Testimony before the FDA's Bone, Reproductive and Urologic Drug Advisory Committee Regarding Romosozumab

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Meena M. Aladdin, Ph.D.
Sidney Wolfe, M.D.
Public Citizen's Health Research Group

We have no financial conflicts of interest.

Major Comment

- This is the second cycle review for romosozumab. On July 13, 2017, the FDA issued a complete response letter after the applicant completed two additional trials comparing romosozumab to placebo and alendronate.
  - **Trial 20110124 (NCT 01631214):** an alendronate-controlled fracture trial in postmenopausal women with osteoporosis
  - **Trial 20110174 (NCT 02186171):** a placebo-controlled bone mineral density study in men with osteoporosis

- These trials demonstrated efficacy but raised safety concerns as there was an increased incidence of cardiovascular serious adverse events in the year of romosozumab treatment in both studies.

We strongly urge the committee to recommend that the FDA not approve romosozumab.

Romosozumab Mechanism of Action

- Sclerostin is a product of the *SOST* gene and an endogenous antagonist of the WNT signaling pathway cascade
  - Loss of function can lead to excessive bone formation
- While sclerostin is primarily expressed by osteoclasts, it is also expressed by a number of other different tissues including the heart and aorta
- Romosozumab is a monoclonal antibody that binds an inhibits sclerostin, ultimately increasing WNT signaling

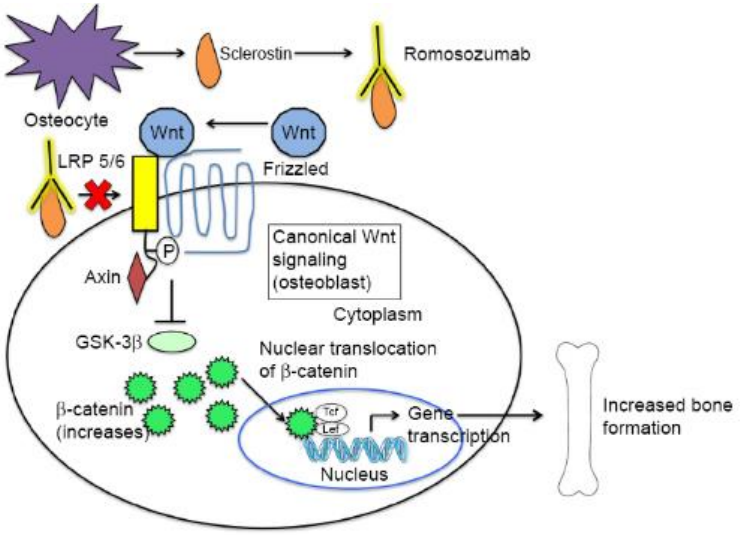

Figure 3 The effect of sclerostin inhibition on Wnt signaling.
Notes: Sclerostin is secreted by the osteocyte. Romosozumab, a humanized MAb against sclerostin, binds circulating sclerostin. This prevents binding of sclerostin to LRP 5/6. Therefore, Wnt is able to bind LRP 5/6 and its co-receptor, frizzled. This activates the Wnt signaling pathway, which eventually leads to osteoblast differentiation, proliferation and survival and, hence, increased bone formation.
Abbreviation: MAb, monoclonal antibody.

Shah AD, Shoback D, Lewiecki EM. Sclerostin inhibition: a novel therapeutic approach in the treatment of osteoporosis. Int J Women's Health. 2 June 2015;7:565-580.

Safety Concerns for Romosozumab

- It is important to consider the potential for off-shoot effects of targeting a cell signaling pathway that plays diverse roles in maintaining many other vital cellular functions.

- This pathway affects many cell types including vascular endothelial cells.
  - There is a growing body of evidence to suggest that the WNT pathway is involved in cardiovascular disease.

Cardiovascular Adverse Events are Enhanced

Table 14: Adjudicated Major Adverse Cardiovascular Events (MACE), Cardiovascular (CV) Serious Adverse Events (SAEs) and Cardiovascular Deaths

Trial	20070337		20110142	
	Placebo	Romosozumab	Alendronate	Romosozumab
n, safety analysis	3576	3581	2014	2040
MACE, n (%)	29 (0.8)	30 (0.8)	22 (1.1)	41 (2.0)
Hazard Ratio (95% CI)	1.03 (0.62, 1.72)		1.87 (1.11, 3.14)	
CV Death, n (%)	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Hazard Ratio (95% CI)	1.13 (0.56, 2.26)		1.42 (0.68, 2.97)	
Myocardial Infarction, n (%)	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Hazard Ratio (95% CI)	1.12 (0.43, 2.91)		3.21 (1.18, 8.77)	
Stroke, n (%)	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
Hazard Ratio (95% CI)	0.80 (0.32, 2.02)		1.86 (0.74, 4.67)	
Any cardiovascular SAE, n (%)	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
Hazard Ratio (95% CI)	1.00 (0.66, 1.50)		1.32 (0.87, 2.01)	
Cardiac ischemic event, n (%)	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Hazard Ratio (95% CI)	1.00 (0.50, 2.00)		2.68 (1.05, 6.84)	
Heart failure, n (%)	5 (0.1)	7 (0.2)	8 (0.4)	4 (0.2)
Hazard Ratio (95% CI)	1.40 (0.44, 4.40)		0.50 (0.15, 1.66)	
Non-coronary revascularization, n (%)	2 (<0.1)	1 (<0.1)	5 (0.2)	3 (0.1)
Hazard Ratio (95% CI)	0.50 (0.05, 5.49)		0.60 (0.14, 2.52)	
Cerebrovascular event, n (%)	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Hazard Ratio (95% CI)	0.91 (0.39, 2.14)		2.30 (0.94, 5.58)	
Periph vascular, no revascular, n (%)	1 (<0.1)	4 (0.1)	2 (<0.1)	0 (0.0)
Hazard Ratio (95% CI)	3.99 (0.45, 35.72)		Not Estimable	

CI = Confidence interval

Lack of Evidence Demonstrating Cardioprotection by Alendronate

- *"The placebo-controlled fracture trial 20070337 did not show a cardiovascular safety signal. However, the alendronate-controlled fracture trial 20110142 and the smaller BMD trial 20110174 in men with osteoporosis did show a cardiovascular safety signal."*

- There is no definitive evidence to suggest that alendronate is cardioprotective
  - *"After conducting additional exploratory analyses…neither the applicant nor the FDA has been able to conclusively determine the cause(s) for the discrepant MACE results between the placebo-controlled postmenopausal osteoporosis trial and the other two phase 3 trials."*
  - *"The multivariate network meta-analysis results, adjusted by treatment group and age, and stratified by country did not differ from the univariate analysis. This finding suggests that the rate of MACE with alendronate was lower than that with placebo, but is limited by cross-study comparisons and cannot definitively establish whether alendronate is cardioprotective."*

Conclusions

- While this drug is effective in increasing bone density and decreasing vertebral fractures in both the placebo- and alendronate-controlled clinical trials, its effects on cardiovascular adverse outcomes in the alendronate clinical trials raises serious safety concerns that must be resolved prior to approval.

- The effects of alendronate on cardiovascular system have not been fully understood and there is no evidence that this drug is cardioprotective.

- Targeting a pathway as versatile as the WNT signaling pathway has the potential to confer additional unforeseen risks.

Consistent with the precautionary principle of public health we strongly urge the committee to recommend that the FDA not approve romosozumab.