FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

BACKGROUND PACKAGE ADDENDUM

DATE: March 2, 2012

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TO: Chair, Members and Invited Guests
Arthritis Advisory Committee (AAC)

RE: Addendum to the Background Package for the March 12, 2012, AAC Meeting, Regarding the Agency Adjudication of Cases of Joint Replacements Occurring in Clinical Trials of Anti-NGF Agents

As mentioned in the original background package, the Agency has conducted two independent adjudications of the almost 500 joint replacement cases submitted to the Agency by the three Sponsors, in order to assess the occurrence of rapid and unexpected joint destruction in the clinical trials of the Anti-NGF agents, to compare our adjudication results with those of the Sponsors, and to assist in the determination of the nature of the safety signal associated with these agents. You have already received the results of the Sponsors' adjudications in their briefing books. This addendum includes the two adjudication reports submitted on behalf of the Agency. One adjudication was conducted by Nona Colburn, M.D., a Medical Officer in the Center for Devices and Radiological Health (CDRH). Dr. Colburn is a Board Certified Rheumatologist who has also received residency training in orthopedic surgery. She has completed an Orthopedic Research Fellowship, and a Rheumatology Clinical Fellowship at NIH. The second adjudication was conducted by Dr. Joan Bathon, the Director of the Division of Rheumatology in the Department of Medicine at Columbia University Medical Center, and a Professor of

Medicine at Columbia University College of Physicians and Surgeons. Previously, Dr. Bathon was Deputy Director of the Division of Rheumatology and Director of the Arthritis Center at Johns Hopkins. Dr. Bathon is the Editor-in-Chief of the American College of Rheumatology journal, *Arthritis and Rheumatism.* Dr. Bathon's colleagues, including a radiologist, a pathologist and two rheumatology fellows, assisted Dr. Bathon in culling the relevant information from the Sponsors' data.

The adjudication methods used by Drs. Colburn and Bathon are described in their summaries, which are included in this addendum. You will see that there were limitations imposed by the lack of electronic access to data (Dr. Bathon), and limitations in both time to complete the task and resources for both Drs. Bathon and Colburn, that resulted in differences in the adjudication methods compared to the Sponsors. These limitations were due in part to the Agency processes and restrictions that must be followed to obtain expert assistance from persons outside the Agency, and the large amount of data that needed to be reviewed in a relatively short period of time. However, despite the limitations, we believe that both adjudicators were able to answer the questions posed to them: 1) Would the joint related adverse events of rapid joint destruction that occurred in the clinical trials of the Anti-NGF agents be expected to occur in the populations studied, and 2) Whether these events were likely related to study drug?

The following are summaries of Dr. Bathon's and Dr. Colburn's adjudications. Since the patient exposure to the Regeneron anti-NGF agent was quite small, the conclusions are based on findings from the Janssen and Pfizer programs, unless stated otherwise. Details regarding their methods and analyses are presented in separate documents in this addendum:

The category of "non-OA process" was used by Dr. Bathon in her adjudication rather than rapidly progressive OA (RPOA). This was due to the poor film quality (paper PDF copies) which precluded accurate measurement of joint space width; moreover, none of these studies obtained joint radiographs in a systematic manner that would allow such measurements even if the films were of otherwise good quality. Based on review of images, there was either high suspicion, low or no suspicion, or indeterminate suspicion of 'non-OA process' as reflected by presence or absence of severe bone loss or other severe joint deformity i.e., subchondral defects, deformity, collapse, impaction, fragmentation, bone resorption and severe subluxation. These are referred to as 'non-OA' features because they raise suspicion for possible osteonecrosis (ON) or Charcot-like joint but recognizing that collapse of OA related subchondral cysts could give same appearance).

In summary, the results of Dr. Bathon's adjudication are:

1. When analyzed by specific anti-NGF agent, a significant association of a highly suspicious non-OA process with tanezumab use was observed, but not with the other two agents (though numbers were smaller for the latter two).

2. Based on Dr. Bathon's adjudication, the combination of anti-NGF agent with NSAIDs was significantly associated with presence of a highly suspicious non-OA process when compared to placebo +/- NSAIDs, and when compared to anti-NGF agent without NSAIDs. These significant associations held true when the analyses were restricted to the tanezumab studies only.

3. Based on Dr. Bathon's review of the Sponsors' adjudication, for tanezumab and fulranumab, there was a significant association between adverse outcome (primary osteonecrosis or rapidly progressive osteoarthritis) in the anti-NGF treatment group compared to placebo. This association persisted when each of the individual anti-NGF agents was analyzed separately in comparison to placebo.

4. There were high rates of agreement in the adjudication processes (Sponsors and Dr. Bathon) in the following groups: 1) presence of ON/RPOA by Sponsor adjudication with high suspicion of non-OA process by Dr. Bathon's adjudication; and 2) absence of ON/RPOA by Sponsor adjudication with absence of high suspicion of non-OA process by Dr. Bathon's adjudication.

    a. When analyses were restricted to participants for whom there was concurrence in adjudication, anti-NGF therapy was significantly associated with high suspicion for ON/RPOA/non-OA process compared to placebo treatment.

    b. The combination of anti-NGF therapy with NSAIDs, when analyzed as a group, was associated with a higher rate of adverse outcomes compared to anti-NGF therapy without NSAIDs and to placebo +/- NSAIDs. When the analysis was restricted to tanezumab, tanezumab with NSAIDs was associated with a higher rate of adverse outcomes compared to placebo +/- NSAIDS, but was not significantly increased compared to tanezumab without NSAIDs.

In summary, the results of Dr. Colburn's adjudication are:

1. The adjudication of the cases of total joint replacement was in general agreement with the Sponsors' adjudications for the diagnoses of normal progression of osteoarthritis and rapidly progressing osteoarthritis, with some disagreement regarding the diagnosis of osteonecrosis, due to differences in definition of ON.

2. The majority of cases adjudicated as RPOA and ON appeared related to study drug.

3. Lower doses of Anti-NGF and less frequent administration of study drug, and placebo were more likely be associated with the normal progression of OA adjudication.

4. Higher doses of Anti-NGF and concomitant use of NSAIDS appeared more likely associated with the adjudicated diagnoses of RPOA and ON.

5. Several cases adjudicated as RPOA demonstrated considerable and rapid joint destruction, most notably of the femoral head and medial femoral condyle that appeared to be beyond the bony destruction described in the literature associated with RPOA. The joint destruction seen in these cases appears to be a unique clinical form of rapidly destructive arthropathy.

Overall, both sets of adjudications are in general agreement with the adjudications conducted by the Sponsors. Differences in the adjudications may be due to differences in the adjudication processes and definitions used to determine the diagnoses, in addition to differences in the interpretation of the data by the adjudicators.

There appears to be a safety signal of rapid joint destruction, (whether it is labeled ON, RPOA, a non-OA process, or some combination of these) associated with both Anti-NGF agent monotherapy and Anti-NGF agent plus NSAID therapy. The incidence of this event is more pronounced in patients receiving both the Anti-NGF agent and NSAID concurrently, but is clearly present in both treatment groups. The occurrence of these events was markedly disproportional, favoring drug treatment over placebo treatment, which supports that these events of joint destruction are related to drug treatment, and are not occurring as part of the natural history of osteoarthritis. In fact, some cases occurred in patients without a history of OA, which further supports this conclusion. There is some evidence that the joint destruction seen in some cases may be a unique clinical form of rapidly destructive arthropathy.

20 February 2012

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Columbia University Medical Center (CUMC)

CUMC Adjudication Report on Adverse Events Related to Studies Involving Anti-NGF Antibodies

I.Introduction

Dr. Bathon was requested to provide an independent review of 492 cases of adverse events from participants of studies involving anti-nerve growth factor (NGF) antibodies. These adverse events consisted of either total joint replacement or other adverse joint outcome in the absence of joint replacement surgery (usually an abnormal finding on imaging). The cases were from studies in which participants received either placebo or one of three anti-NGF antibodies (tanezumab [Pfizer]; furlanumab [Janssen]; or REGN475 [Regeneron]). Most of the studies were performed in participants with pre-existing osteoarthritis (OA) of the knee(s) and/or hip(s). In these studies larger than anticipated numbers of osteonecrosis and total joint replacements, reported as serious adverse events (SAEs) to the FDA, were reported either during or shortly after the studies. 'Osteonecrosis' or 'possible osteonecrosis' was frequently cited on local imaging reports, pathology reports or post-operative surgical reports. This raised concern for a drug related effect and led to a halt in the anti-NGF clinical trials.

The question that was asked by the FDA is whether the articular adverse event would be expected or not (given that most of the study participants had pre-existing OA) and, if not, whether these events were likely related to study drug or not.

II.General Comments - Limitations of the DATA

The timeline for review and adjudication of the cases was very short. Lengthy administrative procedures precluded the ability of the FDA to provide the original radiographs and MRIs in time to meet the adjudication deadline. Instead, limited radiographic images were provided as prints from copies of the original digital images. Similarly, limited pathology images were provided as prints from photos of the original slides. Reports of MRI results were provided but no original images. In summary, the available data were as follows:

1. Clinical data and narrative provided to the FDA relevant to each adverse event. This included medical history but not primary study (efficacy) data.
2. Printed copies of joint images but no original images.
3. Printed copies of pathology images but no original images.
4. MRI reports but no original images.

Images. Due to the poor quality and limited scope of the available imaging and pathology data, and availability only of the local MRI report without accompanying images, the adjudication process was, of necessity, very conservative. The printed copies of the images were routinely too poor to be able to confidently rule in or out subtle classic features of osteonecrosis (such as 'crescent sign' on radiographs and 'double-line sign' on MRIs). Furthermore, most of the patients had pre-existing (frequently severe) OA which, coupled with poor quality images, made disentanglement of joint deterioration due to collapse of OA-related subchondral cysts versus other process virtually impossible. Therefore, radiographs were examined primarily to determine whether severe bone loss or joint deformity (i.e., collapse, fragmentation, marked subluxation) was present and, if pre-study films were available, whether these marked changes had occurred since the pre-study time point.

Local reports of MRIs were reviewed but did not weigh heavily into the adjudication process since many of these reports that cited 'osteonecrosis' enumerated features that could also represent severe OA.

Pathology data. Pathology data were present in only a minority of cases. There was no information as how the tissue sections were sampled. It was unclear if they had been sampled from the area of greatest involvement of the OA or not, or from the area of suspected infarct or not (since the two, if present, need not be contiguous). Furthermore, only one or two printed photos were usually provided per case and magnification varied from case to case. Therefore, when osteonecrosis was seen on the images, there was confidence that this was a real finding. When osteonecrosis was not seen, there was no confidence that osteonecrosis could be definitively ruled out.

Blinded Review and Adjudication. The case review and adjudication processes were both performed in a blinded fashion, with no knowledge of the drug assignment. Drug assignment/randomization data were provided by the FDA only after the adjudication process was complete. At this point, adjudication results were compared to the sponsor's adjudication.

III.Study Population

492 cases were received from the FDA. Of these, 188 had no radiographs or pathology and were not reviewed or adjudicated given the short timeline. The remaining 354 cases were reviewed. Of these, additional cases were found to have either no radiographs or had radiographs that were of such poor quality that no adjudication could be reliably performed. The remaining cases progressed to the adjudication process. The final numbers are given in the Tables below.

IV.Case Review

Clinical: The narrative for each case was reviewed by one of two rheumatology post-doctoral fellows and relevant data were collected systematically in tabular form. These data included demographics, baseline medications, risk factors for osteonecrosis, baseline and end-of-study WOMAC scores, duration on blinded study drug, number of doses of blinded study drug, etc.

Pathology: Printed copies of images from pathology slides were reviewed by the pathologist without clinical information and scored as follows:

0 neither OA nor non-OA process
1 suspicious for non-OA process
2 suspicious for OA
3 overlapping features (OA + non-OA)
4 indeterminate

Imaging: Printed copies of joint radiographs (and local MRI reports) were reviewed by the radiologist without clinical information and scored. Two assessments were made :

1) *State of the joint pre-surgically*. Images from date after entry into the study and closest in proximity to surgery were scored for:
    - K-L score: 1, 2, 3, 4 and 0 (no OA) and 5 (indeterminate)
    - Images were reviewed for high suspicion, low or no suspicion, or indeterminate suspicion of 'non-OA process' as reflected by presence or absence of severe bone loss or other severe joint deformity– i.e., subchondral defects, deformity, collapse, impaction, fragmentation, bone resorption and severe subluxation. These are referred to as 'non-OA' features because they raise suspicion for possible osteonecrosis (ON) or Charcot-like joint (but recognizing that collapse of OA related subchondral cysts could give same appearance).

    Final categorization of joint images was as follows:

    1 OA only
    2 Both OA + non-OA process*
    3 Non-OA process only
    4 OA + indeterminate non-OA process**
    5 No OA + indeterminate non-OA process
    6 Indeterminate OA + non-OA process
    7 Indeterminate OA + indeterminate non-OA process
    8 Neither

    high suspicion for non-OA process'
    ****low suspicion for 'non-OA process'***

2) *Change in the joint.* Pre-study films were compared with pre-surgical films and scored for:

    1. marked deterioration of joint from pre-study to pre-surgical images
    2. no marked deterioration
    3. indeterminate deterioration (no pre-study film, or uninterpretable poor quality films)

V.Adjudication Process

Clinical information, imaging and pathology data in total were reviewed and adjudication was performed using the same categories as above *for state of the joint pre-study* and for *change in the joint.* Note that a category of rapidly progressive OA (RPOA) was not formally created since the poor film quality precluded accurate

measurement of joint space width; moreover, none of these studies obtained joint radiographs in a systematic manner that would allow such measurements even if the films were of otherwise good quality. However, the decision was made in advance to note cases suggestive of RPOA as those in which a subjective observation of dramatic loss of joint space width was made without confounding collapse/fragmentation of bony structures.

VI. CUMC Adjudication: Results

State of Joint at Pre-surgical Time Point. Data from 353 individuals (and 420 joints) were available for review.

Table I. Outcome		
	Joint #1 (n=353)	Joint # 2 (n=67)
No evidence of non-OA process, n (%)	128 (36.3)	24 (35.8)
High suspicion for non-OA process, n (%)	76 (21.5)	12 (17.9)
Low suspicion for non-OA process, n (%)	78 (22.1)	15 (22.4)
Indeterminate, n (%)	71 (20.1)	16 (23.9)

There were 288 individuals with at least one evaluable joint for whom determination of a non-OA process could be made (in some participants with more than one involved joint, one joint was evaluable and the other was not). Among these, 80 (28%) had high suspicion for non-OA process in at least one joint. There were 72 with high suspicion in one joint, and 8 with high suspicion in two joints. Treatment allocation was known in 285 of these 288 participants:

Table II. Treatment Allocation			
	Placebo (n=40)	Anti-NGF (n=245)	p
No high suspicion for non-OA, n (%)	34 (85.0)	172 (70.2)	0.053*
Any high suspicion for non-OA, n (%)	6 (15.0)	73 (29.8)	
* Fisher's exact test			

Data are presented below according to specific anti-NGF agent:

Table III. Specific Drug Allocation							
	Placebo (n=40)	Tanezumab (n=177)	p	Fulranumab (n=64)	p	REGN475 (n=4)	p
No high suspicion	34 (85.0)	118 (66.7)	0.022*	51 (79.7)	0.61*	3 (75.0)	0.51*
Any high suspicion	6 (15.0)	59 (33.3)		13 (20.3)		1 (25.0)	
* Fisher's exact test compared to placebo							

Data are presented below according to concomitant NSAIDs (as part of study design):

Table IV. Treatment Allocation with and without concomitant NSAIDs						
	Placebo +/- NSAIDs (n=40)	Anti-NGF without NSAIDs (n=190)	p*	Anti-NGF with NSAIDs (n=55)	p**	p***
No high suspicion	34 (85.0)	142 (74.7)	0.22	30 (54.6)	0.002	0.007
Any high suspicion	6 (15.0)	48 (25.3)		25 (45.5)		

* comparison of placebo vs. anti-NGF without NSAIDs ** comparison of placebo vs. anti-NGF with NSAIDs * ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs all comparisons using Fisher's exact test

Same as Table IV except Tanazemab only (Fulranumab didn't randomize with NSAIDs)

Table V. Treatment (Tanezumab only) Allocation with and without concomitant NSAIDs						
	Placebo +/- NSAIDs (n=40)	Tanezumab without NSAIDs (n=123)	p*	Tanezumab with NSAIDs (n=55)	p**	p***
No high suspicion	34 (85.0)	89 (72.4)	0.14	30 (54.6)	0.002	0.024
Any high suspicion	6 (15.0)	34 (27.5)		25 (45.5)		
* comparison of placebo vs. tanezumab without NSAIDs ** comparison of placebo vs. tanezumab with NSAIDs * ** comparison of tanezumab without NSAIDs vs. tanezumab with NSAIDs all comparisons using Fisher's exact test						

Change in Joints. There were n=167 individuals with at least one joint in which longitudinal assessment was possible. Among these, CUMC adjudication rated 54 (32.3%) as marked deterioration of the joint. Among the 167, 164 had known treatment allocation.

Table VI. Treatment Allocation in Joints with and without Marked Deterioration			
	Placebo (n=24)	Anti-NGF (n=140)	p
No marked deterioration, n (%)	21 (87.5)	90 (64.3)	0.032*
Marked deterioration, n (%)	3 (12.5)	50 (35.7)	
* Fisher's exact test			

Below are same data but further broken down by with and without NSAIDs.

Table VII. Treatment Allocation with and without NSAIDs in Joints with and without Marked Deterioration						
	Placebo +/- NSAIDs (n=24)	Anti-NGF without NSAIDs (n=100)	p*	Anti-NGF with NSAIDs (n=40)	p**	p***
No marked deterioration, n (%)	21 (87.5)	66 (66)	0.047	24 (60)	0.025	0.56
Marked deterioration, n (%)	3 (12.5)	34 (34)		16 (40)		
* comparison of placebo vs. anti-NGF without NSAIDs ** comparison of placebo vs. anti-NGF with NSAIDs * ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs all comparisons using Fisher's exact test						

Summary: In these descriptive analyses, a borderline significant (p=0.053) association was observed between anti-NGF treatment and presence of a highly suspicious 'non-OA' process at the pre-surgical time point. When analyzed by specific anti-NGF agent, a significant association of a highly suspicion non-OA process with tanezumab use was observed, but not with the other two agents (though numbers were smaller for the latter

two). The combination of anti-NGF agent with NSAIDs was significantly associated with presence of a highly suspicious non-OA process when compared to placebo +/- NSAIDs, and when compared to anti-NGF agent without NSAID. These statistically significant associations held true when the analyses were restricted to the tanezumab studies only.

Marked deterioration of the joint between pre-study and pre-surgical timepoints (analyzed only in participants with interpretable data from both time points) was significantly associated with anti-NGF therapy. However, incidence of marked deterioration was not significantly higher in the combination group (anti-NGF therapy with NSAIDs) compared to anti-NGF therapy alone.

VII.Sponsor's Adjudication:

Below are our descriptive analyses/summaries of the Sponsor's adjudication data. Pfizer and J&J used a similar categorization for outcomes, focusing on osteonecrosis vs rapidly progressive OA vs normal progression of OA. As noted above, the term 'progression' was used without distinction as to whether one, or more than one, time point was examined. RPOA and primary ON were considered the adverse outcomes for these analyses.

Data on 352 participants (405 joints) were available.

Table VIII. Outcome		
	First joint (n=352)	Second joint (n=53)
No adjudication, n (%)	15 (4.3)	3 (5.7)
Primary ON, n (%) [1]	1 (0.3)	1 (2.0)
RPOA, n (%) [2a]	81 (23.0)	9 (17.0)
OA: normal progression, n (%) [2b]	182 (51.7)	30 (56.6)
OA: can't determine progression, n (%) [2c]	12 (3.4)	1 (2.0)
Other, n (%) [3]	28 (8.0)	4 (7.6)
Insufficient information, n (%)	11 (3.1)	3 (5.7)
N/A, n (%)	16 (4.6)	2 (3.8)
No consensus, n (%)	6 (1.7)	0 (0)

Based on this, there were n=305 individuals with fully adjudicated joints (i.e. falling into groups 1, 2a-c, and 3). Among these 305, 217 (71%) did not have ON or RPOA in any joint; 84 (28%) had one joint with ON or RPOA; and 4 (1.3%) had two joints with ON or RPOA. Among these, drug allocation status was known in n=304.

Outcomes according to treatment allocation are shown below.

Table IX. Treatment Allocation			
	Placebo (n=47)	Anti-NGF (n=257)	p
No ON or RPOA, n (%)	43 (91.5)	174 (67.7)	0.001*
Any ON or RPOA, n (%)	4 (8.5)	83 (32.3)	
* Fisher's exact test			

Outcomes according to specific anti-NGF agent are shown below. [Only sponsor adjudicated cases are included here—thus, the Regeneron drug does not contribute to these analyses.]

Table X. Specific Drug Allocation					
	Placebo (n=47)	Tanezumab (n=188)	p	Fulranumab (n=69)	p
No ON or RPOA, n (%)	43 (91.5)	122 (64.9)	<0.001*	52 (75.4)	0.029*
Any ON or RPOA, n (%)	4 (8.5)	66 (35.1)		17 (24.6)	
* Fisher's exact test					

Outcomes are shown below according to concomitant NSAIDs (as part of study design):

Table XI. Treatment Allocation with and without concomitant NSAIDs						
	Placebo +/- NSAIDs (n=47)	Anti-NGF without NSAIDs (n=197)	p*	Anti-NGF with NSAIDs (n=60)	p**	p***
No ON or RPOA, n (%)	43 (91.5)	139 (70.6)	0.003	35 (58.3)	<0.001	0.084
Any ON or RPOA, n (%)	4 (8.5)	58 (29.4)		25 (41.7)		
* comparison of placebo vs. anti-NGF without NSAIDs ** comparison of placebo vs. anti-NGF with NSAIDs * ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs all comparisons using Fisher's exact test						

Same as Table XI except with Tanazemab only

Table XII. Treatment (Tanezumab only) Allocation with and without concomitant NSAIDs						
	Placebo +/- NSAIDs (n=47)	Anti-NGF without NSAIDs (n=129)	p*	Anti-NGF with NSAIDs (n=60)	p**	p***
No ON or RPOA, n (%)	43 (91.5)	88 (68.2)	0.002	35 (58.3)	<0.001	0.16
Any ON or RPOA, n (%)	4 (8.5)	41 (31.8)		25 (41.7)		
* comparison of placebo vs. anti-NGF without NSAIDs ** comparison of placebo vs. anti-NGF with NSAIDs * ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs all comparisons using Fisher's exact test						

Summary: In these analyses, there was a statistically significant association between adverse outcome (primary ON or RPOA) in the anti-NGF group compared to placebo (p 0.001). This association persisted when each of the individual anti-NGF agents was analyzed separately in comparison to placebo. However, combination of anti-NGF therapy with NSAIDs, whether analyzed as a group or as tanezumab only, was not associated with a higher rate of adverse outcomes than anti-NGF therapy without NSAIDs.

VIII. Comparison of Adjudication Results from CUMC and Sponsors

Determination of agreement between the two adjudications was challenging because the Sponsors' adjudication teams had primary images while CUMC did not. In addition, the categories of outcomes were different, with sponsors' adjudication process focusing *on primary ON versus rapid progression of OA versus normal progression of OA*, while CUMC adjudication (due to poor image quality) focused more *on severe or catastrophic joint findings present pre-surgically and/or developing during study*. Furthermore, sponsors' adjudicators used the term 'progression' and 'rapid vs normal' even if a pre-study film was not available while CUMC reserved the word 'deterioration' for those cases in which both pre-study and pre-surgical (post study) films were available.

Given that poor image quality precluded CUMC from distinguishing severe articular findings suggestive of ON and/or Charcot like joints from OA-related collapse of subchondral cysts (or insufficiency fractures), it was *considered reasonable to consider CUMC's categories of high suspicion for non-OA process and Sponsor's categories of ON and rapidly progressive OA as potentially congruent.*

There were n=267 individuals for whom both adjudicators (CUMC and Sponsors') indicated that at least one joint could be fully evaluated for these outcomes. Rates of 'agreement' in these categories were as follows:

1. Sponsor adjudicated no ON or RPOA, and CUMC adjudicated no high suspicion for non-OA process: n=174 (65.2%)

2. Sponsor adjudicated ON or RPOA, but CUMC adjudicated low suspicion for non-OA process: n=18 (6.7%)

3. Sponsor adjudicated no ON or RPOA but CUMC adjudicated high suspicion for non-OA process: n=15 (5.6%)

4. Sponsor adjudicated ON or RPOA and CUMC adjudicated high suspicion for non-OA process: n=60 (22.5%)

Thus, there was concurrence for n=234 (87.6%) and non-concurrence for n=33 (12.4%).

Of the 234 participants for whom there was **concordant** adjudication, 233 had treatment assignment information available. Re-analysis of the adverse outcome according to initial treatment allocation in **only those participants whose adjudication outcome was concordant** between CUMC and Sponsor is shown below.

Table XIII. Outcome by Treatment Assignment for those with Concordant Adjudications

	Placebo (n=36)	Anti-NGF (n=197)	p
No high suspicion for ON/RPOA/non-OA process, n (%) (Category 1 above)	32 (88.9)	142 (72.1)	0.037*
Any high suspicion for ON/RPOA/non-OA process, n (%) (Category 4 above)	4 (11.1)	55 (27.9)	
* Fisher's exact test			

Below are outcomes by Drug Allocation with and without NSAIDs in participants with concordant adjudication.

Table XIV. Outcome by Treatment Outcome with and without NSAIDs for those with Concordant Adjudication

	Placebo +/- NSAIDs (n=36)	Anti-NGF without NSAIDs (n=151)	p*	Anti-NGF with NSAIDs (n=46)	p**	p***
No high suspicion	32 (88.9)	115 (76.2)	0.12	27 (58.7)	0.003	0.025
Any high suspicion	4 (11.1)	36 (23.8)		19 (41.3)		
* comparison of placebo vs. anti-NGF without NSAIDs						

** comparison of placebo vs. anti-NGF with NSAIDs
* ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs
all comparisons using Fisher's exact test

Below are same data as Table XIV except in the Tanezumab only group.

Table XV. Outcome by Treatment Outcome (Tanezumab only) with and without NSAIDs for those with Concordant Adjudication

	Placebo +/- NSAIDs (n=36)	Anti-NGF without NSAIDs (n=100)	p*	Anti-NGF with NSAIDs (n=46)	p**	p***
No high suspicion	32 (88.9)	74 (74)	0.099	27 (58.7)	0.003	0.056
Any high suspicion	4 (11.1)	26 (26)		19 (41.3)		

* comparison of placebo vs. anti-NGF without NSAIDs
** comparison of placebo vs. anti-NGF with NSAIDs
* ** comparison of anti-NGF without NSAIDs vs. anti-NGF with NSAIDs
all comparisons using Fisher's exact test

Summary: There were high rates of agreement in the two adjudication processes in the following groups: 1) presence of ON/RPOA by Sponsor adjudication with high suspicion of non-OA process by CUMC adjudication; and 2) absence of ON/RPOA by Sponsor adjudication with absence of high suspicion of non-OA process by CUMC adjudication. When analyses were restricted to participants for whom there was concordance in adjudication, anti-NGF therapy was significantly associated with high suspicion for ON/RPOA/non-OA process compared to placebo treatment. The combination of anti-NGF therapy with NSAIDs, when analyzed as a group, was associated with a higher rate of adverse outcomes compared to anti-NGF therapy without NSAIDs and to placebo +/- NSAIDs. When the analysis was restricted to tanezumab, tanezumab with NSAIDs was associated with a higher rate of adverse outcomes compared to placebo +/- but was not statistically significantly increased compared to tanezumab without NSAIDs.

CUMC and Sponsor adjudication data could not be compared for Deterioration of Joints since the Sponsors' adjudication committees did not separately adjudicate 'state'of joint from 'change in joint'.

Division of Orthopedic Device Evaluation

Food and Drug Administration
Office of Device Evaluation
Center for Devices and Radiological Health
WO66 New Hampshire Avenue
Silver Spring, MD 20993-0002

Date: 2/27/12
To: Division of Anesthesia, Analgesia, and Addiction Products

From: Nona T. Colburn, M.D., Medical Officer
Subject: Medical Officer Adjudication Review of TJR and ON Occurring with Anti-NGF exposure
Sponsors: Regeneron, Janssen, and Pfizer

I. Executive Summary

This memo summarizes the result of an adjudication review of 355 cases of total joint replacements (TJR) and osteonecrosis (ON) occurring in patients exposed to either placebo or one of three therapeutic recombinant anti-nerve growth factors (anti-NGF) (tanezumab [Pfizer]; furlanumab [Janssen]; or REGN475 [Regeneron]). With some cases involving multiple joints, there were a total of 401 joints adjudicated as follows: Pfizer (284), Janssen (105), and Regeneron (12).

Each of the sponsor's studies involved multi-center, prospective, randomized, concurrently controlled trials of anti-NGF in the medical treatment of patients with KL-graded osteoarthritis of the hip and/or knee, and one study of patients with chronic low back pain. From the original datasets, I have reviewed digital imaging, imaging reports, digital pathology, pathology reports, medical history narratives (operative reports, consultation reports, history and physicals), MedWatch reports, and Case Report Forms in a blinded manner. In addition, after completing my blinded reviews, I considered the sponsors'own adjudication results.

Joints were assigned one of the following five adjudication categories: Osteonecrosis (ON), Rapid Progression of Osteoarthritis (RPOA), Normal Progression of Osteoarthritis (NPOA), Other (with diagnosis specified), and Insufficient Information. Those cases, where information was insufficient to assign an adjudication category, were designated Not Adjudicated (NA). An outline of the classification methods used to determine each diagnosis is provided in Section V. Specifically, I considered characteristic MRI and pathologic descriptions to be diagnostic for ON. RPOA was considered if there was abnormal bony destruction or significant loss of joint space (dramatic change in KL grade) from baseline imaging and/or report compared to those post-exposure. If no baseline and/or post study imaging and/or report were available, this was classified as Insufficient Information.

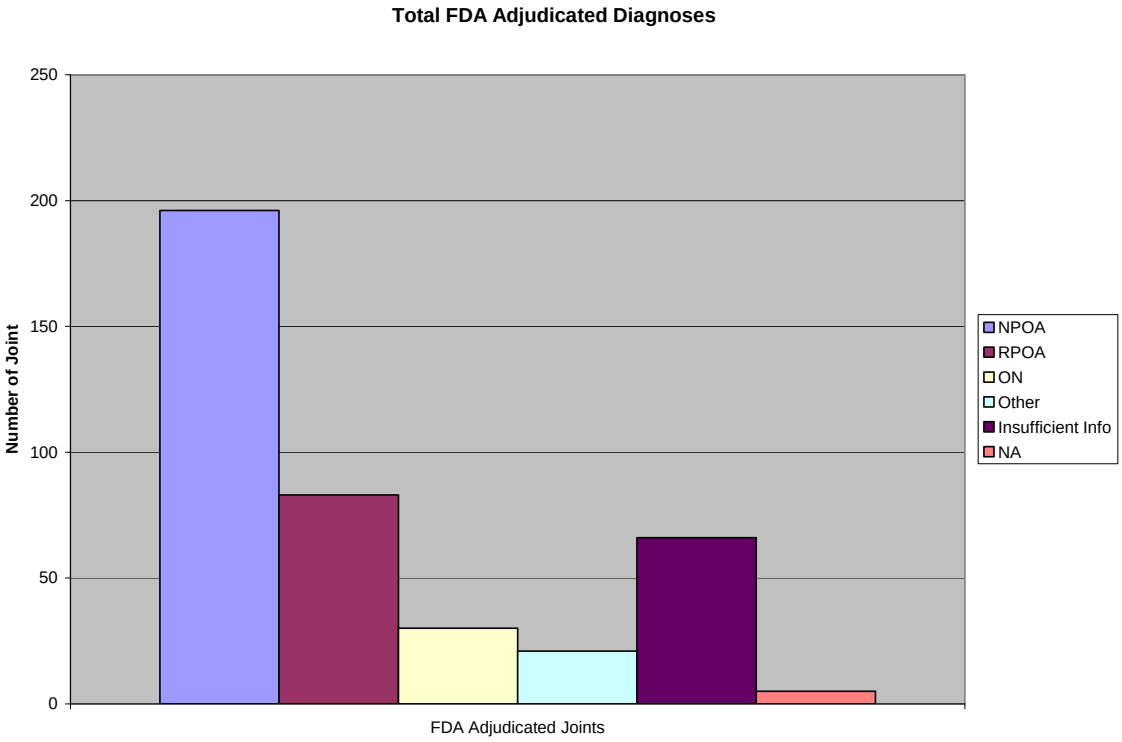
In my review, a total of 401 joints were adjudicated into each diagnosis as follows:

Table 1 Overall Adjudication Results

NPOA	RPOA	ON	Other Dx	Insufficient Info	NA
196	83	30	21	66	5

As depicted in the graph below, the majority of joints were assigned a diagnosis of NPOA, with a significant number of RPOA and ON cases (28%).

Figure 1



The overall extent of agreement with the sponsors' adjudication was determined by comparing the FDA adjudicated diagnosis to the sponsors' adjudicated diagnosis and assigning a binomial determination. A breakdown of the level of agreement is as follows:

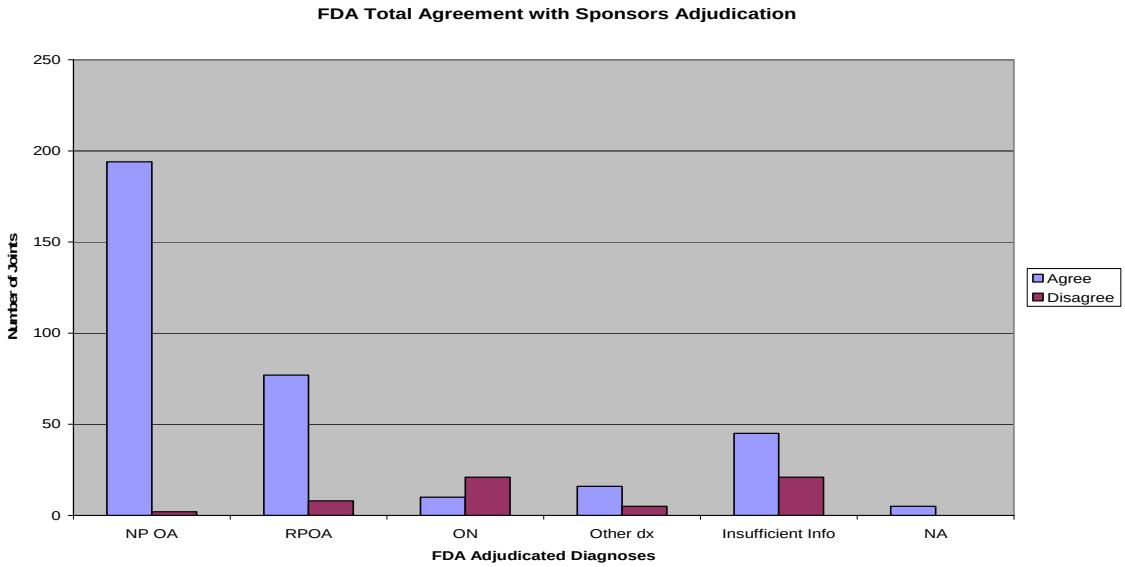
Table 2 Extent of FDA/Sponsor Adjudication Agreement

	NP OA	RPOA	ON	Other dx	Insufficient Info	NA
Agree	194	77	10	16	45	5
Disagree	2	8	21	5	21	0

Overall there was considerable agreement between the FDA and sponsor adjudications. As noted in the chart below, two major areas where there were differences in the adjudication results were cases of ON and Insufficient Information. The major reasons for these divergences were: 1) ON was diagnosed by FDA if there were clear

pathological and/or imaging criteria met; and 2) Insufficient Information was the adjudicated result if no baseline or post study imaging or imaging reports were available. Although each sponsor had specified methods of adjudication, their adjudication conclusions were more likely to differ in cases of ON and Insufficient Information. Pfizer was more likely to consider the diagnosis of RPOA and Spontaneous Osteonecrosis of the Knee (SPONK) over that of ON.

Figure 2

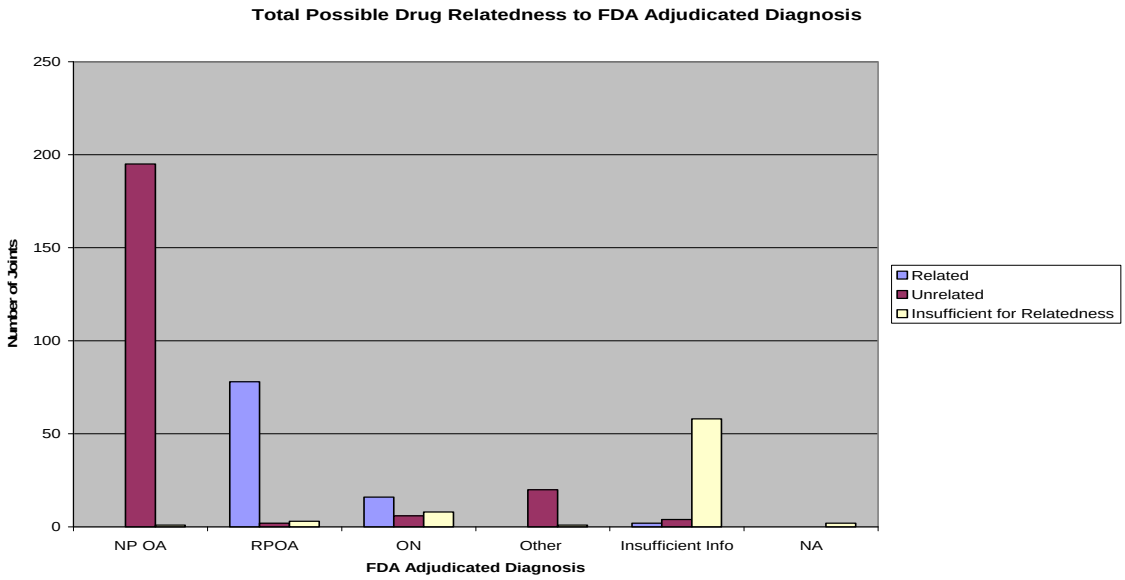


The possible relatedness of study drug to the adjudicated diagnosis was determined separately by considering all components of the clinical presentation. A breakdown of drug relatedness is depicted in the table and chart below. Relatedness to drug exposure was more likely in cases of RPOA and ON, and less likely in cases of NPOA.

Table 3 Relatedness of Study Drug to Joint Event

	NP OA	RPOA	ON	Other	Insufficient Info	NA
Related	0	78	16	0	2	0
Unrelated	195	2	6	20	4	0
Insufficient for Relatedness	1	3	8	1	58	2

Figure 3



Drug dosages, administration, and trial design differed among the three sponsors. However, as depicted in the graphs below, lower doses and/or less frequent administration of anti-NGF, as well as placebo, were more likely associated with NPOA. Higher doses and the addition of NSAIDs with higher doses were more likely associated with RPOA and ON.

Several cases adjudicated as RPOA demonstrated considerable and rapid destruction, most notably of the femoral head and medial femoral condyle. This appeared to be over and above the bony destruction described in previous literature. I consider the RPOA seen with drug exposure to anti-NGF to be a unique clinical form of rapidly destructive arthropathy.

Figure 4 FDA Adjudication of Cases by Treatment Assignment - Regeneron

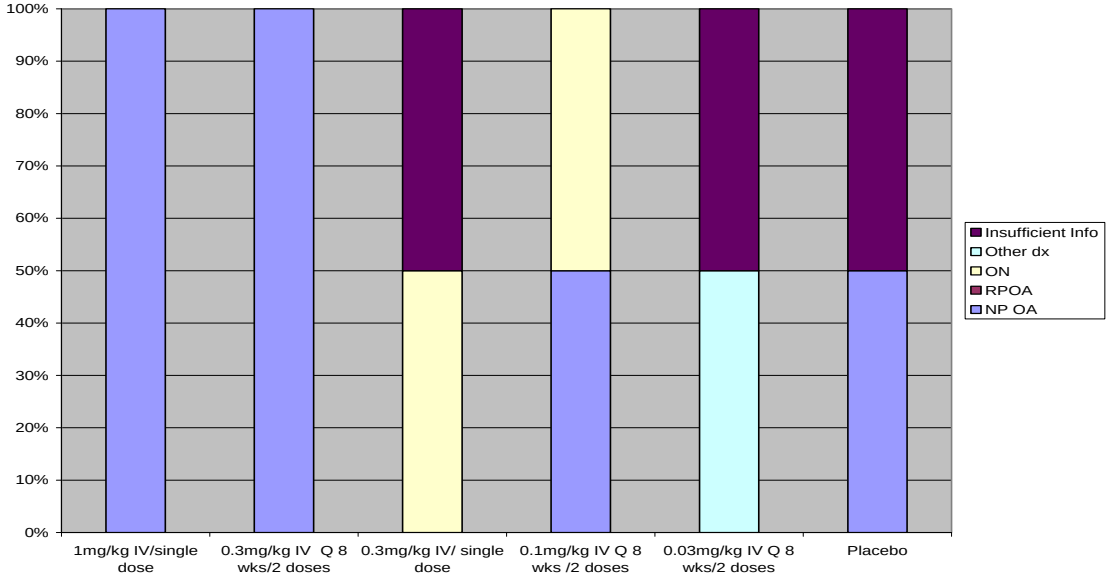


Table 4 FDA Adjudicated Cases - Regeneron

	NPOA	RPOA	ON	Other Dx	Insufficient Info
Treatment assignment (Total N=12) (100%)	6 (50%)	0 (0%)	2 (16.67%)	1 (18.33%)	3 (25%)
Placebo	1	0	0	0	1
1 mg/kg IV SD	1	0	0	0	0
0.3 mg/kg IV Q8w, 2 doses	3	0	0	0	0
0.3 mg/kg IV, SD	0	0	1	0	1
0.1 mg/kg IV Q8w, 2 doses	1	0	1	0	0
0.03 mg/kg IV Q8w, 2 doses	0	0	0	1	1

Figure 5 FDA Adjudication of Cases by Treatment Assignment -Janssen

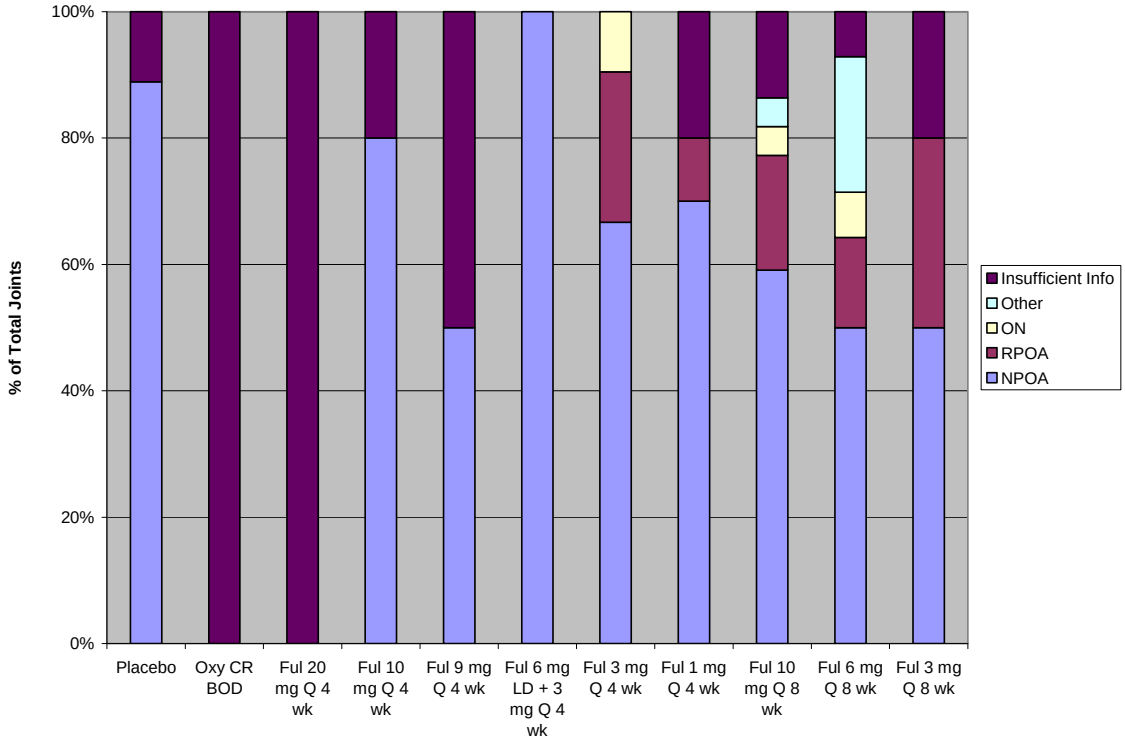


Table 5 FDA Adjudicated Cases – Janssen

	NPOA	RPOA	ON	Other Dx	Insufficient Info
Treatment assignment (Total N= 100) (100%)	62 (62%)	15 (15%)	4 (4%)	4 (4%)	15 (15%)
Placebo	8	0	0	0	1
Full 3 mg Q8W	5	3	0	0	2
Full 6 mg Q8W	7	2	1	3	1
Full 10 mg Q8W	13	4	1	1	3
Full 3 mg Q4W	14	5	2	0	0
Full 6 mg LD +3 mg Q4W	2	0	0	0	0
Full 9 mg Q4W	2	0	0	0	2
Full 10 mg Q4W	4	0	0	0	1
Full 20 mg Q4W	0	0	0	0	2
Oxycodone CR	0	0	0	0	1

Figure 6 FDA Adjudication of Cases by Treatment Assignment - Pfizer

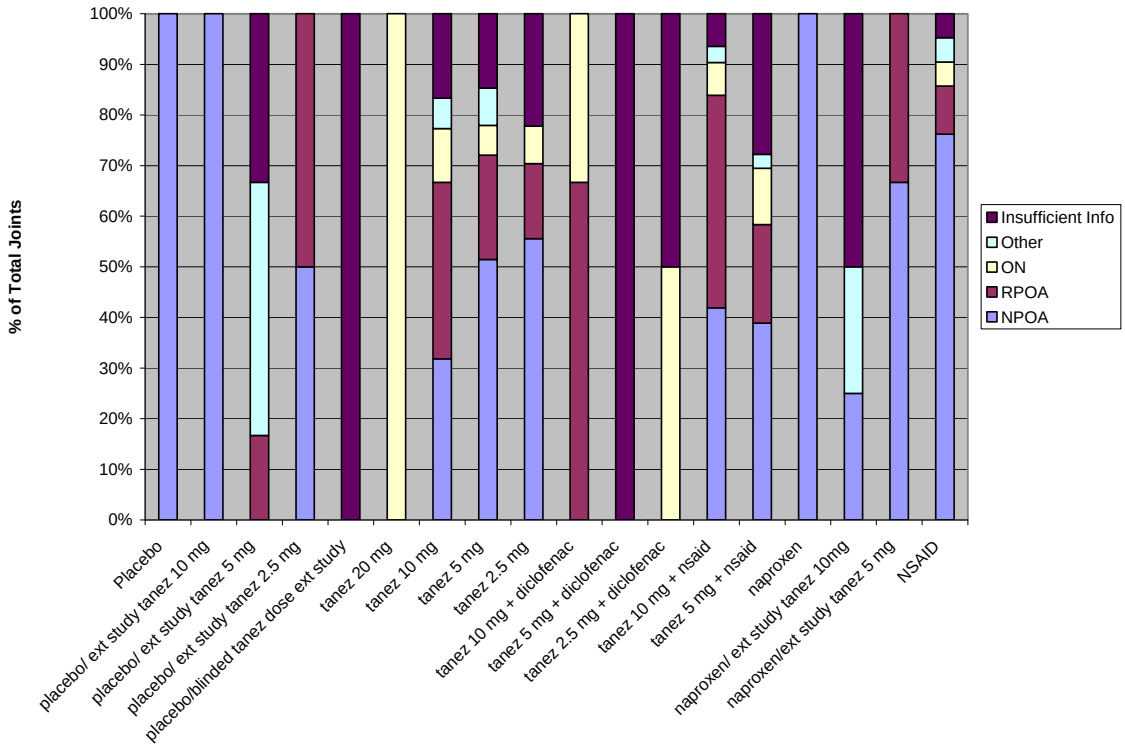
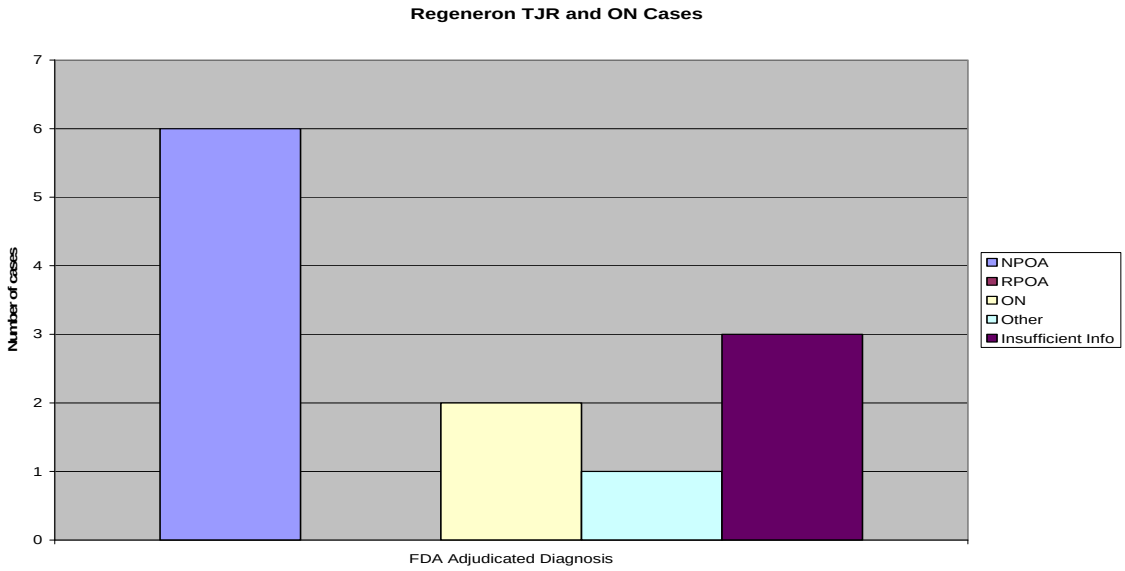


Table 6 FDA Adjudicated Cases –Pfizer

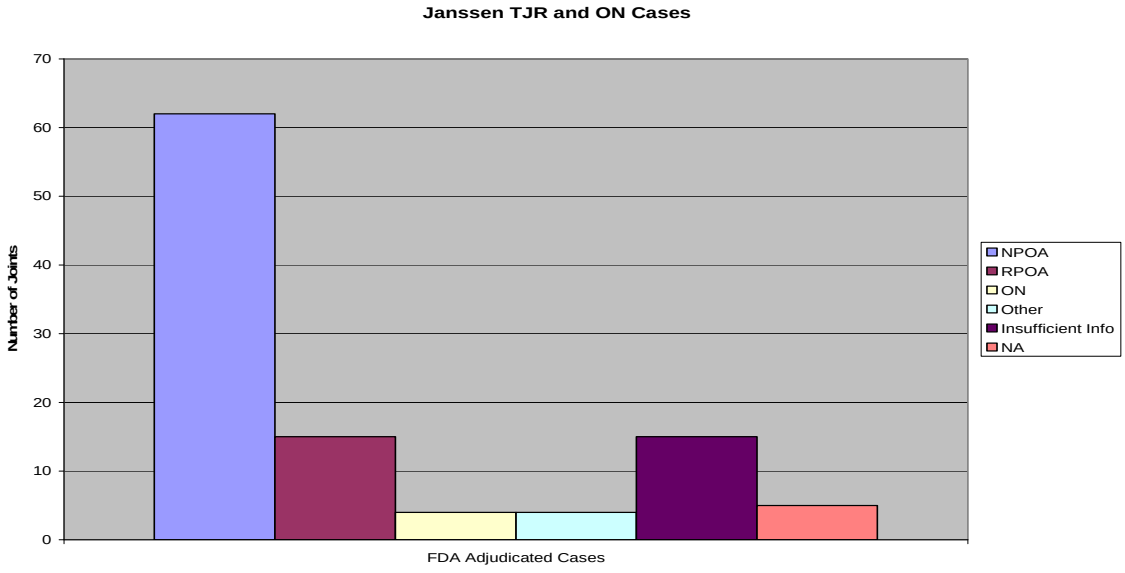
	NP OA	RPOA	ON	Other	Insufficient Info
Placebo	4	0	0	0	0
Placebo/ ext study Tanezumab 10 mg	5	0	0	0	0
Placebo/ ext study Tanezumab 5 mg	0	1	0	3	2
Placebo/ ext study Tanezumab 2.5 mg	1	1	0	0	0
Placebo/blinded Tanezumab dose ext study	0	0	0	0	1
Tanezumab 20 mg	0	0	2	0	0
Tanezumab 10 mg	21	23	7	4	11
Tanezumab 5 mg	35	14	4	5	10
Tanezumab 2.5 mg	15	4	2	0	6
Tanezumab 10 mg + Diclofenac	0	2	1	0	0
Tanezumab 5 mg + Diclofenac	0	0	0	0	2
Tanezumab 2.5 mg + Diclofenac	0	0	1	0	1
Tanezumab 10 mg + NSAID	13	13	2	1	2
Tanezumab 5 mg + NSAID	14	7	4	1	10
Naproxen	1	0	0	0	0
Naproxen/ ext study Tanezumab 10mg	1	0	0	1	2
Naproxen/ext study Tanezumab 5 mg	2	1	0	0	0
NSAID	16	2	1	1	1
Totals	128	68	24	16	48

II. Breakdown of FDA Adjudicated Diagnoses by Sponsor

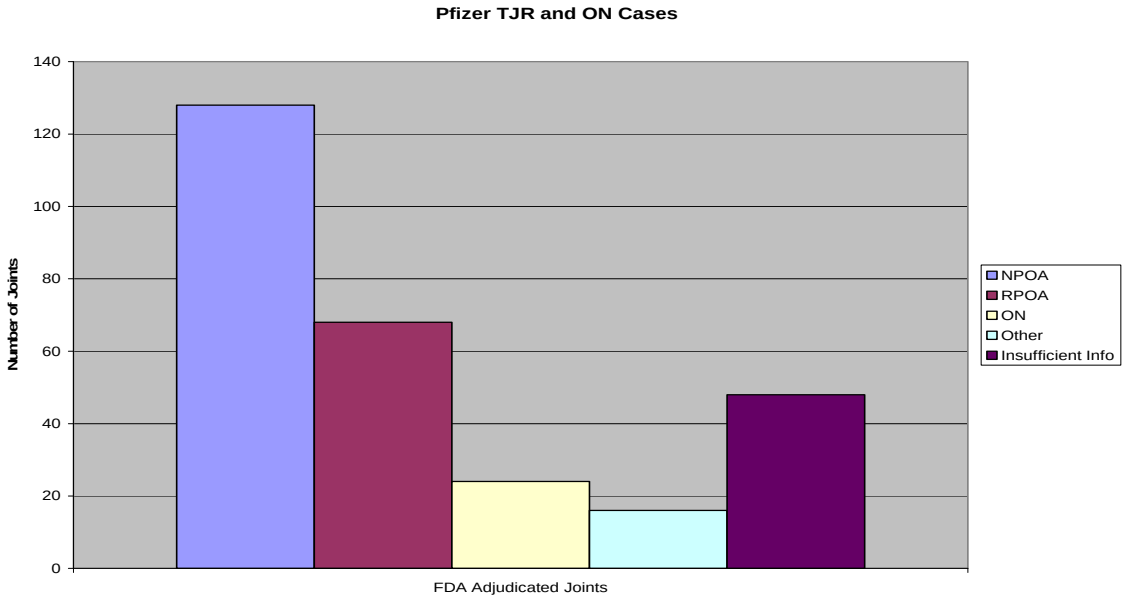
- **Regeneron**



- **Janssen**

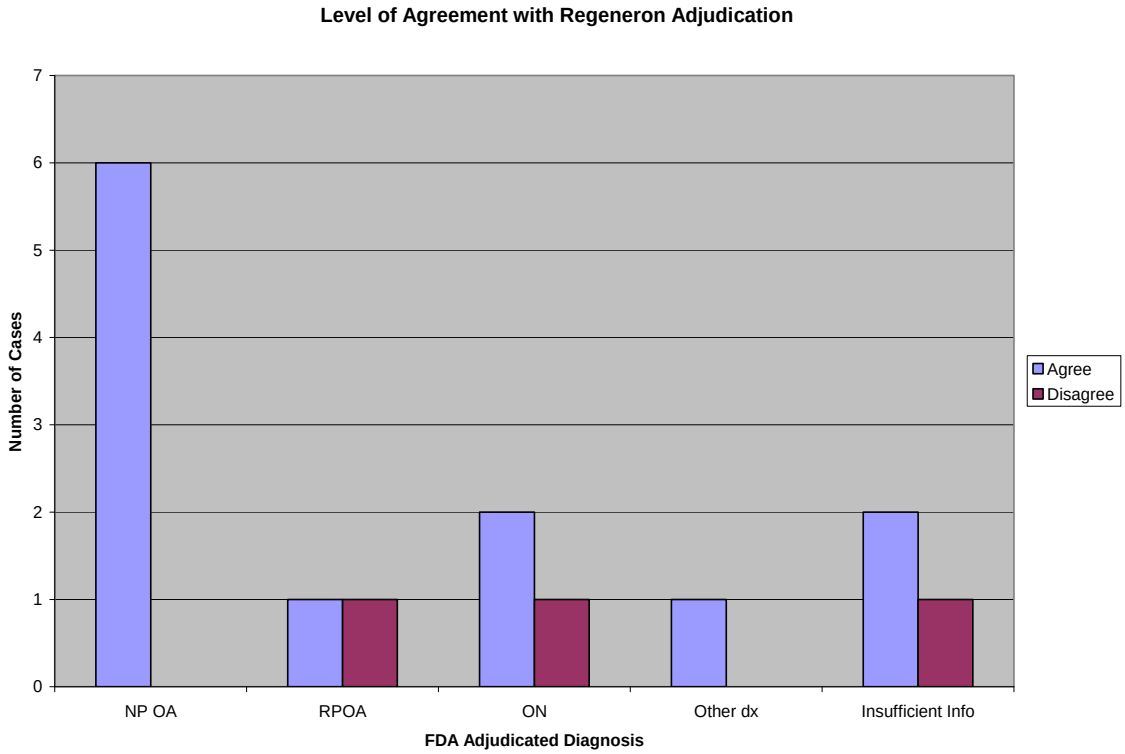


- **Pfizer**

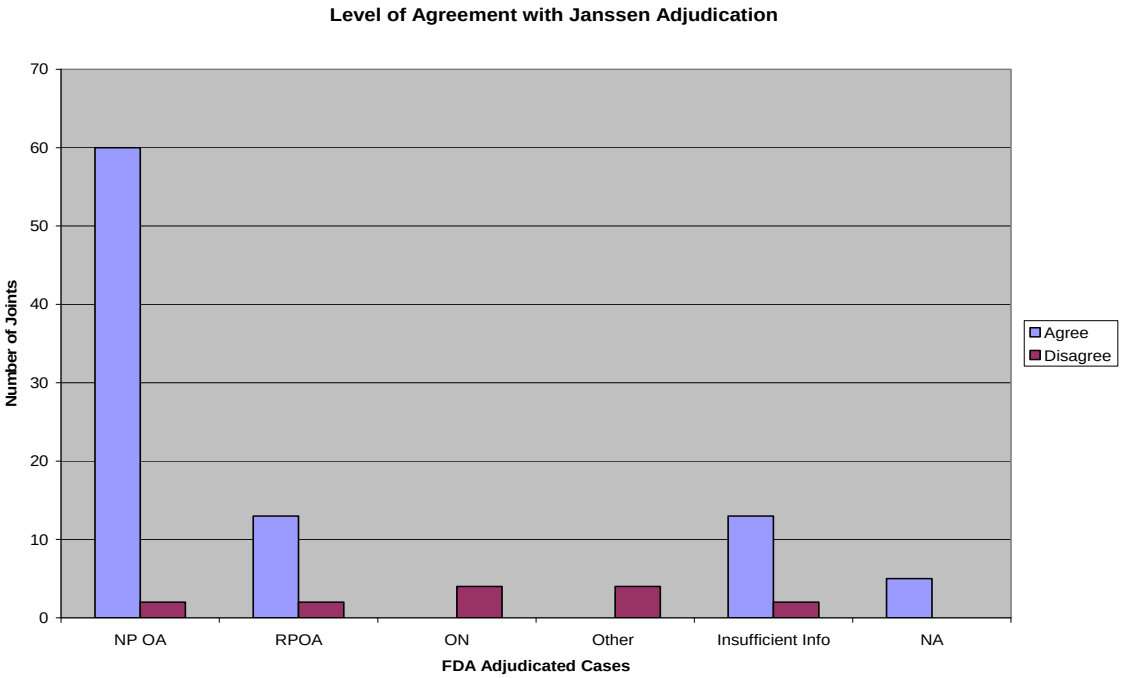


III. FDA Adjudicated Diagnosis Level of Agreement to Sponsor Adjudicated Diagnosis By Sponsor

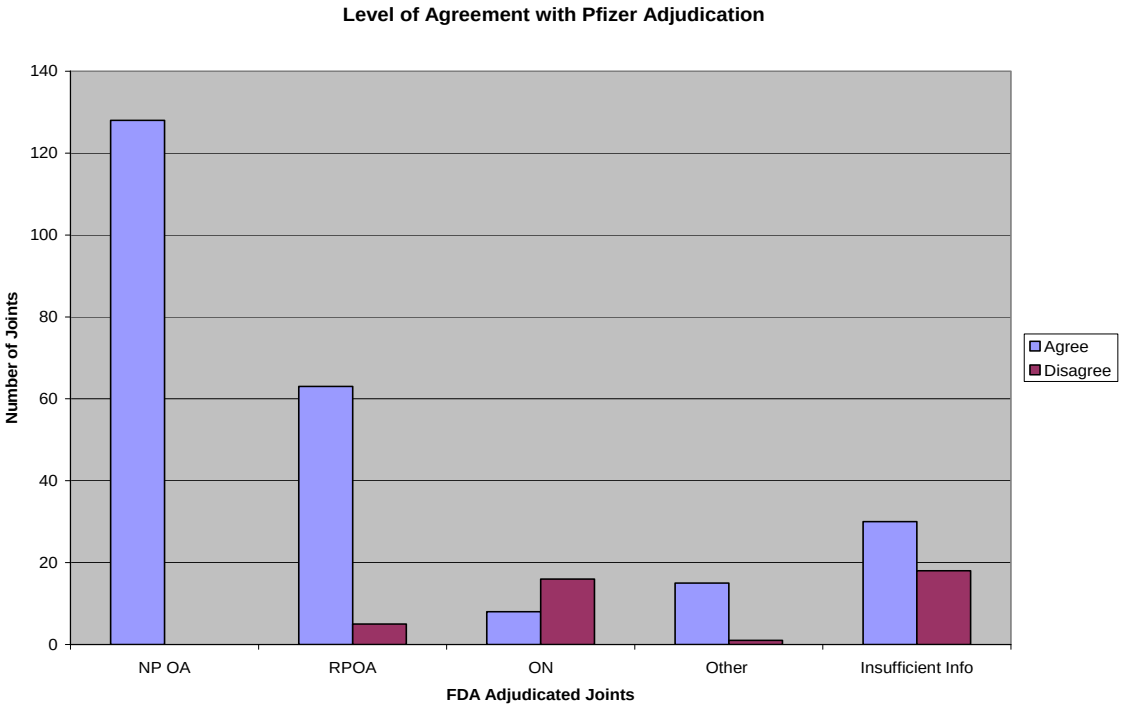
- **Regeneron**



Janssen

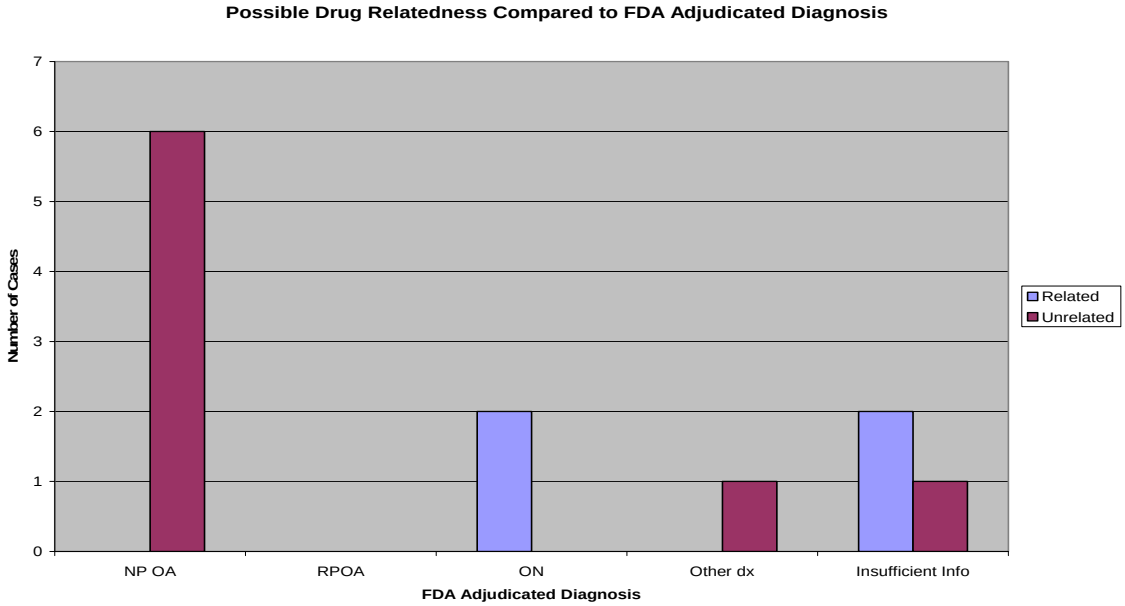


Pfizer

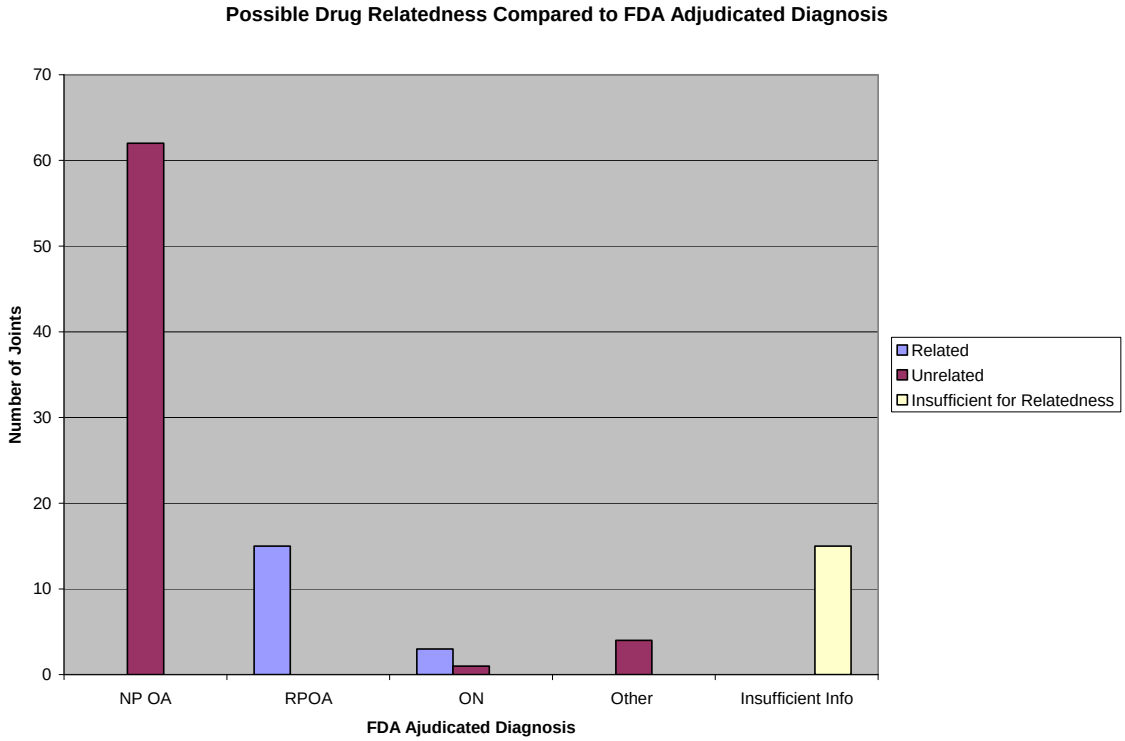


IV. Breakdown of Drug Relatedness by FDA Adjudicated Diagnosis By Sponsor

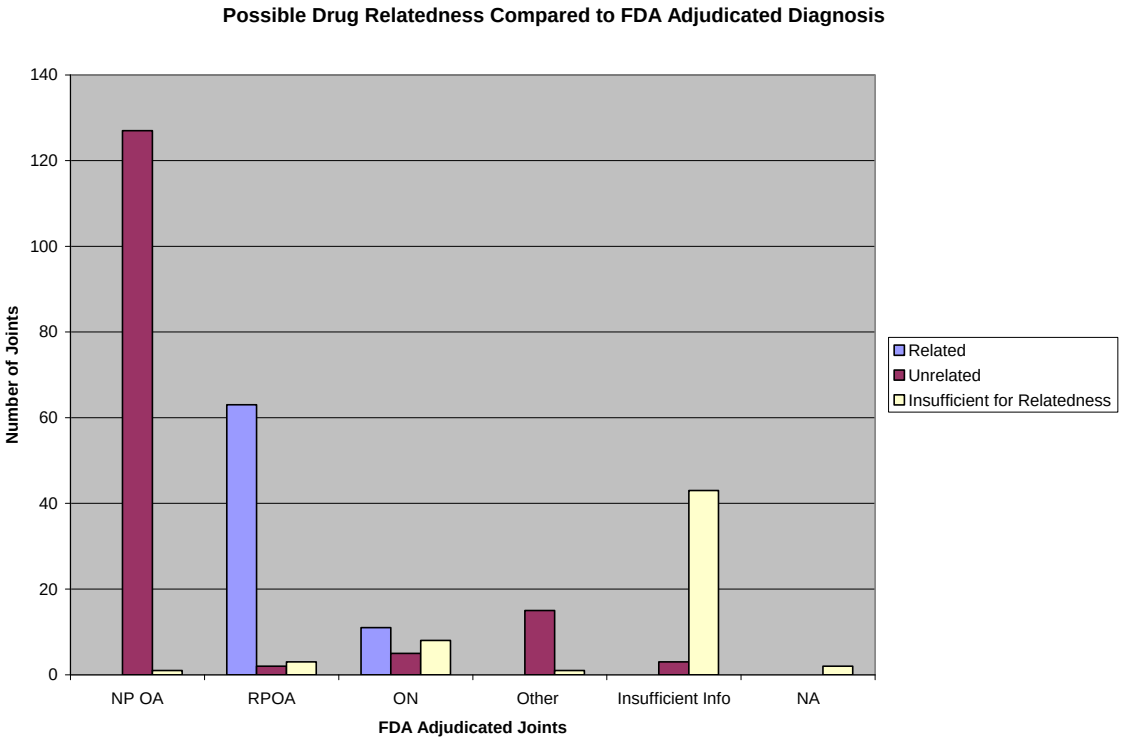
- **Regeneron**



- **Janssen**



- **Pfizer**



V. Adjudication Process and Methods Used for Event Classification

1. Objectives
    a. Diagnose cases of Osteonecrosis (ON), Rapidly Progressive Osteoarthritis (RPOA), Normal Progression of Osteoarthritis (NP of OA), and Other in patients who underwent joint replacement after exposure to either 1 of 3 different recombinant anti-nerve growth factors
        i. Fulranumab (J&J)
            1. 94 cases (105 joints)
        ii. Tanezumab (Pfizer)
            1. 249 cases (284 joints)
            2. Excludes 137 cases not adjudicated by the company
        iii. REGN475 (Regeneron)
            1. 12 cases
    b. Diagnosis based on imaging, clinical presentation, and pathology (if available)
2. Classification Methods used in Diagnoses
    a. Osteonecrosis
        i. Imaging
            1. X-Rays
                a. Cystic or sclerotic changes

b. Collapse or change in contour of the femoral head/condyles or tibial plateau
c. "Crescent Sign"
i. A pathognomonic radiolucent line
ii. Early collapse of cancellous bone beneath subchondral plate
iii. Represents the earliest irreversible lesion of ON
iv. Articular surface collapses and flattens
v. Further collapse almost inevitable once in this stage
d. No joint space narrowing

2. MRI
a. Well defined margins surrounding a focus of fat or fluid-like signal or low signal intensity +/- surrounding edema
b. Collapse or change in contour of the femoral head/condyles or tibial plateau
c. Bone marrow produces high-signal intensity in both T1 and T2
d. Subchondral bone appears as dark striations
e. **Line of decreased signal** on both T1 and T2 images
i. Demarcation between live regenerating bone and necrotic tissue
f. Characteristic **serpiginous pattern** with combined signals

3. Steinberg Staging of ON of the Femoral Head on Pre-operative X-ray (if available)

ii. Pathology
1. "Gold standard" of diagnosis
2. Histologically proven dead bone may stand alone to make the diagnosis

iii. Clinical History
1. Concomitant at risk comorbidities
2. Concomitant at risk medications

iv. Distinguish Primary versus Secondary ON

b. Rapid Progression of Osteoarthritis
i. Imaging
1. Diagnosis **requires** the availability of baseline comparison X-rays
2. Initial baseline X-ray
a. OA Kellgren and Lawrence score 0-3
3. Follow-up X-ray
a. Focal joint space narrowing

i. Greater than 2 mm/year rate of joint space narrowing
ii. Loss of more than 50% of the joint space within 1 year

b. Abnormal marked bony resorption and bone loss not commonly seen in normal OA
c. Flattening of the femoral head/condyles or tibial plateau
d. Small marginal osteophyte formation > laterally
e. Lack of a line of demarcation between necrotic and healthy bone

ii. Pathology (if available)
1. Consistent with clinical and X-ray finding
2. Small marginal osteophytes > laterally
3. Lack of inflammation
4. No ON should be present

iii. Clinical History
1. Temporal relationship
a. Time of occurrence compared to study entrance
2. Diagnosis of exclusion, rule out confounding diagnoses
a. Hematologic disorders
b. Steroid use
c. Neuropathic osteoarthropathy
d. Rheumatoid and seronegative arthritis
e. Septic arthritis
f. Primary osteonecrosis
g. Chondrocalcinosis

c. Normal Progression of Osteoarthritis
i. Imaging
1. Killigren and Lawrence scores pre- and post-event
ii. Clinical history

d. Other
i. Another diagnosis not definitely assessed as any of the 3 categories above
ii. Diagnosis consistent with any of the 3 categories above but unconfirmed
iii. Insufficient information to make a diagnosis

3. Source Information Reviewed
a. Imaging and Imaging Reports
b. Pathology and Pathology Reports
c. Narratives
i. PMH: Comorbidities
ii. PMH: Medications
d. Surgery Reports
e. Orthopedic Consult Reports
f. Med Watch Reports