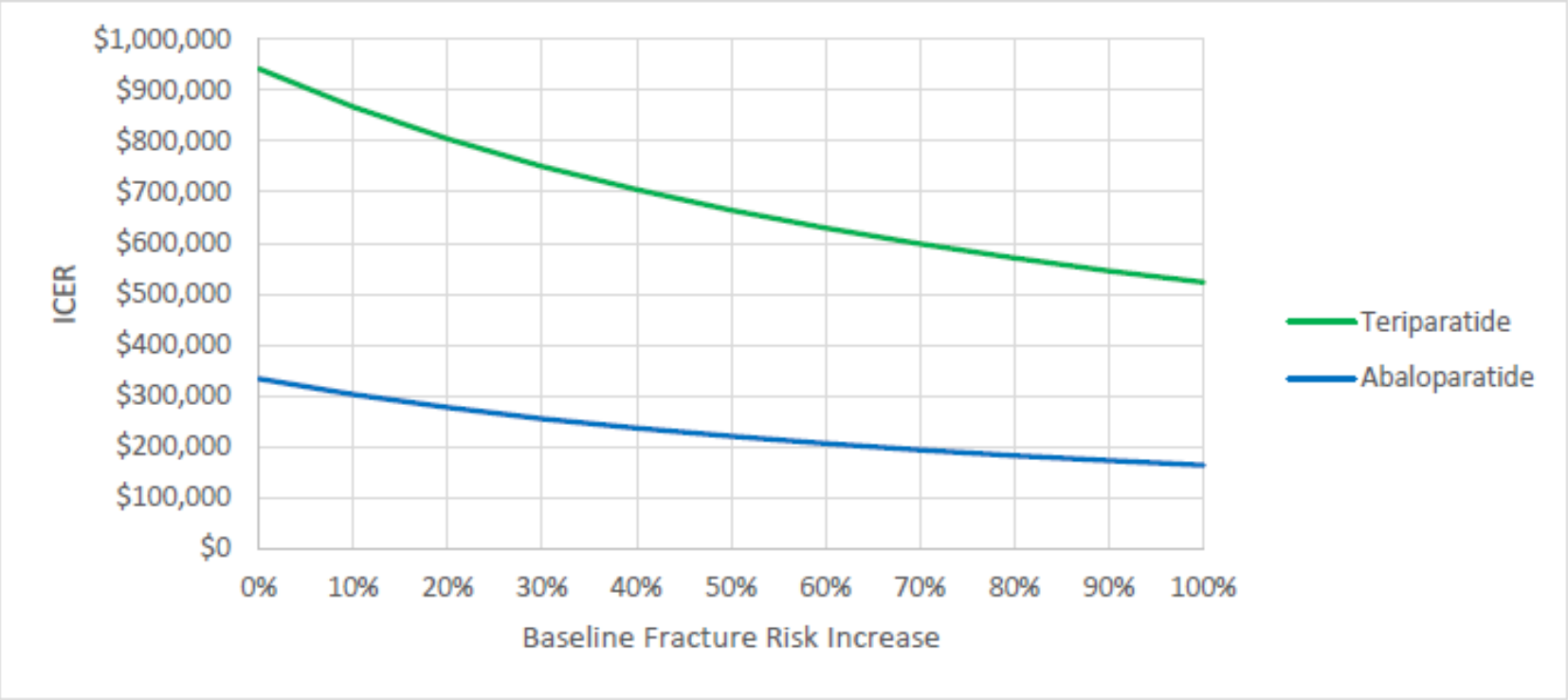
Abaloparatide versus Zoledronic Acid



Probabilistic Sensitivity Analysis

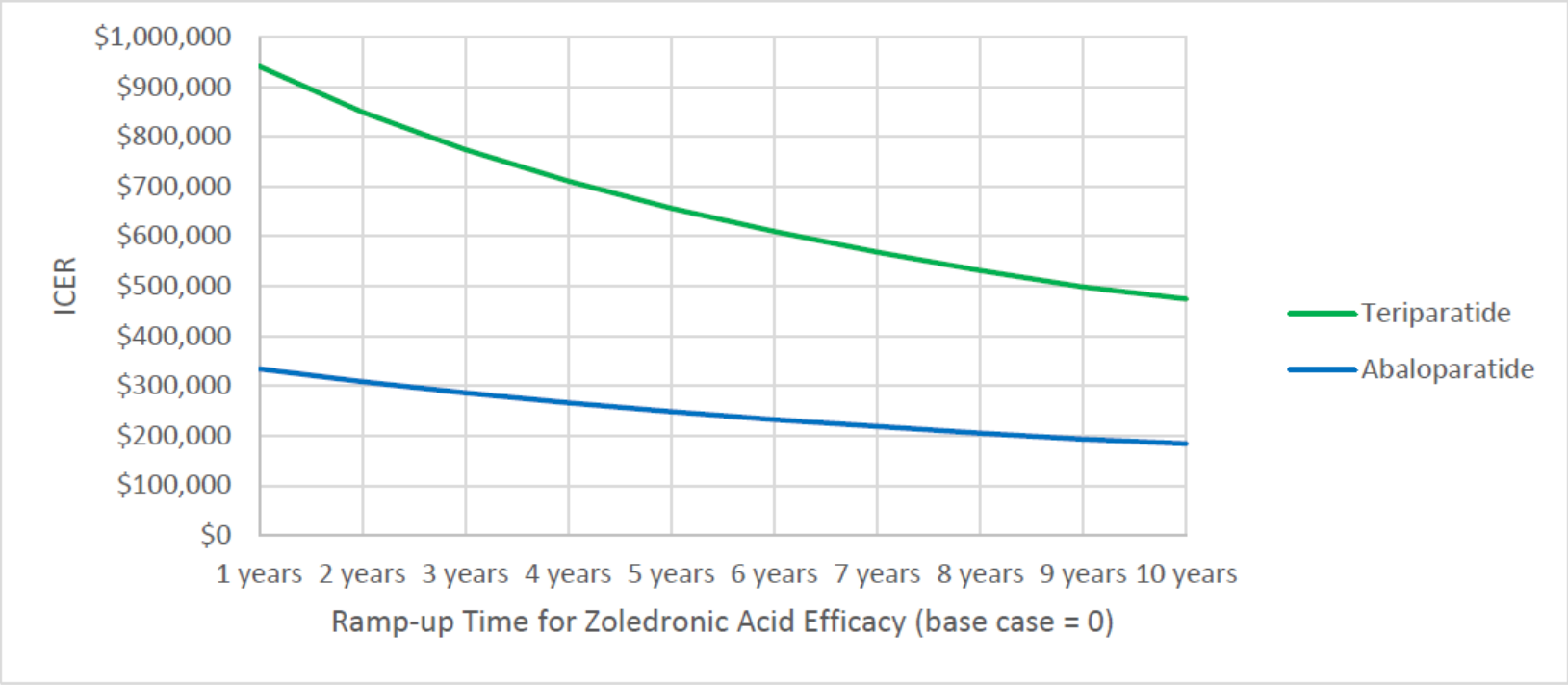


Scenario Analysis – Higher Baseline Fracture Risk



Annual Fracture Probabilities Increase	Hip (0% - 100%)	Vert (0% - 100%)	Other Non-Vert (0% -100%)
Hip / Non-Vert / Other Vert (age 70-74)	0.006 - 0.012	0.034 - 0.068	0.024 - 0.048
Hip / Non-Vert / Other Vert (age 85+)	0.031 - 0.062	0.091 - 0.182	0.079 - 0.158

Scenario Analysis – Ramp-up Time to Full Zoledronic Acid Efficacy



Scenario Analysis – Comparison to No Treatment

- Reflects a scenario in which pa tients may not be able to take zoledronic acid

Regimen	Cost	QALYs	Life Years
No Treatment	$30,038	8.825	12.181
Teriparatide	$73,162	8.886	12.182
Abaloparatide	$52,919	8.893	12.183

QALY: quality-adjusted life year

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. No Treatment
Teriparatide	$43,124	0.060	0.002	$715,878
Abaloparatide	$22,881	0.067	0.002	$339,027

ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year

Limitations

- Fracture hierarchy prevents patients from having a fracture classified as less severe than their last fracture.
- Adherence not modeled due to a lack of data
- Base-case cost and cost-effectiveness results for anabolics reflect our current assumptions about drug prices.

Comments Received

- Baseline fracture risk inputs do not reflect a high-risk population
  - Scenario analysis
- Adverse events are not considered
  - Infusion-related events modelled in scenario
- There is an excess mortality risk for clinical vertebral and other fractures
  - Scenario analysis
- Morphometric fractures have a disutility
  - Scenario analysis

Summary

- The cost per additional QALY was estimated to be above $150,000 per QALY for each anabolic agent.
- This finding remained over a wide range of sensitivity and scenario analyses, including patients at even higher risk for fracture.
- Results were most sensitive to uncertainty in relative risk estimates for hip fracture, long-term fracture utility multipliers, and drug costs.
- When anabolic agents are compared to no treatment, results suggest that anabolic treatments would not produce incr. cost-effectiveness ratios <$150,000 /QALY.

Appendix Slides

Clinical Inputs – Fracture Relative Risk Parameters

Model Input	Default	Lower	Upper	Source
Zoledronic acid (baseline)				
Hip Fracture	0.59	0.42	0.83	Black et al., HORIZON trial
Vertebral Fracture (all) *	0.30	0.24	0.37	NMA
Other Non-Vertebral Fractures	0.75	0.64	0.87	NMA
Teriparatide				
Hip Fracture	0.48	0.28	0.75	Derived from NMA and HORIZON
Vertebral Fracture (all)*	0.17	0.09	0.29	NMA
Other Non-Vertebral Fractures	0.61	0.41	0.88	NMA
Abaloparatide				
Hip Fracture	0.40	0.17	0.74	Derived from NMA and HORIZON
Vertebral Fracture (all)*	0.13	0.03	0.33	NMA
Other Non-Vertebral Fractures	0.51	0.28	0.85	NMA

*Relative risks for vertebral fractures were estimated from studies including morphometric vertebral fractures; 35% of estimated vertebral fractures were modeled as clinical vertebral fractures.

Clinical Inputs - Baseline Annual Fracture Probabilities by Age Strata

Fracture and Age (in years) Groups	Default	Lower	Upper	Source
Hip Fracture				
Age 70-74	0.006	0.005	0.007	Pooled trials
Age 75-79	0.011	0.009	0.013	Pooled trials & Melton/FRAX extrapolation
Age 80-84	0.023	0.019	0.028	Pooled trials & Melton/FRAX extrapolation
Age 85+	0.031	0.025	0.038	Pooled trials & Melton/FRAX extrapolation
Vertebral Fracture (Clinical and Morphometric)				
Age 70-74	0.034	0.027	0.041	Pooled trials
Age 75-79	0.046	0.037	0.055	Pooled trials & Melton extrapolation
Age 80-84	0.076	0.061	0.091	Pooled trials & Melton extrapolation
Age 85+	0.091	0.074	0.111	Pooled trials & Melton extrapolation
Other Non-Vertebral Fracture				
Age 70-74	0.024	0.019	0.029	Pooled trials
Age 75-79	0.037	0.030	0.044	Pooled trials & Melton extrapolation
Age 80-84	0.053	0.042	0.063	Pooled trials & Melton extrapolation
Age 85+	0.079	0.063	0.095	Pooled trials & Melton extrapolation

Clinical Inputs – Mortality, Utilities

Age Range	Default	Lower	Upper	Source
Age 70-74	0.0025	0.0020	0.0029	Tosteson
Age 75-79	0.0075	0.0060	0.0090	Tosteson
Age 80-84	0.0336	0.0269	0.0403	Tosteson
Age 85+	0.0727	0.0581	0.0872	Tosteson

Fracture related excess mortality for hip

- Utility inputs by age strata
- Utility multipliers for fractures year 1 and years 2+

Model Input	Default	Lower	Upper	Source
General Population Utilities				
Age 70-79	0.770	0.616	0.924	Hanmer et al.
Age 80+	0.720	0.576	0.864	Hanmer et al.
Utility Multipliers				
Hip Fracture Year 1	0.700	0.560	0.840	Peasgood et al.
Hip Fracture Year 2+	0.800	0.640	0.960	Peasgood et al.
Clinical Vertebral Fracture Year 1	0.590	0.472	0.708	Peasgood et al.
Clinical Vertebral Fracture Year 2+	0.931	0.745	1.000	Kanis/Oleksik et al.
Other Non-Vertebral Fracture Year 1	0.902	0.722	1.000	Burstrom et al.
Other Non-Vertebral Fracture Year 2+	1.000	0.800	1.000	Assumption

Economic Inputs – Drug Costs

Drug Name, Labeled Dose, Administration Route	Strength (Pen Size)	WAC/Pen	Net Price*	Base-Case Tx Duration	Acquisition Cost Per Tx Course†
Teriparatide 20 mcg SC QD	250 mcg/ml (2.4 ml)	$2,997.90	$1,866.34‡	2 years	$48,691
Abaloparatide 80 mcg SC QD	3,120 mcg/1.56 ml	$1,625	$1,186.25§	2 years	$29,312
Zoledronic Acid 5 mg IV Q year	5 mg/100 ml	$306#	$306#	6 years	$1,837

IV: intravenous, SC: subcutaneous, QD: once daily, Q mo: once monthly, Q year: once yearly, Tx: treatment, WAC: wholesale acquisition cost

*Net price is the estimated price after discounts and rebates from WAC. No discounts have been applied to generic zoledronic acid.

†Acquisition cost of initial drug using net price (or average generic WAC for zoledronic acid) and assuming full course of treatment; costs would be lower if a modeled patient died before completing a course of therapy.

Costs do not include the additional costs of post-anabolic zoledronic acid therapy.

‡Price per pen including 38% discount

§Price per pen based on announced list price and assumed 27% discount

#Annual dose cost based on average generic WAC

Economic Inputs – Fracture Costs

Model Input	Default	Lower	Upper	Source
Hip Fracture Cost	$44,395	$35,516	$53,274	Bonafede
Post-Hip Fracture Annual Cost	$10,835	$8,668	$13,002	Parthan
Clinical Vertebral Fracture Cost	$27,906	$22,325	$33,487	Bonafede
Post-Clinical Vertebral Fracture Annual Cost	$309	$247	$371	Parthan
Other Non-Vertebral Fracture Cost	$12,764	$10,211	$15,317	Bonafede
Post-Other Non-Vertebral Fracture Annual Cost	$0	$0	$0	Assumption

Background on Inclusion of Vert/Other Excess Mortality, from Johnell et al.

	Relative Risk of Mortality vs. Normal Population	
Age	Clinical Vertebral, y1	Shoulder and Forearm, y1
70-74	7.42	6.05
75-79	5.46	5.07
80-84	3.73	4.06
85+	2.36	2.51

- Relative risks were multiplied by the age-stratified background mortality of the US population.
- Because these inputs were not controlled for comorbidity, we applied a 50% reduction.

Scenario Analysis – Inclusion of Excess Mortality Due to Clinical Vertebral and Other Non-Vertebral Fractures*

Regimen	Cost	QALYs	Life Years
Zoledronic Acid	$25,051	8.819	12.027
Teriparatide	$68,588	8.886	12.062
Abaloparatide	$47,260	8.917	12.080

QALY: quality-adjusted life year

Regimen	Incr. Cost	Incr. QALYs	Incr. LYs	ICER vs. No Treatment
Teriparatide	$43,537	0.067	0.035	$649,845
Abaloparatide	$22,209	0.098	0.053	$226,259

ICER: incremental cost-effectiveness ratio, Incr.: incremental, LY: life year

ICER

*Johnell O, Kanis JA, Odén A, Sernbo I, Redlund-Johnell I, Petterson C, De Laet C, Jönsson B. Mortality after osteoporotic fractures. Osteoporos Int. 2004 Jan;15(1):38-42.

Manufacturer Public Comment and Discussion

Speakers

Name	Title	Company
Jorge Arellano, MSc, MPhil	Executive Director Global Health Economics Therapy Area Lead: Bone, Nephrology, and Supportive Oncology Care	Amgen
John Krege, MD, FAHA	Medical Fellow	Eli Lilly
Lorraine Fitzpatrick, MD	Chief Medical Officer	Radius Health

Public Comment and Discussion

Robin Dore, MD
Robin K. Dore, MD, Inc.; UCLA
Rheumatologist; Clinical Professor of Medicine

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000

Dr. Dore serves on speakers bureaus, advisory boards, and as a consultant for:

- *Amgen*
- *Eli Lilly*
- *Novartis*
- *Radius Health*

Benjamin Leder, MD
American Society for Bone and Mineral Research; Massachusetts General Hospital
Chair, Professional Practice Committee (ASBMR)

Conflicts of interest:

- Manufacturer support of research in the clinical area of this meeting

Dr. Leder has received support (medication supply) from the following manufacturers on an investigator-initiated trial:

- *Amgen*
- *Eli Lilly*

Lisa Tent

Patient

No conflicts of interest disclosed

Lunch

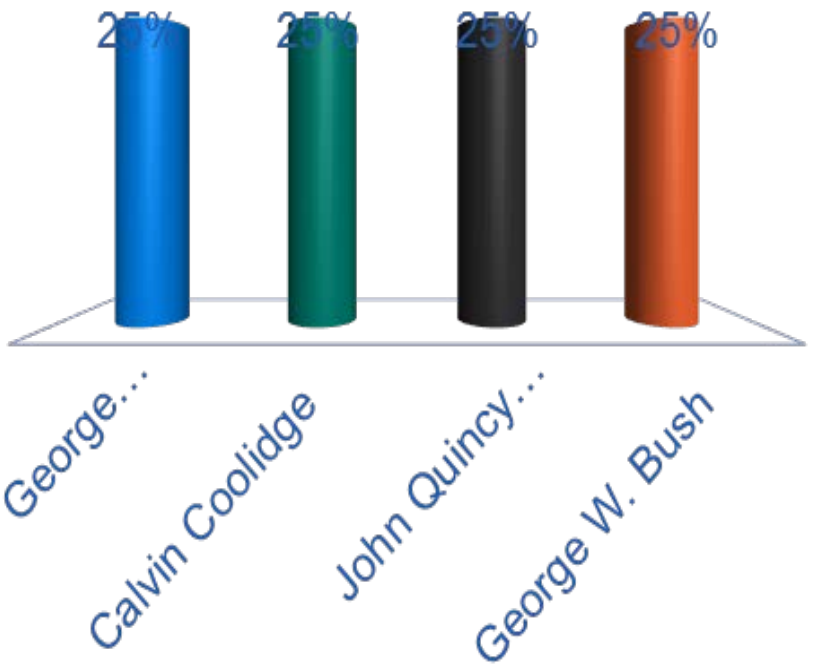
Meeting will resume at 12:45 pm

Voting Questions

WIFI: TCEGuest

0. Which US President was born on July 4?

A. George Washington
B. Calvin Coolidge
C. John Quincy Adams
D. George W. Bush



1. For postmenopausal women with osteoporosis and a high risk of fracture, is the evidence adequate to demonstrate that the net health benefit of treatment with **teriparatide (Forteo®, Eli Lilly and Co.)**, is greater than that of treatment with **zoledronic acid**?

A. Yes

B. No

2. For postmenopausal women with osteoporosis and a high risk of fracture, is the evidence adequate to demonstrate that the net health benefit of treatment with **abaloparatide (Tymlos™, Radius Health Inc.)**, is greater than that of treatment with **zoledronic acid**?

A. Yes

B. No

3. For postmenopausal women with osteoporosis and a high risk of fracture, is the evidence adequate to distinguish between the net health benefit of **teriparatide** and **abaloparatide**?

A. Yes

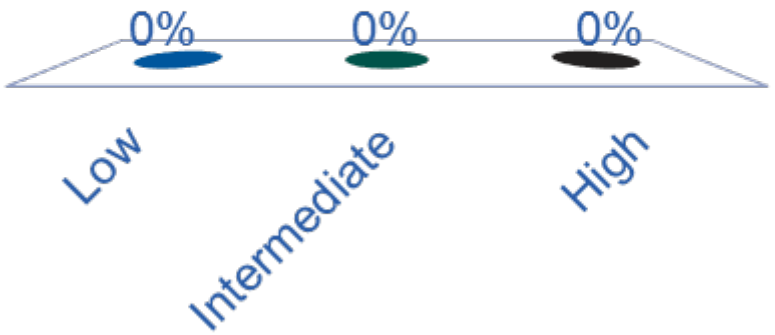
B. No

4. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **teriparatide followed by zoledronic acid** versus treatment with **zoledronic acid alone** for postmenopausal women with osteoporosis at high risk for fracture?

A. Low

B. Intermediate

C. High

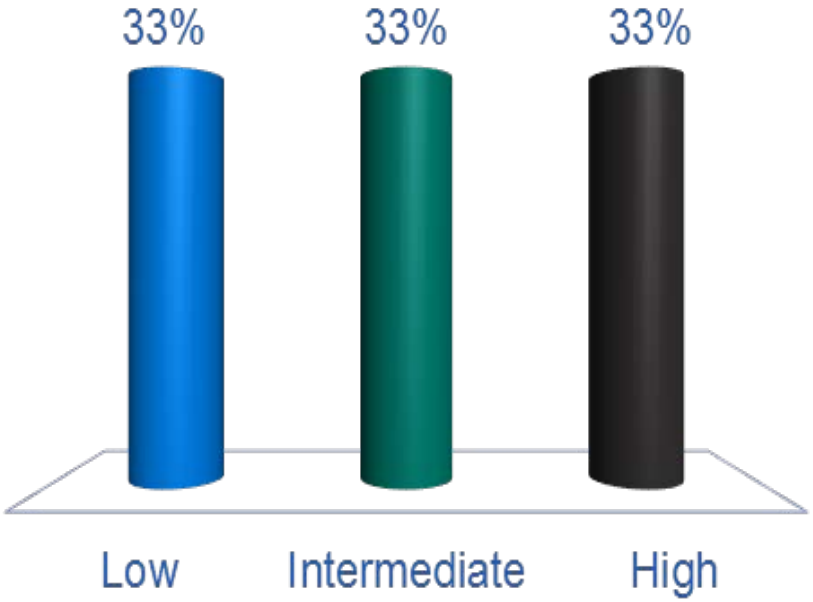


5. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with **abaloparatide followed by zoledronic acid** versus treatment with **zoledronic acid alone** for postmenopausal women with osteoporosis at high risk for fracture?

A. Low

B. Intermediate

C. High



Break
Meeting will resume at 2:00 pm

Policy Roundtable

Policy Roundtable Participants

Name	Title	COI Declaration
Victoria Dang, PharmD	Director, CDAG Program Performance, UnitedHealthcare Medicare and Retirement	United Healthcare employee and stockholder
Matthew Drake, MD, PhD	Consultant, Division of Endocrinology, Department of Medicine; Associate Professor of Medicine, Mayo Clinic	None
Deborah Kado, MD, MS	Professor, Department of Family Medicine and Public Health; Osteoporosis Clinic Director, Department of Medicine; Deputy Director of Clinical Research and Education, Sam and Rose Stein Institute for Research on Aging, University of California, San Diego	Scientific Advisory Board: Amgen (romosozumab), Kalytera
John Krege, MD, FAHA	Medical Fellow, Eli Lilly and Co.	Lilly employee and stockholder
Shireen Fatemi, MD, FACE, FACP	Healthy Bones Regional Co-Lead, Kaiser Permanente Southern California; National Clinical Lead for Osteoporosis, Kaiser Permanente; Assistant Area Medical Director, Kaiser Permanente Panorama City	None
Stuart L. Silverman, MD, FACP, FACR	Clinical Professor of Medicine, Cedars-Sinai Medical Center and UCLA School of Medicine; Medical Director, Osteoporosis Medical Center Clinical Research Center; Member, National Bone Health Alliance Osteoporosis Messaging Group	Advisory Board, Speaker: Amgen, Lilly, Radius Consultant: Amgen Research Grants: Amgen, Lilly, Novartis, Pfizer, Roche Former Officer: Kalytera
Roselyne Smith	Patient	None
Martin Zagari, MD	Vice President, Global Health Economics, Amgen, Inc.	Amgen employee, officer, and stockholder

CTAF Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about July 14
  - Includes description of CTAF votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/topic/osteoporosis/

Adjourn