Denosumab Safety

FDA Analysis

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Safety Review

- **Methods**
  - Review of verbatim terms and event coding
  - Review of subject narratives

- **ISS**
  - Modified database to include only the four primary studies (216, 132, 135, 138)
  - Safety Populations: PMO=8091 HA=1705

Adverse Event Rates: Osteoporosis Trials

	Trial 216		Trial 132	
n (%)	**Placebo**	**Denos**	**Placebo**	**Denos**
n, Safety	3876	3886	165	164
Deaths	90 (2)	70 (2)	0	0
Serious AE	972 (25)	1004 (26)	9 (6)	19 (12)
AE / trial withdrawal	81 (2)	93 (2)	2 (1)	1 (1)
AE / IP discontinue	203 (5)	192 (5)	6 (4)	5 (3)
Any AE	3608 (93)	3605 (93)	157 (95)	156 (95)

Adverse Event Rates: Hormone Ablation Trials

	Trial 135		Trial 138	
n (%)	**Placebo**	**Denos**	**Placebo**	**Denos**
n, Safety	120	129	725	731
Deaths	1 (1)	1 (1)	46 (6)	44 (6)
Serious AE	11 (9)	19 (15)	222 (31)	253 (35)
AE / trial withdrawal	5 (4)	1 (1)	44 (6)	51 (7)
AE / IP discontinue	5 (4)	2 (2)	47 (6)	49 (7)
Any AE	108 (90)	117 (91)	627 (86)	638 (87)

Deaths in the Phase 1/2 Studies

- Two deaths in the Phase 1 program (one MVA; one progression of breast cancer)
- Four deaths in Trial 223 (dose-finding), all received denosumab
  - Cerebrovascular accident (n = 1)
  - Neoplasms (n = 3)
    - Brain tumor
    - Adenocarcinoma (probable lung)
    - Adenocarcinoma (gastric)
- One additional death in the extension phase of 223
  - unknown cause

Deaths in the Primary Phase 3 Trials

- **Postmenopausal Osteoporosis**:
  - 90/4041 (2.2%) placebo; 70/4050 (1.7%) denosumab
  - Most common: Neoplasms, Cardiac disorders, Respiratory disorders, Nervous System disorders
- **Hormone Ablation Trials**:
  - 47/845 (5.6%) placebo; 45/860 (5.2%) denosumab
  - Most common: Cardiac disorders, Respiratory disorders, Nervous System disorders, Neoplasms
- **No imbalances in deaths in any of the phase 3 trials**

Serious Adverse Events: PMO Trials

- **Trial 216** (N=3876 plac, N=3886 denos; mean age 72 yr):
  - 972 (25.1%) placebo; 1004 (25.8%) denosumab
  - Increased in denosumab: Cardiac disorders, Musculoskeletal disorders, Infections, Neoplasms
  - Increased in placebo: Injuries (incl. fractures)
- **Trial 132** (N=165 plac, N=164 denos; mean age 59 yr):
  - 9 (5.5%) placebo; 19 (11.6%) denosumab
  - Most Common:
    - Infections: 1 (0.1%) placebo, 8 (4.9%) denosumab
    - Neoplasms: 1 (0.1%) placebo, 4 (2.4%) denosumab

Serious Adverse Events: Hormone Ablation

- **Trial 135** (N=120 plac, N=129 denos; mean age 59 yr):
  - 11 (9.2%) placebo; 19 (14.7%) denosumab
  - Most Common:
    - Musculoskeletal: 1 (0.8%) placebo, 4 (3.1%) denosumab
    - Neoplasms: 1 (0.8%) placebo, 3 (2.3%) denosumab
- **Trial 138** (N=725 plac, N=731 denos; mean age 75 yr):
  - 222 (30.6%) placebo; 253 (34.6%) denosumab
  - Most Common:
    - Cardiac: 75 (10.3%) placebo, 69 (9.4%) denosumab
    - Nervous system: 35 (4.8%) placebo, 50 (6.8%) denosumab
    - Neoplasms: 42 (5.8%) placebo, 37 (5.1%) denosumab
    - Infection: 33 (4.6%) placebo, 43 (5.9%) denosumab

Most Common Adverse Events Leading to IP Discontinuation in the PMO Trials

	Placebo N=4041	Denos N=4050
AE / IP discontinuation	209 (5.1)	197 (4.9)
Preferred Term	**n (%)**	**n (%)**
breast cancer	10 (0.2)	20 (0.5)
back pain	10 (0.2)	6 (0.1)
constipation	6 (0.1)	6 (0.1)
colon cancer	4 (0.1)	5 (0.1)
lumbar vertebral fracture	12 (0.3)	2 (<0.1)
thoracic vertebral fracture	8 (0.2)	1 (<0.1)

Adverse Events of Special Interest

- Infection
- New Malignancy
- Tumor Progression
- Dermatologic Events
- Pancreatitis
- Ocular Adverse Events
- Cardiovascular Adverse Events
- Hypocalcemia
- Osteonecrosis of the Jaw
- Hypersensitivity / Immunogenicity
- Bone Histomorphometry Findings

Infections

Infections: Reason for Concern

- **Biologic Plausibility**
  - Denosumab is an inhibitor of RANKL
  - RANKL in B- and T-cell differentiation
  - RANKL is also involved in dendritic (antigen-presenting) cell survival
- **Phase 1:** Three subjects, two of which were healthy subjects under the age of 35, required hospitalization for pneumonia after a single dose of denosumab
- **Phase 2**, Trial 223:
  - Infection SAEs: 10/314 (3.2%) of denosumab cohort, 0/46 (0%) placebo, 0/46 (0%) alendronate

Infections

- **Serious Adverse Events**
  - 216: **133**/3876 (3.4%) placebo; **159**/3886 (4.1%) denos
  - 132: **1**/166 (0.6%) placebo; **8**/166 (4.9%) denosumab
  - 135: **1**/124 (0.8%) placebo; **3**/125 (2.3%) denosumab
  - 138: **33**/725 (4.6%) placebo; **43**/731 (5.9%) denosumab
- **Adverse Events**
  - Balanced across all treatment groups in the PMO trials
  - Increased in the denosumab groups in the hormone ablation trials
- **No imbalances in opportunistic infections**

Skin Infection SAEs – Trial 216

3/3876 **placebo subjects**

- Cellulitis -1
- Paronychia – 1
- Subcutaneous abscess – 1

14/3886 **denosumab subjects**

- Erysipelas – 7
- Cellulitis – 6
- Skin bacterial infection – 2
- Infected skin ulcer -1

Infection SAEs of Concern

Serious ear infections in Trial 216:

- **0** / 3876 **placebo subjects**
- **5** / 3886 **denosumab subjects**
  - Labrynthitis - 4, Otitis media - 1

Serious UTIs in Trial 216:

- **17** / 3876 **placebo subjects**
  - Cystitis – 2, Kidney infection – 1, Pyelonephritis – 3, Renal abscess – 1, UTI – 10
- **28** / 3886 **denosumab subjects**
  - Cystitis – 6, Pyelonephritis – 7, UTI – 16

Endocarditis

Trial 216:

- **0** / 3876 **placebo subjects**
- **3** / 3886 **denosumab subjects**
  - 1 fatality
  - 1 valve replacement
  - Event occurred ~59-149 days from last dose

Infective Arthritis

Trial 216:

- **0** / 3876 **placebo subjects**
- **8** / 3886 **denosumab subjects**
  - Affected joints include: elbows, knee, hip, ankle, shoulder
  - None reported as serious

Infections - Summary

- There is an imbalance in the number of serious infections in the denosumab group
- Most notable were infections of the skin, ear, and urinary tract.
- An imbalance in endocarditis was noted
- An imbalance in infective arthritis was noted
- There was no evident increase in opportunistic infections

New Malignancies

New Malignancies: Reason for Concern

- Denosumab is specific to human and non-human primate RANKL and is not active in the rodent
- No carcinogenicity studies were performed due to a lack of an animal model
- Dose-finding trial (Trial 223) – 3 deaths due to neoplasms in 100 mg Q6months cohort
- Common AE leading to discontinuation in PMO trials

New Malignancies: PMO Trials

High Level Group Term	Placebo N=4041 n (%)	Denosumab N=4050 n (%)
Any event, Neoplasm SOC	285 (7.1)	316 (7.8)
Malignant or unspecified neoplasm	**168 (4.2)**	**192 (4.7)**
Gastrointestinal neoplasm malignant & unspecified	24 (0.6%)	35 (0.9%)
Breast neoplasms malignant & unspec	29 (0.7%)	35 (0.9%)
Reproductive neoplasms female malig & unspec	9 (0.2%)	21 (0.5%)
Respiratory & mediastinal neoplasms malignant & unspecfied	24 (0.6%)	15 (0.4%)

New Malignancies, Summary

- No carcinogenicity studies were performed due to a lack of an animal model
- Three subjects in a high dose denosumab group in the dose finding trial died of a new malignancy
- In the primary PMO studies, there was an imbalance in the incidence of malignancies in the denosumab group, driven by breast, reproductive and gastrointestinal cancers

Tumor Progression

Tumor Progression: Reason for Concern

- Hormone ablation trials not designed to evaluate cancer outcomes
- There was an imbalance in metastatic events:
  - In trial 135
    - placebo 5 (4.2%), denosumab 9 (7.0%)
  - In trial 138:
    - placebo 40 (5.5%), denosumab 60 (8.2%)

Dermatologic Adverse Events

Dermatologic Adverse Events

- A significant imbalance was noted in adverse events related to skin and soft tissue disorders, not including skin infections
- Not specific to the injection site
- Mainly driven by epidermal and dermal conditions

n (%)	**Placebo** N=4041	**Denosumab** N=4050
Epidermal and dermal conditions, all	340 (8.4)	447 (11.0)
Dermatitis and eczema	81 (2.0)	147 (3.6)
Pruritis, NEC	97 (2.4)	110 (2.7)
Rashes, eruptions, exanthems, NEC	89 (2.2)	116 (2.9)

Dermatologic Serious Adverse Events

- **Skin SAEs** occurred in 7 (0.2%) placebo subjects and 10 (0.3%) denosumab subjects
- In many of these cases, while denosumab could not be ruled out as the cause, subjects were noted to be on other medications that could also be the cause
- The four cases of “toxic skin eruptions” were reviewed and do not appear to be secondary to denosumab

Pancreatitis

Pancreatitis: PMO Pooled Data

	Placebo N=4041		Denos. N=4050	
No. of Subjects	4		8	
No. of Events	4		9	
Preferred Term	**Non-serious**	**Serious**	**Non-serious**	**Serious**
Pancreatitis	1	0	0	2
Pancreatitis acute	**1**	**0**	**0**	**5**
Pancreatitis chronic	1	0	0	1
Pancreatic pseudocyst	0	1	0	1
Total Events	3 (0.1%)	1 (< 0.1%)	0 (0%)	9 (2%)

Ocular Adverse Events

Ocular Adverse Events

- Reason for Concern
  - An imbalance in the incidence of cataracts in trial 20040138 (prostate)

	Trial	Placebo n (%)	Denosumab n (%)
Cataract AEs	Trial 138	9 (1.2%)	34 (4.7%)
	Trial 216	253 (6.3%)	229 (5.7%)
Cataract SAEs	Trial 138	0 (0%)	2 (0.3%)
	Trial 216	28 (0.7%)	21 (0.5%)

Cardiovascular Adverse Events

Cardiovascular: Reason for Concern

- Osteoprotegerin (OPG) is a cytokine in the TNF receptor superfamily. Its main function is inhibition of RANKL and osteoclast differentiation.
- Literature reports suggest an association between osteoprotegerin (OPG) levels and arterial wall calcification, cardiovascular disease, and mortality
- There is a theoretical potential for elevated OPG levels with denosumab inactivation of RANKL, as it binds to the same target

Cardiovascular Safety Analysis

- Deaths and Cardiovascular SAEs from studies 216 and 138 were adjudicated by an independent panel of cardiologists
  - ***There was a similar incidence of cardiac deaths, and SAEs in the treatment arms***
- OPG levels were measured in the bone marker substudy of trial 216
  - ***OPG levels did not increase with denosumab use***
- Abdominal aortic calcification scores were assessed using the x-rays collected for fracture analyses
  - ***No differences in the scores were seen***

Hypocalcemia

Hypocalcemia

- Hypocalcemia is a well recognized adverse event with anti-resorptive therapy - essentially these therapies function to shut off bone as a reservoir for calcium
- All subjects in the primary phase 3 trials were supplemented with 1000 mg calcium and 400 – 800 IU vitamin D.
- Timing of the calcium measurements in the primary phase 3 trials **missed** the anticipated calcium nadir (8-11 days post-dose)
- One denosumab-treated subject in trial 138 reported an SAE of hypocalcemia
- In the phase 3 PMO trials, 1.6% of subjects had an asymptomatic calcium < 8.5 mg/dL. Calcium levels < 7.5 mg/dL were rare

Osteonecrosis of the Jaw

Osteonecrosis of the Jaw (ONJ)

- The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling
- Potential cases of ONJ were adjudicated by an independent committee
- There was a balanced distribution of potential ONJ cases, as identified by the search criteria, between arms in all studies.
- No cases met the definition of ONJ
- Cases of ONJ are being reported in denosumab subjects in ongoing & completed advanced cancer trials.

Immunogenicity

Immunogenicity

- Any therapeutic protein has the potential to elicit an immune response
- A three-step process for detection of antibodies was used:
  - A screening immunoassay to detect binding antibodies
  - A second immunoassay to confirm binding antibodies
  - Cell-based bioassay to evaluate for neutralizing antibodies
- Most clinical studies from the denosumab program had evaluations of immunogenicity

Binding Antibodies

Population	Subjects	Pre-existing binding Ab	Binding Ab
Subjects Exposed to Denosumab			
Total	8113	12 (0.1%)	43 (0.5%)
PMO	6111	6 (0.1%)	28 (0.5%)
Cancer	1273	2 (0.2%)	7 (0.5%)
Other*	729	4 (0.5%)	8 (1.1%)
Subjects Exposed to Placebo or Active Control			
Total	5320	8 (0.2%)	16 (0.3%)

* Includes healthy population, rheumatoid arthritis and renal disease