

1 sites. However, the second patient had a three-level
2 laminectomy where one level had been implanted. This
3 table shows the number of levels that were
4 decompressed in each group in the pivotal trial.
5 Again, not all the patients had single-level
6 decompressions. We note that two patients with
7 single-level implantations had single-level
8 decompressions. Four patients had multiple levels
9 decompressed who had previous single-level
10 implantations, and five patients had multi-level
11 decompressions in two-level implantations. When we
12 look at the controls, 7 out of 24 patients had single-
13 level laminectomy, and 13 out of 24 had multiple level
14 laminectomies.

15 This trial included radiographic
16 evaluations as determined by AP and lateral x-ray.
17 I'd like to point out that no flexion or extension
18 radiographs were performed. The radiographic
19 measurements at each level were made only on the plain
20 AP and lateral views to determine this list of
21 measurements, which include interspinous process
22 distance, anterior and posterior disc height,

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1 angulation, foraminal height, and the percentage with
2 spondylolisthesis. These measurements were performed
3 before and after implantation.

4 I'd like to highlight some of the
5 radiographic results, specifically the distraction
6 levels. There were no significant differences between
7 the X STOP and the control groups in any of the mean
8 radiographic measurements made at either 12 or 24
9 months follow-up. Measuring the maintenance of
10 distraction in the X STOP patients was determined by
11 the distance between spinous processes. I'd like to
12 focus for a moment on the results of these
13 radiographic measurements. The information supplied
14 showed that of the 113 levels treated, a decrease
15 greater than four millimeters, which was considered
16 significant in this study, was measured at five levels
17 at baseline, as compared to -- was measured at 24
18 months as compared to six weeks. Fifty levels
19 remained radiographically the same as baseline. The
20 remainder showed some change, that is loss of
21 distraction of one millimeter or more, with 59 percent
22 of those patients showing a greater than two

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1 millimeter measurement of apparent loss of height from
2 baseline at six weeks.

3 Recalling the pre-clinical studies, the
4 radiographic studies performed, the absence of
5 flexion-extension radiographs, the instructions to
6 surgeons to flex the spine as a pre-insertion event,
7 our question to you is what is the best way to
8 interpret the radiographic measurements as they relate
9 to device effectiveness. As an example, these
10 radiographs were samples that were included in your
11 panel packs. One is an example of a patient who was
12 an overall success, and one is an example who was an
13 overall failure. It is not clear that the
14 radiographic measurements that were made were able to
15 predict which patients were a success or a failure,
16 except where obvious dislodgement was noted. This
17 will also be an issue that we'd like you to comment on
18 in your response to the panel questions.

19 I'd just like to say a brief comment about
20 the differences in successful outcomes that were
21 observed by sight. There is a significant difference
22 in outcome between the patients treated by

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1 investigators, as noted in this table. The
2 investigators in the first site were the most
3 experienced in the use of this device. The question
4 arises as to whether or not there is a learning curve
5 for the implantation technique, or there is an
6 improved ability to properly select patients who would
7 benefit from this device. As you can see, there's a
8 wide range of overall successful outcomes depending on
9 the site. The effect of this site to site difference
10 will be further discussed in the statistical review,
11 but again, this is something we'd like you to keep in
12 mind when making your recommendations related to this
13 device, particularly to labeling.

14 Next I'd like to briefly discuss the
15 sponsor's additional analysis, wherein the sponsor
16 provided comparison between the outcomes for the
17 successful X STOP patients and the patients who were
18 failures in both the X STOP and the control groups,
19 and then went on to have laminectomies. Thirty-six
20 patients treated with laminectomy had continued ZCQ
21 scores in follow-up evaluations based on their index
22 procedure or epidural injection. Symptom severity,

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1 physical function, and satisfaction data was collected
2 from the failures who had laminectomies up to a mean
3 of 1.2 years. Improvement was based on ZCQ scores
4 assessed just before and then after laminectomy, up to
5 24 months. It is difficult to draw any conclusions
6 from such a comparison, for the following reasons.
7 There was a pooling of patients with failed treatments
8 in different treatment cohorts, which included
9 patients who received different versions of the
10 device. In addition, there was pooling of patients
11 who were treated with primary laminectomy with those
12 who were treated with a secondary laminectomy. In
13 total, there was a comparison of successful outcomes
14 groups to failure groups. This comparison of
15 successes to failures we believe is not a valid
16 comparison. It is also important to note that the
17 patients who failed initial treatment may have been in
18 worse physical condition, and may have been more
19 likely to require a laminectomy, and this was not
20 considered in the comparison. It is difficult to
21 discern the clinically meaningful implication of this
22 comparison. The statistical presentation will expand

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1 further on this issue.

2 Finally, I'd like to point out the
3 indications for this device, and the population it
4 defines. The X STOP is indicated for patients aged 50
5 or older suffering from mild to moderate symptoms who
6 have undergone a regimen of non-operative treatment,
7 and who experience relief in flexion from symptoms of
8 leg, buttock, and groin pain, with and without back
9 pain. I'd like you to keep this in mind when
10 considering the panel questions we present later.

11 In summary, there are several points that
12 I have presented that the FDA would like you to
13 consider when answering the panel questions. The
14 points we'd like you to keep in mind include the
15 following: the appropriateness and adequacy of the
16 control group, whether the appropriate evaluations for
17 pain and function have been made to show the effect of
18 this device, whether the radiographic evaluations
19 assist in the determination of safety and
20 effectiveness, whether we know or can discern the
21 long-term biomechanical effect on the spine, whether
22 the device is effective and for how long, and whether

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1 we know in whom it should be used. Thank you for your
2 attention.

3 DR. YASZEMSKI: Thanks very much, Dr.
4 Buch. Mr. Kotz?

5 MR. KOTZ: I am Richard Kotz. I will be
6 presenting a statistical review of the clinical trial
7 for the X STOP. Briefly, my outline will include a
8 discussion of the study design, deviations from the
9 protocol, and patient accountability. Then I will
10 comment on the comparability of the treatment groups
11 at baseline, present an analysis of device
12 effectiveness based on the primary endpoint, and
13 critique the sponsor's comparison of their device to
14 laminectomy. In conclusion, I will comment on the
15 safety profile and then summarize my presentation.

16 The study was designed as a controlled
17 partially blinded randomized clinical trial. The
18 control group was conservative care and epidural
19 injections. Note that the patients in this group had
20 already failed conservative care, and about half of
21 them had had epidural injections prior to being
22 enrolled in this study. Note that only the evaluating

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1 physician was blinded. Patients, the treating
2 physician, and radiologists were not blinded. The
3 study was randomized with patients equally likely to
4 receive X STOP or the control. The randomization was
5 stratified by site, with a fixed block size of two. I
6 will elaborate upon this momentarily. Also, the
7 patients were randomized upon determination of study
8 eligibility.

9 The primary endpoint, as already
10 discussed, was a composite based on the ZCQ scores, x-
11 ray, and no complications or dislodgements. The ZCQ
12 scores are based on subjective measurements of symptom
13 severity, physical function, and satisfaction. It
14 should be noted that there is a potential for
15 significant bias when patients and investigators
16 aren't blinded to the randomization assignment, and
17 when the study endpoint is driven by patient
18 assessment. That is, the control patients know that
19 they're receiving a treatment that has not worked for
20 them in the past, while X STOP patients believe they
21 are receiving a treatment that may have great
22 potential to help them.

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1 The sponsor designed their study with the
2 randomization stratified by site and used a fixed
3 block size of two. This means that they randomly
4 selected the first patient at a site, and thus the
5 second patient would automatically receive the other
6 treatment. Therefore an investigator could predict
7 which treatment the second patient of each pair in a
8 block would receive. This could potentially lead to
9 investigator bias. In order to avoid this
10 possibility, it would be better to use a variable
11 block size design. That is, the block size at each
12 site would vary randomly. For example, the first
13 block might be randomly selected to be size six, and
14 the second block might be randomly selected to be size
15 two, a third could be four, or six, and so on. In
16 such a system, there is no predictable pattern, making
17 it difficult to subvert randomization.

18 Another issue of importance is the
19 problems associated with randomizing patients several
20 days to weeks before they will receive their
21 treatment, especially when the patients are unblinded.

22 When patients know their treatment assignment, they

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1 can drop out based on this assignment. In this trial,
2 eight subjects dropped out when they learned they were
3 randomized to the control treatment. Early assignment
4 also gives patients more time to drop out for any
5 number of reasons. The surgeries have to be scheduled
6 in advance. When possible, it is best to randomize
7 patients as close to time of treatment as possible.
8 Doing this should help to reduce the number of
9 patients dropping out of the study before the
10 treatment is given.

11 The study was designed as a comparison of
12 proportions, the alternate hypothesis being that the
13 success proportions were different for the X STOP and
14 control groups. Thus, the study was designed as a 2-
15 sided test. It had a significance level of 0.05 and a
16 power of 80 percent. The expected success percentages
17 were 60 percent for the X STOP and 37.5 percent for
18 the control, with an expected loss to follow-up rate
19 of 15 percent. This resulted in a needed sample size
20 of 100 subjects per study, and the study was conducted
21 across nine centers.

22 There were four X STOP and three control

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1 enrollment deviations. Four subjects had previous
2 disc surgery, and three others had stenosis at the
3 wrong level. In addition, eight X STOP patients had
4 post treatment deviations. Six X STOP patients who
5 received epidural injections for unresolved stenosis
6 were treated as study failures. There were an
7 additional two X STOP patients who received injections
8 for pain following car accidents. These two patients
9 were successes at two years and were treated as such
10 in the pivotal study.

11 Two hundred and twenty-nine patients were
12 enrolled in the study. Thirty-eight of these were not
13 treated under the study protocol for various reasons.

14 Fourteen of these were X STOP, and 24 were controls.

15 As already noted, eight subjects withdrew after they
16 were assigned to the control group, five withdrew for
17 health reasons, two because they didn't meet the
18 inclusion/exclusion criteria, six had scheduling
19 problems, and another 17 elected to forego treatment.

20 This included one X STOP and four controls who chose
21 to go directly to laminectomy instead of being treated
22 under the study protocol.

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1 Of the remaining 191 patients, 100
2 received the X STOP and 91 were in the control group.
3 Of these, 82 X STOP and 54 controls completed the 2-
4 year follow-up. Another seven died, and 30 went on to
5 laminectomy. Twenty-four of these laminectomy
6 patients were from the control group. An additional
7 eight patients had less than one year follow-up, and
8 another 10 had less than two year follow-up. It
9 should be noted that all these patients in the last
10 four categories are considered as failures at two
11 years, except for one X STOP patient who was a success
12 at Day 710, but failed to have a 2-year radiographic
13 exam. Note that this patient at one year was also a
14 success, and had a successful radiographic exam. It
15 should be noted that the results that I am presenting
16 are based on all 191 patients, and will be slightly
17 different from the results the sponsor presented which
18 were based on -- mine are based on all treated
19 patients. Theirs were based on evaluable patients,
20 and basically they excluded the eight patients with
21 less than 1-year follow-up from the presentation of
22 their results.

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1 There were no significant differences at
2 baseline between the X STOP and control groups with
3 respect to age, gender, weight, height, duration of
4 symptoms, occupational status, baseline radiographic
5 findings, current medications, and most medical
6 treatments. But there was a significant difference
7 with respect to previous epidural injections. Sixty-
8 three percent of the X STOP patients versus 44 percent
9 of the controls had previous injections. It should be
10 noted that this test was not adjusted for multiple
11 endpoints. I give a p-value of 0.01 up there. Also,
12 it appears that this difference is mostly accounted
13 for at one site, where 12 of 16 X STOP and only two of
14 15 controls had previous epidural injections.

15 The patients treated with X STOP had a
16 statistically significantly greater proportion of
17 successes at two years than those who received the
18 control treatment. That's the column with the As
19 Treated patients. In addition, I have presented the
20 results for an intent-to-treat analysis, or as
21 abbreviated on the slide, an ITT analysis, where the
22 24 controls and the 14 X STOP patients who were

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1 randomized but not treated are counted as failures.
2 It should be noted this is probably not an appropriate
3 analysis since there was a large imbalance between the
4 two groups with respect to patients dropping out
5 before being treated. In the next row, note that even
6 if we take the worst case scenario in which all 24
7 patients who were not treated are considered
8 successes, and all 14 untreated patients randomized to
9 the X STOP are considered failures, the p-value still
10 indicates a significant difference between the two
11 success proportions.

12 This graph shows the distribution of X
13 STOP success percentages across sites, ordered from
14 the site with the lowest percentage at 12 percent, to
15 that with the highest at 81 percent. In the
16 parentheses at the top of each bar I give the number
17 of subjects treated with the X STOP for that site. We
18 see from this graph that the last site appears to have
19 a percentage much greater than the others. In fact,
20 this site had a significantly greater proportion of X
21 STOP successes than the rest of the sites. The site
22 which treated the most patients had a success rate of

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1 81 percent, while the rest of the sites had success
2 rates ranging from 12 to 50 percent. When this site
3 was removed, there was no statistical difference among
4 the remaining sites with respect to the X STOP
5 proportion of successes. Note that without this site,
6 the overall success rate for the X STOP decreases from
7 43 percent to 33 percent. It has been noted that the
8 investigators at this site were the inventors of the
9 device, and presumably had a great deal of experience
10 with it.

11 The sponsor also presented a statistical
12 comparison of the percentage of successes of their X
13 STOP with laminectomy and claimed they were
14 comparable. But note that this was not a randomized
15 study. Furthermore, most of the laminectomy patients
16 were pivotal study failures who then went on to
17 laminectomy. Seven additional patients were failures
18 from the unwelded study, and seven others came from
19 untreated patients in the pivotal study who went
20 directly to laminectomy. Given the unrandomized
21 nature of this comparison, and the potentially
22 severely biased selection of the laminectomy patients,

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1 it would be very difficult to draw a statistically
2 meaningful comparison of these two groups.

3 Though the adverse event profile was
4 comparable for most areas of the body, the overall
5 difference with respect to musculoskeletal system was
6 statistically significant. In the second column,
7 under the Control, the 22 for patients with adverse
8 events should really be 16. I mistyped. But in
9 particular, there were notable differences among the
10 lower back, lower extremity, and hip.

11 In summary, the X STOP success percentages
12 was superior to that of the control, 43 percent versus
13 4.4 percent, but the percentages were less than that
14 expected, the expected percentages of 60 percent and
15 37.5 percent. We also discussed several potential
16 sources of bias in the study that could affect the
17 results. These included the use of a fixed block size
18 of two for randomization, a subjective primary
19 endpoint, lack of blinding of patients and
20 investigators, and the significant difference in the
21 success rates among one of the sites. Finally, the
22 musculoskeletal adverse events rates were greater in

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1 the X STOP group. And that concludes my presentation.

2 DR. YASZEMSKI: Thanks very much, Mr.
3 Kotz. Now if any of the panel members have questions
4 for any of the FDA presenters, we can do that now.
5 I'll remind you again, though, that we will have time
6 this afternoon to deliberate and ask questions of both
7 the sponsors and the FDA. If there are no questions,
8 I'd like to suggest that we take a break now for 10
9 minutes. Okay, I've got a request to make it 15.
10 We'll make it 15. It's now 10:25. We'll reconvene at
11 10:40 with the presentation from the panel lead
12 reviewers.

13 (Whereupon, the foregoing matter went off
14 the record at 10:25 a.m. and went back on the record
15 at 10:47 a.m.)

16 DR. YASZEMSKI: Please take your seats so
17 we can resume.

18 DR. KIRKPATRICK: I'm John Kirkpatrick.
19 I'm humbled to be asked to present a review from a
20 panel member's perspective of the clinical findings
21 that we've heard this morning as well as in the
22 packet. I would like to thank first of all the two

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1 patients that came forward and spoke to us earlier.
2 They demonstrated great courage and candor in their
3 comments, I was blessed by hearing their stories, and
4 I think their efforts on behalf of their other
5 patients or fellow patients needs to be recognized.
6 And that's appreciated very much.

7 I also would like to acknowledge that I
8 have many colleagues and friends on both sides of the
9 discussion today. The sponsor has done outstanding
10 work in assembling a great deal of data that we need
11 to analyze critically, and I'll try and give some
12 comments on how we might be able to proceed with that.

13 And finally I would like to make the observation that
14 this morning has seemed a little bit like a polite
15 version of CNN's Crossfire. So I hope we can all
16 smile and enjoy the whole day.

17 As we've heard, lumbar stenosis involves
18 the narrowing of the spinal canal. It can be
19 regional, which needs to be clarified, I think. There
20 can be a central canal stenosis, there can be lateral
21 recess stenosis or subarticular stenosis, and there
22 can be foraminal stenosis. The most common that I see

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1 as a surgeon is probably combinations of those three
2 areas.

3 Neurogenic claudication, the symptom that
4 we are hearing about being addressed today, involves
5 the pain into the legs, or one leg. It typically
6 results from a number of etiologies. On the basic
7 science level it's thought to be either from direct
8 compression, from the compression causing a root
9 ischemia, from the compression causing a venous
10 congestion, or from direct blocking of axoplasmic
11 flow. None of those has clearly been identified as
12 the predominant mechanism. They may work all in
13 combination. Unfortunately, we don't have specific
14 studies to tell us one predominates over the others.

15 The X STOP philosophy is basically a
16 device which takes advantage of the posture relief
17 that occurs in flexion of the spine in some patients
18 with spinal stenosis and resultant claudication.
19 Their indications we've heard about several times. I
20 won't belabor that, as well as the contraindications,
21 I won't belabor that.

22 The evaluation that they presented goes

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1 over some pre-clinical issues, and basically
2 demonstrates that it's structurally sound in its final
3 form, that it does effect a change in the space
4 available for the roots, demonstrated in the cadaver
5 model. The clinical study demonstrated some safety
6 issues, some degree of an anatomic change, and showed
7 some improved symptoms and function.

8 Their pre-clinical studies, again, I think
9 the mechanical testing was satisfactory to demonstrate
10 that the device will hold up over time. The insertion
11 and pull-out loads appear to be reasonable and provide
12 what appeared to me to be a reasonable safety factor
13 as an engineer. The kinematics is only affected at
14 the index level, did not appear at other levels,
15 although I do acknowledge that they did a one-level
16 study as opposed to two-level studies. I'm not
17 convinced that that would make a huge difference based
18 upon my own studies with fusion mechanics in actually
19 a T-12 to sacrum model. We did not find a two-level
20 fusion altered the kinematics at the open levels
21 significantly. So I'm not that concerned about the
22 fact that they don't have a two-level kinematic study.

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1 And they also mentioned that canal and
2 foramen dimensions were changed. It does raise some
3 questions that we'll hear about in a few minutes.
4 Basically, the dimensional changes did show that there
5 was a prevention of the amount of decrease of the
6 foraminal area. The subarticular diameter did not
7 decrease as much, and the canal area did not decrease
8 as much in extension with the X STOP. So it does
9 appear to prevent the natural canal narrowing that
10 occurs in extension. It appears to prevent the
11 natural decrease in the subarticular diameter in
12 extension, and it appears to prevent natural decrease
13 in the foraminal area in extension. All of these
14 being, obviously, in a cadaveric model. It's unclear
15 why some of the flexion dimensions seemed to decrease
16 as well after the implantation of the device, but
17 those changes were minor, and may have simply been
18 measurement differences.

19 The clinical results, as we've all heard.
20 They enrolled 229. They basically at the 24-month
21 data they had 92 in study and 81 controls. Their
22 primary measure was the Zurich Claudication

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1 Questionnaire. The symptom function and satisfaction
2 scales on that, additional surgery, maintenance of
3 distraction and device for construct failure. The
4 Zurich Claudication Questionnaire I'll let my
5 colleagues know is also known as the Swiss Spinal
6 Stenosis Questionnaire. In doing search engines, it
7 was easier to find it under the SSS than it was under
8 the ZCQ. It involves the seven symptom questions
9 we've heard about. And I would discuss also the fact
10 that what they describe as a significant difference in
11 the article that Stucki wrote, he describes it as a
12 minimum clinically important difference between
13 unsatisfied and somewhat unsatisfied patients. And
14 that is where the 0.5 comes from. But I would ask
15 that our statisticians among our group as well as
16 those clinicians that are familiar with outcomes data
17 help me understand whether the minimum detectable
18 difference is the same as a clinically significant
19 improvement.

20 An independent study of the Swiss Stenosis
21 Questionnaire was also done in 2002. It is the most
22 reproducible among those measures that were looked at

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1 in that study, and as such I think it was a valid
2 questionnaire to use. The same authors that evaluated
3 it did acknowledge that it may not be reproducible
4 enough to judge the outcome after surgery for an
5 individual patient. The point of view that was
6 associated with that article also indicated that
7 fairly large changes are necessary for the confident
8 determination that a true change has occurred. When
9 we look at the sponsor's definition, 0.5 improvement
10 is success. Depending on how you want to look at the
11 numbers, 0.5 improvement represents about a 10 percent
12 change in symptoms. It's a scale of one to five.
13 Perhaps my math would have been better if I looked at
14 zero to five, then it truly would be a 10 percent, but
15 we're talking a few percentage differences there. At
16 any rate, it's going to be less than 20 percent
17 improvement. On the same token, when we look at the
18 improvement in the function, it's a scale of one to
19 four, so my number really should be changed. I'm
20 doing it in my head very well, but it will be a little
21 bit higher there.

22 The predictors of success that they found

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1 raise questions in my mind. They looked at femoral
2 stretch. However, as we heard this morning, the two
3 patients that described their symptoms sounded a lot
4 more like closer to sciatica than femoral stretch
5 issues. And in that case, why didn't they look at
6 sciatic tension signs, which is also a significant
7 number of spinal stenosis patients in my practice
8 present with as opposed to femoral stretch. I do
9 acknowledge literature recognizes femoral stretch as
10 well, but why not look at all things that are relevant
11 rather than just one particular area.

12 The second thing is about the radiographic
13 signs that they evaluated. Did they look at the
14 specific types of stenosis? Both the patients today
15 talked about unilateral leg pain. That was probably
16 not a central canal stenosis involvement. So I'm
17 wondering if there may be a stratification of the
18 results and find different success rates with
19 different areas of stenosis anatomically.

20 They also presented radiographic data at
21 12 and 24 months. I couldn't find whether there was
22 pre-op or post-op data, and I would ask the sponsors

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1 if they have the pre-op data that I missed please call
2 my attention to it. I could not find flexion-
3 extension data in the clinical study. They did it in
4 the pre-op, and they tried to make the statement that
5 they prevented any extension with the use of the
6 device. I can't verify that in the clinical study.
7 And then they did an excellent MRI analysis pre-
8 clinically to demonstrate the opening up of the
9 foramen, the opening up of the subarticular facet
10 diameter, and the canal diameter. Could this not have
11 been duplicated in the clinical study as well to
12 demonstrate the effectiveness of the device
13 anatomically, and not just with a clinical outcome.

14 Random check of the data. I must say that
15 having a daughter that undergoes math homework, I have
16 to double-check her work sometimes, and I have to
17 remind her of attention to detail. On Table 35, Page
18 53, they indicate that the symptom severity is a 5-
19 point scale, and their division is on that scale. My
20 concern is that if we're looking at the five points
21 that you have, the denominator should be five instead
22 of one. So 0.99 over 5 would be 19.8, as opposed to

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1 the 24.8 indicated there. When I double-checked the
2 next category on the same table, they used the same
3 denominator to get the same percentage. So one of
4 those needs to be changed. Perhaps the function scale
5 needs to be a higher percentage on their computation,
6 or the symptom severity needs to be lower, depending
7 on which convention we're going to assume. And the
8 question is, with that difference, are there other
9 areas in the data reports that might need to be
10 double-checked. I did not have time to review all the
11 tables.

12 Our panel deliberations will involve the
13 FDA reviewers' questions, and the clinical review
14 questions, as well as the independent questions that
15 we've come up with. Our key focus should be the
16 safety and efficacy of the device. As you remember,
17 our definitions are, and this is shortened to make it
18 simple, reasonable assurance based upon valid
19 scientific evidence that the benefits outweigh the
20 risks. In my opinion, the safety events related to
21 the device or implantation were few or relatively
22 minor, and are considered reasonable for a surgical

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1 procedure. I did not find that the life-threatening
2 complications or irreversible complications appeared
3 to be related to the device itself, and were more
4 likely related to the patient population instead of
5 the intervention.

6 Efficacy is the reasonable assurance that
7 in a significant portion of the population, the use of
8 the device will provide clinically significant
9 results. A significant portion of the population,
10 45.7 percent is not a significant portion of the
11 population in most surgical circumstances. Of course,
12 you can't compare back pain with knee pain, but when
13 you look at arthritis in the knee and look at success
14 rates, patient satisfaction's in the 95 percent range
15 at 15 years. That's certainly a difference in a
16 device evaluation. However, I do think we need to
17 temper our thoughts on what sort of percentage would
18 be significant because we are dealing with a much more
19 complicated and difficult pain relief situation to
20 deal with in the spine than we are in the knee. I
21 think that a better definition of the population may
22 help clarify some of these issues. As I mentioned a

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1 few moments ago, stratifying by the type of stenosis
2 may be of benefit, eliminating or limiting
3 comorbidity. And then they found that the patients
4 with worse function scores did better with the
5 procedure, yet their indications indicate that they
6 want mild to moderate symptoms. And I'm wondering if
7 they looked at the more severe functions for
8 symptomology issues they would find that those
9 patients since they did better might be a better
10 patient to have the indicated procedure.

11 Clinically significant results. This
12 means does the patient find a significance. The 0.5
13 improvement was selected by the sponsor. Again, I
14 mentioned that my numbers may be a few points off as
15 far as how you want to compute them, but essentially
16 the way I computed it was between a 10 and 12.5
17 percent change. That may go up five points or so if
18 we change the computation method. However, the
19 question is is that a clinically significant
20 improvement to an individual. It also approximates
21 the minimum clinically important difference as
22 described in the original paper discussing the

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1 measure. And the question I would pose to you all is
2 is this amount of improvement significant to the
3 individual patient.

4 Thank you very much.

5 DR. YASZEMSKI: Thanks very much, Dr.
6 Kirkpatrick. We've heard Dr. Kirkpatrick's lead
7 clinical review from the panel. We'll now ask Dr.
8 Jonas Ellenberg to give the panel's lead statistical
9 review. Dr. Ellenberg?

10 DR. ELLENBERG: I would like to echo the
11 prior speaker's commendation to the sponsor for
12 providing us with an excellent overview and ability to
13 look at facts very quickly, and have everything cross-
14 referenced.

15 What I'd like to talk about now,
16 fortunately, is somewhat redundant. I'm the last
17 formal speaker, so I'll be talking about things that
18 have been to some degree covered already. And my main
19 theme will be the flow that we have with the pivotal
20 clinical trial, starting with study design, going to
21 observed results, and then taking the observed results
22 and see how we can use those to come to conclusions.

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1 That is our task here as a panel. What I'll talk
2 about is how we judge the smooth and credible flow
3 related to equivalent patient populations in the two
4 groups that were randomized, and the issue of uniform
5 intervention, and the issue of whether or not we have
6 an objective outcome in the analysis that has been
7 presented. And then the time that the analyses were
8 done, that is, the primary analysis being done at 24
9 months.

10 So, beginning with the issue of the
11 equivalent patient populations. In terms of the
12 randomization, the statistical review has already
13 mentioned the issue of block size of two, and I am
14 reasonably concerned about that. It's already been
15 explained that if you have a block size of two an
16 investigator can theoretically select a patient coming
17 through the door to put them on which arm they feel
18 they might do better with. And what we're sort of
19 challenged with here as a group that's reviewing this
20 is in no way, shape, or form a question of impugning
21 anyone's integrity, but basically the issue of this
22 opens up the door for an opportunity for investigators

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1 to inadvertently, with no intended bias, to push
2 patients towards one arm or the other. And we have
3 to, in the end, ask the question is this reasonably --
4 are we reasonably sure that this did not happen. And
5 with a block size of two, and not being there at the
6 time that these decisions were made, we have to make
7 that decision. So that's one of the considerations
8 we'll have as we deliberate.

9 The second issue in terms of the
10 equivalent patient populations goes to the
11 expectations. And for this I go to the informed
12 consent document. This is in the panel's workbooks.
13 These are the three points that relate to the issue of
14 what the patient is told in coming on to this study.
15 The first point, "My physician will explain the study
16 to me and how the X STOP may relieve my symptoms that
17 I experience." Second bullet relevant to the informed
18 consent, "The alternative to this procedure is to
19 continue a conservative care program that may include
20 physical therapy and/or medications or a laminectomy
21 procedure." Third statement, "Neither my surgeon nor
22 I will know what group I am in until the sponsor of

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1 the study tells us." Now, I'm not sure why that
2 statement was in the informed consent. It seems to me
3 not to be true. But the first two points, in my view,
4 do not give the potential for success for the
5 alternative therapies. And in light of what we heard
6 this morning whereby most people coming onto this
7 study are essentially failed patients for the
8 conservative flow, my sense is that going into this
9 study, patients who will know what arm they are on by
10 definition come into the study with an expectation
11 that is different between the two arms. So this fact,
12 coupled with the issue that the block size is two, it
13 seems to me at a minimum could show an appearance of
14 the potential for a biased selection of subjects onto
15 the study arms.

16 The second issue with regard to the
17 equivalent populations. Actually, this was just
18 brought up indirectly by Dr. Kirkpatrick. The
19 association of baseline with later assessments for
20 severity and physical score components. If we look at
21 the results of the physical score changes from
22 baseline, in those subjects who did not have a

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1 laminectomy, and they maintained the distraction in
2 the X STOP group versus the control group, it's not
3 important to see all the individual points, but just
4 note that the red X's are those on the X STOP
5 treatment, and the black squares or circles are those
6 that are in the control group. If you have a terrific
7 eye, you might notice that the relationship between
8 the baseline physical score and the change in the
9 score over time, which is one component of the outcome
10 that is the primary outcome, that one treatment, the
11 arm for the X STOP, appears to be related in a
12 different fashion than the control arm.
13 Statistically, this is the case. This arm has a
14 steeper slope than that arm. And basically what this
15 is showing, since the measurement is higher scores are
16 good in terms of achieving success. Going up means
17 that you've reduced your score. And on the CVQ it is
18 good to reduce the score, rather than increase the
19 score. It's seen that as you go up with baseline
20 physical score, the more dramatic increase is going to
21 come from the X STOP group than from the control arm.
22 And this relates specifically to one of the panel

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1 questions: is there a group of patients in which this
2 procedure might be most effectively used. So again,
3 do we have equivalent patient populations? It's not
4 clear. This may be strictly a treatment effect being
5 shown here, or it may be the fact that there's some
6 differential in the way the patients came in to the
7 two arms.

8 Next issue. Do we have a uniform
9 intervention? We've seen already, and it's been
10 mentioned by several of the speakers, that there is a
11 differential center by X STOP success rate. One
12 center being as high as 80 percent plus in success.
13 That's disconcerting when you look at a study like
14 this and try to see whether or not all patients within
15 center and between the centers actually were receiving
16 the same uniform intervention.

17 The second issue is there is no protocol
18 for the use of laminectomy. And if one goes back to
19 the issue of the informed consent, and the issue of
20 expectations of the patients and the investigators, I
21 would like to raise for the panel's consideration the
22 potential that the use of laminectomy in the X STOP

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1 group for which I believe the number was six, as
2 contrasted to the control group where the number was
3 24, the use of laminectomy conceivably, indirectly,
4 without any potential bias, could have been
5 forestalled in the X STOP group. Because of an
6 expectation or a wanting to make the X STOP group work
7 better.

8 The use of epidural in the X STOP arm.
9 Again, there was no specific procedure in either the
10 control or the X STOP arm. The use of epidural was
11 considerably less frequent than in the X STOP arm than
12 in the control arm. Nonetheless, there's no protocol
13 for the use of an epidural in either of the arms, and
14 there's no protocol for the use of laminectomy. And
15 laminectomy is a major endpoint. We know that 24 of
16 the control patients had a laminectomy, and they were
17 considered a failure. And six of the X STOP patients
18 had a laminectomy, and they were considered a failure.

19 So do we have a uniform intervention? This is
20 something that I think we as a panel have to consider
21 as we look at the numbers that very simply say, okay,
22 success was 45 percent in the X STOP group versus five

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1 to six percent in the control group.

2 Do we have an objective outcome? Mr. Kotz
3 has already covered some of these issues. But we need
4 to make sure that we're considering this as we look at
5 the results being seen, which appear to be extremely
6 objective. As has already been stated, the ZCQ is a
7 totally subjective series of questionnaires in three
8 parts. I couldn't find in the package that we had to
9 review exactly what circumstances the patients were
10 given these tests in. Were they allowed to be
11 prompted with questions with the investigator in the
12 room, or someone else associated with the study, or
13 was this simply done on their own. So there's the
14 potential for an influence by the investigator. But
15 even if the ZCQ was totally done by the subject, if
16 there were from the IC or other discussion with the
17 entering investigator, would the patient -- that push
18 the patient to have a higher expectation. Then it's
19 really, really difficult to understand the subjective
20 outcome. And I think it was interesting today when
21 that was mentioned, that the ZCQ outcome score for
22 clinical significance was noted at 0.5 in this study,

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1 but that's not really necessarily the clinically
2 important result. And I'll bring in some data that I
3 think is very interesting to address that.

4 There was no masking possible. So
5 everyone, mostly everyone knew what was going on. In
6 the informed consent, was there really equipoise,
7 which ethically and legally is required in order for
8 someone to be randomized into a study. And from my
9 reading of the informed consent, it's not clear that
10 that was the case. But that's a legal issue, not an
11 issue that I think this panel is addressing. Was
12 there balanced expectations? I'm bringing this point
13 up again under the objective outcomes, even though
14 I've already mentioned it, because it carries through
15 everything that we do.

16 Was there an objective component as part
17 of the primary outcome? Well, the laminectomy appears
18 to be an objective component, but as I've already
19 discussed before, if the laminectomy was held off on,
20 then perhaps there is a subjective element, even in
21 that objective component.

22 The analysis. Do we have an analysis that

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1 fairly assesses what we have done and what we have
2 seen? The statistical review has already covered the
3 missing data. The randomized but not treated issue
4 has been covered by the sponsor in terms of doing a
5 sensitivity analysis. So in my view in reading that I
6 don't think that's a major issue.

7 The ZCQ cutpoint choice that Dr.
8 Kirkpatrick just raised, is this clinically
9 meaningful. What I did was look at the frequency
10 distribution of the differences in the ZCQ scores.
11 And let me explain the graph. On the X axis, what you
12 see here is a difference from baseline in the change
13 of the severity score. And this is the epidural
14 group, the control group, and this is the X STOP
15 group. Again, because this confused me for awhile, a
16 positive score is a good thing, and a negative score
17 is a bad thing. That means that there's a worsening.

18 The score that was chosen for this study to be a
19 clinically meaningful result was a change of 0.5 in
20 the good direction. Meaning that the score dropped
21 from baseline. And if you compare the two arms, it is
22 clear that we have a shift in the distribution from

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1 the control group to the X STOP group. And the shift
2 is in the right direction. You're supposed to be
3 going to the right if you want to show improvement.

4 The meaningfulness of the 0.5 as a measure
5 of success is not at all clear to me. It's clear that
6 there are more subjects who were to the right of 0.5
7 in the X STOP group than there were to the right of
8 0.5 in the control group, and that is a good thing.
9 It wasn't clear to me that if you used a higher
10 cutpoint that this difference might change. So if
11 we're looking at a comparison of 45 percent versus
12 four or five percent, maybe that's due to the fact
13 that this cutpoint was too low, that 0.5 is not a
14 clinically important difference. And if you're really
15 looking for something important, maybe you should be
16 having a cutpoint that's higher. I went through
17 essentially redoing the analysis using all values up
18 to the value of 2, and found no difference. No matter
19 where you put the cutpoint, the shift in the X STOP
20 group was clearly better than the shift in the control
21 group. Looking at the actual values at baseline for
22 the control group and the X STOP group, it turns out

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1 that this 0.5 is approximately one standard deviation
2 of the baseline data for the severity score and
3 equivalently for the physical exam score. Whether or
4 not this is something I think the panel should look
5 at, 0.5 as one standard of deviation as a meaningful
6 clinical difference I think it's important.

7 However, and let me just show this. The
8 next slide is for the baseline physical score, and the
9 comments are exactly the same. There's no difference.

10 I think it's important to note that this is a
11 complicated composite endpoint. The primary endpoint
12 includes three components of the ZCQ. It includes the
13 use of laminectomy in both groups, and it includes an
14 assessment of whether in the X STOP group there was a
15 maintenance of distraction. So to me, I sort of
16 started getting confused as to how we deal with the
17 lumping of all this data together as one endpoint.
18 And as a result, I looked at many, many configurations
19 of this where I only included patients in looking at
20 these baseline physical and severity scores, and
21 looking at that change. And I overrode the
22 laminectomy if there were scores available for the

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1 physical and the severity score ZCQ components. No
2 matter which way I did it, the results came out the
3 same. So I'm feeling fairly confident that whatever
4 this endpoint is, if you like it, don't like it, no
5 matter which way you really thrash it, move it around,
6 the results are still the same from the point of view
7 of having a statistically significant result. But the
8 issue remains as to whether or not the result is
9 clinically important.

10 The analysis aspects. The missing data
11 issues were covered in the statistical review in the
12 packets that you've received. The randomized but not
13 treated group was covered. And I'm sorry -- time to
14 laminectomy. I've already covered the first part. I
15 wasn't sure what would be found here. And I went
16 through several machinations on how to look at this.
17 This is a Kaplan-Meier curve where we're looking at
18 the time to laminectomy in the two groups. The red
19 line is the X STOP group, and the other color line,
20 probably green or black, is the control group. These
21 are all subjects that were actually evaluated. As
22 would be expected, the time to laminectomy curve for

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1 the X STOP group is higher than the curve for the
2 control group, which reading up here. This says over
3 time. Reading up here, at the end of the day, after
4 24 months, fewer patients actually had a laminectomy
5 in the X STOP group as contrasted to the control
6 group. And that's to be expected. Everything that
7 we've seen so far would indicate that would be the
8 result.

9 The only data that I had available to me
10 was so to speak disjoint. I knew the results for
11 laminectomy at six weeks, six months, I've forgotten.

12 There were four points at which it's presented in the
13 book. When I looked at only those subjects that had a
14 laminectomy, the six subjects in the X STOP group and
15 the 24 subjects in the control group I found the
16 results surprising. I would have expected that it
17 might take longer for the subjects on the X STOP group
18 to need a laminectomy than the subjects in the control
19 group. And from this curve, you can see that the
20 curve's essentially superimposed. The sample sizes
21 are not huge. I don't know how much we can relate to
22 any p-values here, but clearly the curves are

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1 superimposed on each other. And it raises the
2 question as we deliberate why this is the case. If
3 this treatment is effective, why are those subjects
4 that are destined to go on to laminectomy essentially
5 going on to laminectomy at the same speed, so to
6 speak.

7 Under the results and conclusions part of
8 what's been presented by the sponsor, and also by
9 panel members today, the time of the outcome is 24
10 months. It's been noted that there appears to be a
11 lessening of the difference between the control and
12 the X STOP group between the 12 months and 24 months.

13 And it would seem to me, given that these patients
14 are probably available for contact, it might make some
15 sense for us to consider re-looking at the success
16 rates at, say, 36 months, something along that line,
17 with a possible additional follow-up.

18 And I believe that covers what I wanted to
19 talk about that I hope complemented, rather than was a
20 series of redundant comments. And I'll stop there.

21 DR. YASZEMSKI: Thanks very much, Dr.
22 Ellenberg. We're going to move on now to the general

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1 panel discussion regarding the presentations we've
2 heard this morning. I'll remind the panel members
3 that you may call any member of the FDA or of the
4 sponsor to answer a question that you have concerning
5 the presentations. Any questions. Dr. Kirkpatrick?

6 DR. KIRKPATRICK: I asked this in my
7 presentation. Can the sponsor help me in the
8 computations on Table 35, please?

9 DR. YERBY: It was a very good
10 observation, Dr. Kirkpatrick. And we in fact made
11 that same mistake in our draft of the PMA to the FDA.
12 What it seems to me is that you're looking at a
13 difference of 0.99, and you've divided by the upper
14 limit of the scale of that domain. However, the
15 appropriate thing to do is to divide by the range of
16 that domain. Since each one starts at 1, if you
17 subtract that 1 off you divide by 4. so 0.99 divided
18 by 4 should be about 24 percent.

19 DR. KIRKPATRICK: Thank you for that
20 clarification. Can you also clarify how you computed
21 the physical function number on the same table?

22 DR. YERBY: Sure, that's right. 0.76 I

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1 think was the change you're referring to, is that
2 correct?

3 DR. KIRKPATRICK: That's correct.

4 DR. YERBY: So 0.76 divided by the range
5 of that scale would be 4 minus 1, which would be 3,
6 which is a little over 25 percent.

7 DR. KIRKPATRICK: So your table reflects
8 19 percent. So that's an error?

9 DR. YERBY: In fact it is. That's the
10 error that I'm referring to.

11 DR. KIRKPATRICK: Okay. So in essence,
12 for my understanding and for the panel's
13 understanding, I think we can agree that their
14 argument on the range should be the denominator,
15 correct?

16 DR. YERBY: The range, yes.

17 DR. KIRKPATRICK: The range on symptom
18 severity is a 4-point range, because it have five
19 responses. So the number that they provided of 24.8
20 is correct as a percent change from baseline.
21 However, the range on the physical function scale,
22 which gives us a scale from 1 to 4, should be 25.3

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1 percent, as opposed to 19 percent as presented?

2 DR. YERBY: That's correct.

3 DR. KIRKPATRICK: Okay. Now, would you
4 mind just making sure we've done them right on the
5 control values? Do you have somebody with a
6 calculator that can verify that 0.17 divided by 4 is
7 4.3? In my mind it seems close. And assuming that
8 that's correct, how about the 0.8 divided by 3. Is
9 that indeed 2 percent, or should it be higher like
10 your X STOP number should be higher?

11 DR. YERBY: I'm not sure. I don't have my
12 calculator. If anybody does.

13 DR. YASZEMSKI: May I interject. Maybe
14 what we can do is ask somebody during this session to
15 just punch those numbers, and ask you folks to come
16 back later and answer that question.

17 DR. YERBY: Yes, I think that would be
18 more appropriate.

19 DR. YASZEMSKI: Thank you.

20 DR. KIRKPATRICK: Thank you for that
21 clarification.

22 DR. YASZEMSKI: Any further questions, Dr.

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1 Kirkpatrick?

2 DR. KIRKPATRICK: I don't know at this
3 time.

4 DR. YASZEMSKI: Okay. Dr. Naidu?

5 DR. NAIDU: I have a question for the
6 sponsor in general. Is this device intended to be
7 inserted by the surgeons, or is it -- is it a
8 recommendation by the sponsor that it should be a
9 board-certified surgeon who is inserting this device,
10 or is it going to be relegated to any pain clinic
11 doctors as well? Because it seems like it can be done
12 as an outpatient procedure.

13 DR. ZUCHERMAN: I'm Dr. Zucherman. I'm
14 the inventor and principal investigator. I also have
15 a interest in St. Francis economically. The device is
16 designed to be done by either neurosurgeons or spine
17 surgeons.

18 DR. NAIDU: Thank you.

19 DR. YASZEMSKI: Thanks Dr. Naidu.
20 Additional questions? Dr. Kim.

21 DR. KIM: I have a simple question about
22 the clinical x-rays. Were they standing x-rays or

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1 were they supine x-rays?

2 DR. ZUCHERMAN: They were all standing x-
3 rays.

4 DR. YASZEMSKI: Thanks. For the
5 transcriptionist, that was Dr. Zucherman again. Dr.
6 Kim, any further questions? Dr. Doyle? No questions.
7 Ms. Maher?

8 MS. MAHER: I'd like to hold off.

9 DR. YASZEMSKI: I'm sorry, I didn't hear
10 you.

11 MS. MAHER: I'd like to hold off a little
12 bit.

13 DR. YASZEMSKI: Okay, thank you. Dr.
14 Diaz?

15 DR. DIAZ: I don't have a question, I just
16 have a clarification. Since this is a public record,
17 I want to highlight to Dr. Zucherman that
18 neurosurgeons are also spine surgeons. There is no
19 distinction.

20 (Laughter)

21 DR. YASZEMSKI: Thank you, Dr. Diaz. Dr.
22 Rudicel? Dr. Finnegan?

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1 DR. FINNEGAN: Surprise, surprise, I
2 actually have a couple of questions. And they're
3 probably for Dr. Zucherman or Dr. White. The first
4 one is an add-on to the radiographs. Did you set up
5 standard conditions for everyone as far as distance
6 from the patient so that your measurements were
7 actually fairly real? We're talking very small
8 measurements, and I'm trying to get a feel for whether
9 these were consistent across the centers.

10 DR. ZUCHERMAN: Well, the definition of
11 how the x-ray's done was just a standing AP and
12 lateral. So the variations in technique weren't
13 accounted for.

14 DR. FINNEGAN: Okay. And next question is
15 I notice that you chose the age of 50, but in our
16 present population, and this would appear to be a
17 trend that's going to continue over the next 20 or 30
18 years, there's a difference between a physiological
19 age of 50 and a chronological age of 50. And I would
20 suggest that the wonderful patients you had speak this
21 morning definitely are not physiologically the same as
22 their chronological ages. And how are you going to

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1 account for this? Because it would seem, at least
2 mentally, mental calculation, that a physiological 70
3 is going to have different response than a
4 physiological 50.

5 DR. ZUCHERMAN: Yes, that's a good
6 question. The age of -- picking 50 was fairly
7 arbitrary. We realize that some 50-year-olds are like
8 40-year-olds, and some, some 70-year-olds are like 90-
9 year-olds. But we found in the -- the average age of
10 the study was 70. In the pilot study the average age
11 was 79. So at the longer end where the patients
12 demand less from the device, we've found that it
13 seemed to work quite well in the older age group and
14 in the --

15 DR. FINNEGAN: But flexibility, or muscle
16 testing, that sort of thing were not done?

17 DR. ZUCHERMAN: Well, they weren't done,
18 but in the study correlates, it showed the younger the
19 patient was, the better result. It correlated with
20 better result.

21 DR. FINNEGAN: With all due respect to
22 spine surgeons, both back pain and chronic pain have a

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1 certain amount of psychological and emotional
2 attachments which have been well documented. Did you
3 do any kind of testing, MMPI, or anything like that on
4 your patient population?

5 DR. ZUCHERMAN: The only testing that
6 would have any mental component would be the mental
7 part of the SF-36.

8 DR. FINNEGAN: And that was done both pre
9 and post intervention?

10 DR. ZUCHERMAN: Yes. And there was no
11 change in the mental component for the X STOP and no
12 change in the control group.

13 DR. FINNEGAN: Even in your workers -- you
14 were very brave to include workers comp in here. Even
15 in the workers comp?

16 DR. ZUCHERMAN: Yes. Although in this age
17 group there weren't really a lot of workers comp
18 patients.

19 DR. FINNEGAN: And my last question has to
20 do with a bigger concern about expulsion. Because
21 this is an older age group, balance is a problem. And
22 we know from the vertebral fractures that it's mostly

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1 axial load with a little bit of lateral twist. Was
2 there any testing done on this? I couldn't pull out
3 that there had been any testing done on this kind of
4 mechanism for expulsion.

5 DR. ZUCHERMAN: In our biomechanical
6 testing?

7 DR. FINNEGAN: Yes.

8 DR. ZUCHERMAN: No, we only tested simple
9 maneuvers, no complex maneuvers.

10 DR. FINNEGAN: Thank you.

11 DR. YASZEMSKI: Thank you, Dr. Finnegan.
12 May I ask before we move on to Dr. Ellenberg, we're
13 going to begin the discussion of the specific FDA
14 questions prior to lunch. Dr. Holden, could I ask you
15 while we're finishing up the general discussion to
16 perhaps get them ready for us on the screen? Mr.
17 Melkerson's up. Thanks. Dr. Ellenberg?

18 DR. ELLENBERG: This is directed to the
19 sponsor. I wonder if you could describe briefly how
20 the ZCQ was administered for each patient.

21 DR. ZUCHERMAN: Each of the sites had one
22 of the clerical people assigned to the study who was

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1 the local coordinator, and that individual would hand
2 the questionnaire to the patient.

3 DR. ELLENBERG: Was that person in the
4 room when the patient was completing the
5 questionnaire? Were they available for questions?

6 DR. ZUCHERMAN: Well, they were available
7 for questions. They would only stay in the room -- in
8 some cases, some of these patients are quite old and
9 had troubles with it, or had a family member in there
10 with them helping. So in those patients that had
11 mental issues with the questionnaire, the coordinators
12 would help them out to try and explain things to them.

13 DR. ELLENBERG: And were the coordinators
14 trained on the issue of so to speak unbiased help?

15 DR. ZUCHERMAN: The coordinators were
16 trained.

17 DR. ELLENBERG: On the issue of --

18 DR. ZUCHERMAN: Training sessions were set
19 up, and -- I don't know that the particular matter was
20 set out to them, because I wasn't at that particular
21 training sessions. But it was clear to them that this
22 is a study, and it's supposed to be unbiased.

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1 DR. ELLENBERG: Maybe this is you also.
2 Can you describe the informed consent process, and who
3 was involved with that, and how the question and
4 answer session went with the potential subject?

5 DR. ZUCHERMAN: Well, in general, after
6 the surgeon would have discussions with the patient
7 about whether they were interested in this study. The
8 investigator would usually give the patient the
9 questionnaire, give the patient some time to look at
10 it.

11 DR. ELLENBERG: The questionnaire?

12 DR. ZUCHERMAN: I'm sorry, the --

13 DR. ELLENBERG: Informed consent.

14 DR. ZUCHERMAN: The informed consent, give
15 the patient some time to look at it, come back in and
16 ask if there's any questions, and then sign the form
17 with the patient.

18 DR. ELLENBERG: So there would be a
19 preliminary discussion with the surgeon and the
20 potential subject. And in general, how would that go?
21 That was presumably not scripted. Again, were these
22 surgeons trained in presenting the options to the

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1 patient in a manner that would not influence either
2 their decision to join the study, or perhaps more
3 importantly for the study itself not to influence
4 their expectations as to what would happen if they
5 went onto the X STOP arm?

6 DR. ZUCHERMAN: I think it was clear to
7 the surgeons who went through IRB process and so
8 forth, and almost all -- virtually all the surgeons
9 had been involved in other studies of the
10 responsibilities of the surgeons to explain to the
11 patient the possible outcomes of entering the study.

12 DR. ELLENBERG: Okay. And the final
13 question is is it feasible at this late date to track
14 the patients who completed the study?

15 DR. ZUCHERMAN: It would certainly be
16 possible for many of the patients. You know, it just
17 depends on patients having left the areas, or patients
18 being old. In our pilot study patients, many of them
19 are now in their mid-80s, and we have tried to contact
20 them and sometimes it's difficult to get them to
21 cooperate.

22 DR. ELLENBERG: I'm sorry, I didn't hear

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1 the last.

2 DR. ZUCHERMAN: Sometimes difficult to get
3 them to cooperate.

4 MS. LYSAKOWSKI: I'd like to -- My name's
5 Yvonne Lysakowski. I'd like to add to that, if I may.

6 DR. ELLENBERG: Sure.

7 MS. LYSAKOWSKI: Yes, well at this point
8 in time the study is closed, so in answer to your
9 question is it possible to contact them, yes it is.
10 But of course we'd have to go through the process of
11 IRB approval, et cetera, which in fact we are very
12 interested in doing, and plan to do in the future.
13 We're very interested in knowing what the longer term
14 outcomes of these patients are.

15 DR. ELLENBERG: And most of these patients
16 were in care at the particular clinics, or did they
17 get sent to the clinics as sort of a tertiary last
18 resort?

19 MS. LYSAKOWSKI: Well, that would be a
20 mixed bag. And in answer to your question, again, it
21 may not be possible to contact every single patient,
22 but certainly that would be the effort put forth.

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1 DR. ELLENBERG: Thank you.

2 DR. YASZEMSKI: Thanks Dr. Ellenberg. Dr.
3 Li?

4 DR. LI: Yes, I have a few questions that
5 relate more to the mechanical testing of the device,
6 and a couple of just general questions on function.
7 I'm not sure who wants to take the questions.

8 One general question is there doesn't
9 appear to be much that actually holds this device in
10 place. It kind of just floats in that position. So
11 have you made any attempts to examine the amount of
12 motion that that device actually goes through,
13 especially in the AP direction? In other words, as
14 the patient flexes and extends, does this device
15 actually move at all in any direction, or do you see
16 any signs from immediately post-op and at 24 months
17 that the device is actually where it was in the
18 beginning?

19 DR. YERBY: I can address that from a more
20 biomechanical standpoint than a clinical standpoint.
21 From a biomechanical standpoint, yes we did monitor
22 the motion during flexion-extension experiments. And

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1 we did this both on a gross basis as well as a
2 radiographic basis. And in no cases did we notice
3 migration unless the implant was placed posterior to
4 what we call the apices, which is a very posterior
5 position. In the normal position as dictated by the
6 surgical technique, we notice no motion. From a
7 clinical standpoint, stepping out of my bound just
8 slightly, what does happen is within six weeks, and
9 this has been identified on retrievals, the implant is
10 almost always encapsulated in fibrous tissue which
11 indicates that it's pretty securely in place.

12 DR. LI: Okay, thank you.

13 DR. YASZEMSKI: Please give, again, the
14 transcriptionist your name.

15 DR. YERBY: Oh, sorry. Scott Yerby.

16 DR. YASZEMSKI: Thanks, Dr. Yerby.

17 DR. LI: As far as detail about your
18 cadaver testing. I didn't notice that once you've
19 fixed your cadaver specimen, did you cycle the implant
20 a few times to get to some kind of equilibrium
21 position? Or did you just mount the samples and go
22 right at it and start making measurements?

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1 DR. YERBY: Sure, that's another good
2 question. Typically in experimental testing what we
3 do is we do cyclically load it, but this type of
4 loading is typically for creep purposes, to dehydrate
5 the -- usually when you test a specimen, the specimen
6 is superhydrated in the discs. And what we do is we
7 typically creep load it for anywhere from 15 minutes
8 to an hour to bring the hydration of the discs back to
9 a normal level. And in that case, yes, we did
10 cyclically load it to a point where we were satisfied
11 that the test was ready to begin.

12 DR. LI: Okay. And a follow-up question
13 to that. Did you do any testing -- you did tons of
14 testing, by the way, which I congratulate you for.
15 Did you do any more or less kind of not really fatigue
16 testing, but essentially the effect of cyclic loading
17 on the measurements that you make? In other words,
18 after the equilibration you just discussed, you went
19 ahead and for instance measured flexion-extension.
20 Did you do any experiments where you perhaps cycled
21 the whole structure for several thousand cycles, and
22 then measure again to see if there's any change in

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1 flexion-extension? That would be a more direct
2 measure if there was any motion, or any kind of change
3 in orientation of the device.

4 DR. YERBY: That's another good question.
5 We didn't do any cycles, let's say beyond five cycles
6 within a cadaver model for various reasons. One is
7 that it's typically not indicative of, for instance,
8 the response that could occur between the implant and
9 the bone in a cadaver model. All of our cyclic
10 loading was done just on a purely mechanical
11 standpoint. So the migration that you're referring to
12 wasn't addressed in any of the biomechanical studies.

13 DR. LI: Okay. Obviously what I'm fishing
14 for is perhaps some mechanical or biomechanical
15 explanation of some of the clinical results that
16 you've got that perhaps indicate that the 24-month
17 result isn't quite as good as the 12. So I'm kind of
18 struggling to see if you had any laboratory or
19 clinical data that would've suggested that would be a
20 possible outcome.

21 DR. YERBY: No. The only analogies that
22 we can get from our biomechanical testing would be

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1 that -- several factors. And these are all clinical
2 factors as opposed to biomechanical. But on the
3 biomechanical standpoint, the MRI testing that we did
4 show, possibly the amount of impingement that was
5 occurring pre-implantation wasn't relieved enough
6 following surgery with the X STOP procedure. That's
7 the only analogy that I can say, and I'm not -- it's
8 not my expertise to say from a clinical standpoint
9 whether or not that was the case.

10 DR. LI: In kind of a related question,
11 and I don't know if one of the physicians wants to
12 jump in on this question also. It seems like the
13 performance of this device is strongly related to the
14 sizing of the device. Like in other words, what size
15 spacer do you put in this location. But there seems
16 to be some discussion over how much flexion, for
17 instance, you put the patient into while you're doing
18 the insertion. So is there a standard method for how
19 much the patient is flexed? And you know, or for that
20 matter, if the surgeon just has a penchant for wanting
21 to make it tighter than another physician. In other
22 words, just exactly what variation are we seeing.

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1 Given the same patient, for instance, can one surgeon
2 pick a 4-millimeter insert and another surgeon pick a
3 6-millimeter insert, and they both felt they've done
4 the right thing, but you would probably end up with
5 different amounts of flexion-extension reduction. So
6 how do you account for all that?

7 DR. YERBY: Again, from the clinical
8 standpoint that's a little bit outside my expertise,
9 but what we did find, and I'll let Dr. Hartjen refer
10 to this, is that from the clinical standpoint in terms
11 of inserting the implant, there was an endpoint. It
12 was based on the tension on the supraspinous ligament
13 palpated during surgery. And I'll let him address
14 that.

15 DR. HARTJEN: Charles Hartjen. The
16 patient was basically placed in a right lateral
17 decubitus position and asked to flex as much as they
18 could. That includes flexion of the hips and knees,
19 sort of getting into a fetal position. After the
20 patient was in a comfortable position that they could
21 withstand for 45 minutes to an hour, they were
22 administered local anesthesia and IV sedation. And

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1 then the initial dilator starter was introduced
2 between the ligamentum flavum and the most anterior
3 portions of the interspinous ligament. And then there
4 was a secondary dilator, and this was followed by a
5 device, a distracting device. And the selection was
6 based on just empirically the elastic limits at the
7 level. We had a device with a gauge, and basically
8 the surgeon would distract manually, and when he felt
9 he was reaching elastic limits of the tissue, would
10 wait for a few seconds for physiologic creep, and then
11 just give a maximum distraction manually that he felt
12 was safe. And then we had a specific measurement for
13 that height. We selected the implants based on that.

14 DR. LI: Do you have a correlation or some
15 association of that feel to actual clinical benefit?
16 In other words, should the patient be stretched as far
17 as they could go, or do you need to go a little
18 further than that, or should you back off? In other
19 words, I get your endpoint now, but how do you know
20 that endpoint was the clinically appropriate endpoint?

21 DR. HARTJEN: Maybe Yvonne could have some
22 numbers for that, but that was empirically how it was

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1 done for all of my patients.

2 DR. LI: So in other words, so is it
3 possible for one patient, you'd get to that endpoint
4 and it's sufficient distraction, but to another
5 patient it might be perhaps even too much or too
6 little?

7 DR. HARTJEN: It's quite possible. It's
8 possible that it's too little, more likely than too
9 much. Most of the patients that had a small implant
10 had fairly advanced degenerative disease, and had
11 probably with the patients that were more in the
12 moderate to moderately severe stenotic range.

13 DR. LI: Is there a way to break down the
14 data for the success or failures, or perhaps even from
15 the different centers where there were wildly
16 different success rates, if there was a size issue in
17 that case then?

18 DR. ZUCHERMAN: Dr. Zucherman. From the
19 onset of the inception of the device, we were thinking
20 in terms of matching the sitting position, because
21 that's the position in which the patients weren't
22 uncomfortable in. So by starting the procedure with

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1 the patient flexed at least as much as in a sitting
2 position, we were all presuming that matching at or
3 exceeding it will get us where we want to get. And
4 the endpoint of elastic limit that Dr. Hartjen was
5 mentioning is pretty obvious when you do the
6 procedure. There's distraction, and then distraction
7 stops, and you don't get much distraction with greater
8 force. And so that's been the instructions to all the
9 investigators, do it like that. We haven't noted that
10 there's any size-related instance of better results.
11 The older people tend to take smaller sizes because
12 their segments are stiffer. By the fact that the
13 patient has relief with sitting, all we have to do is
14 match what happens with sitting.

15 DR. LI: And perhaps one last detailed
16 question, not to beat the dead horse here. But if you
17 gave five surgeons the chance to tension the same
18 patient to where they thought the endpoint was, do you
19 have any idea what the variation in that tension would
20 be? Because my own experience with other orthopedic
21 surgeons is, you know, that range could be huge and
22 they all think they did it exactly right.

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1 DR. ZUCHERMAN: Since all the
2 investigators were trained either by myself, or my
3 partner, or one of the people that we trained, I can
4 tell you that it would be within one size difference.

5 Because a lot of times it's borderline whether you'd
6 go up or down to the size on the measuring device.
7 But I don't think the -- deciding what to do with the
8 size gets easily conveyed to the surgeon in the
9 training.

10 DR. LI: Then perhaps one last question
11 then. Basically, all this was I was fishing around
12 for why one center seems to be so much better than the
13 rest. And I was kind of hoping that there was
14 something either by process, or by design, that would
15 actually explain that. So do you have an explanation
16 of why one center seems to be so much better than the
17 other? Or vice versa, why one center seems to be so
18 much worse than the others?

19 DR. ZUCHERMAN: I think the best
20 explanation was shown in the presentation. But if you
21 look at the variables that correlated with good
22 results at the center that had the best results, about

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1 six or seven of the variables that correlate with good
2 results were statistically at that center. So they
3 had a better selection of patients in the group. And
4 of course, what that selection is we didn't know until
5 the study data came out. And basically it was younger
6 patients, it was patients who were employed, it was
7 patients who started out with worse scores. And the
8 worse results started out with older patients, about
9 eight years difference between the center with the
10 best results and patients that had better scores to
11 start out. So it's harder for them to make the leap
12 into success because starting out with scores that are
13 lower. I think that along with the fact that the
14 center with the best results were the original
15 inventors of the device, so they'd have more
16 experience with it, and more experience with
17 selection, accounts for the differences.

18 DR. LI: Well, given that list of possible
19 explanations, then would you -- knowing what you know
20 now, would you change the indications for use for the
21 device?

22 DR. ZUCHERMAN: No, because it's -- even

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1 if you take the best center out and look at all the
2 rest of the data with the best center out of it, it
3 still is a very effective device. So the
4 effectiveness may drop down somewhat in certain
5 situations, just like any surgery does, but it still
6 is effective for this problem across the board, I
7 believe.

8 DR. LI: Thank you.

9 DR. YASZEMSKI: Thanks, Dr. Zucherman.
10 We're going to move on to the questions. I might,
11 before we go, Dr. Yerby, has anybody from St. Francis
12 got the number to answer Dr. Kirkpatrick's question
13 yet? If not, I'll ask you then to do that as part of
14 the sponsor summary later. Yes, Dr. Kirkpatrick.

15 DR. KIRKPATRICK: If you don't mind, I did
16 request the opportunity to think about another
17 question.

18 DR. YASZEMSKI: Please go ahead.

19 DR. KIRKPATRICK: Okay. And to answer
20 your question on the number, my brief hand calculation
21 indicates that it should be 2.6 percent instead of 2
22 percent. If you would double-check me, I'd appreciate

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1 it.

2 Now, I mentioned a couple of things in my
3 presentation that I would like to know earlier rather
4 than later. One is did you stratify your results
5 based upon unilateral leg pain versus bilateral leg
6 pain?

7 DR. ZUCHERMAN: Dr. Zucherman. No, we did
8 not.

9 DR. KIRKPATRICK: Thank you. Did you
10 stratify your results based upon any kind of
11 determination whether the predominant stenosis was
12 foraminal, subarticular, or central?

13 DR. ZUCHERMAN: We did not. When we
14 looked at the MRI findings, over 90 percent of the
15 patients had both lateral and central stenosis.

16 DR. KIRKPATRICK: Thank you.

17 DR. YASZEMSKI: Thanks Dr. Kirkpatrick.
18 Ms. Maher?

19 MS. MAHER: I was actually hoping someone
20 else would ask this, but I was wondering if the
21 sponsor could explain to me what a 0.5 improvement
22 actually means to the patient's quality of life. I

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1 mean, I've heard people say it's minimally
2 significant. I've heard people say it's clinically
3 significant. If somebody could give me an
4 explanation, I'd appreciate it. I would understand if
5 it's intangible, if it means that somebody who hasn't
6 been able to go grocery shopping all of a sudden can.
7 I just need to sort of get a baseline for what it
8 overall might be.

9 DR. YASZEMSKI: Thanks. Dr. Hartjen?

10 DR. HARTJEN: I'm far from the expert.

11 DR. YASZEMSKI: Dr. Hartjen, let me ask
12 you again, pull the microphone a little closer so we
13 can. Thanks.

14 DR. HARTJEN: I'm sorry. I don't think
15 that I can get into great details on all of the
16 numbers, but if you look at some of the entry points
17 as in walking, one change in entry is from walking two
18 blocks to two miles. So I don't think that the
19 sensitivity of each individual entry is that important
20 as the patient's overall clinical improvement. And I
21 think the satisfaction rates reflect that more than a
22 single entry point.

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1 MS. MAHER: Thank you.

2 DR. YASZEMSKI: Thanks. Other questions?

3 Okay, let's move on to the FDA's questions. The
4 first question, Mr. Melkerson or Dr. Holden, are you
5 going to summarize the questions, either of you? Then
6 we'll start with one of the panel members and go
7 around and ask for commentary on those questions.

8 DR. HOLDEN: We don't have so much a
9 summary. They're summarized on these slides. The
10 entire question is on the printed form, which probably
11 should be read into the record.

12 DR. YASZEMSKI: Okay. I'll go ahead and
13 do the reading. Or you can read. Do you want to read
14 it?

15 DR. HOLDEN: Doesn't matter.

16 DR. YASZEMSKI: Go ahead.

17 DR. HOLDEN: Okay. Question Number 1.
18 Patients who had the X STOP implanted had a higher
19 incidence of musculoskeletal events, including lower
20 back disorders, lower extremity disorders, hip
21 disorders, upper back disorders, and neurological and
22 neuropathological disorders compared to the control

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1 group. Although these adverse events were considered
2 by the sponsor to be not device-related, changes in
3 spinal biomechanical function that occur with the
4 limits to extension could also be a potential source
5 of pain. The sponsor provides a report of a pre-
6 clinical study which characterizes the effects of the
7 device in cadaveric specimens showing an increase in
8 canal and foraminal dimensions at the implanted level
9 in the extended position with no change in the
10 dimensions at the adjacent levels. Please discuss the
11 clinical significance of the musculoskeletal and other
12 adverse events seen in the trial, and discuss whether
13 the effects of the device on surrounding segments or
14 on spinal biomechanics have been adequately addressed.

15 DR. YASZEMSKI: Thanks Dr. Holden. Dr.
16 Finnegan, let's start with you and go around the table
17 toward Dr. Rudicel.

18 DR. FINNEGAN: Well, actually I have
19 significant concerns in this area. I do agree with
20 the sponsors that not all of the musculoskeletal
21 things that have been listed, including some of the
22 neurologic, could possibly be related to this device.

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1 But I think there are others that need to be
2 explained. Certainly over the last 20 years, which
3 has shown a significant increase in the number of
4 spinal instrumentations and implants that are
5 available, ignoring the biology of altered spinal
6 mechanics is an unwise thing for anyone to do. And
7 there have been a number of problems with people who
8 have ignored the altered biomechanics.

9 One of my concerns is that there was no
10 animal model done to look at the biology of these
11 altered mechanics. And while it is true that the only
12 upright is a primate, and those are expensive and
13 difficult to deal with, there's been a number of
14 spinal instrumentation work done in goats and sheep,
15 and goats appear to be a pretty good model. So I have
16 some concerns that there was no attempt, or there was
17 no obvious attempt in the materials we were given to
18 do some sort of animal model to look at the long-term
19 biological response to this implant.

20 I'm also somewhat concerned that the
21 results ended fairly abruptly at 24 months. I'm not
22 exactly sure why they weren't followed out, because

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1 you obviously have patients who could be followed out.

2 Regardless of how you look at statistics, and I'm not
3 a statistician, and I know you can make statistics do
4 whatever you want them to do, there does appear to be
5 regardless of who is looking at the statistics a
6 decline at the 24-month period. And this would make
7 one concerned that perhaps the implant in its present
8 form has a limited usefulness, and it may be time-
9 related. I do think that upper back pain and some of
10 the other neurological or musculoskeletal complaints
11 are potentially related to the implant and to altered
12 biomechanics, and do need to be explained.

13 The other concern is that the control
14 group really wasn't a control group. It's people who
15 have failed, basically, their treatment, and continue
16 to fail the treatment. And as a consequence, they're
17 almost the natural history of the disease. And the
18 question is whether the altered biomechanics are just
19 a different, and I'm not sure I'm explaining this
20 properly, but it's just sort of a different natural
21 history of the disease.

22 So my response would be that I think that

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1 there are effects that have not been demonstrated or
2 discussed, or the reasons for the problem has been
3 outlined and I think there are several means of
4 obtaining this information.

5 DR. YASZEMSKI: Thanks Dr. Finnegan. Dr.
6 Rudicel?

7 DR. RUDICEL: The only comment I have in
8 conjunction with the musculoskeletal complaints is I
9 didn't quite understand how the low back pain
10 incidence was felt to be non-device related. If
11 anybody could expand upon that.

12 DR. YASZEMSKI: Would you like somebody
13 from the sponsor to comment on that, Dr. Rudicel?

14 DR. RUDICEL: I would.

15 DR. YASZEMSKI: Thank you.

16 DR. ZUCHERMAN: Dr. Zucherman. We were
17 asked specifically to look at those neurological and
18 spine, musculoskeletal cases that were reported as
19 adverse events. This didn't include the hip. And the
20 charts were reviewed in detail in that group of
21 patients, and 63 percent of them, the musculoskeletal
22 complaints were -- this is including back and lower

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1 extremities -- were due to comorbidities that
2 preexisted.

3 DR. RUDICEL: But specifically the back
4 pain.

5 DR. ZUCHERMAN: Well, obviously some of
6 the back pain patients, the patients that failed the X
7 STOP treatment are going to be included in that group.
8 So the failures are included because they're
9 failures, also reported as an adverse event. So some
10 of the back complaints are also counted as failures in
11 the study. And obviously, the study data as it comes
12 out, if the patient has some adverse phenomena that's
13 affecting their back, it comes out as a failure in the
14 study data. And the study data nevertheless, despite
15 the increased adverse events in musculoskeletal
16 system, came out so strongly in favor of the X STOP
17 group.

18 DR. RUDICEL: Might some of the patients
19 who were considered a success have also had back pain?

20 I mean, it seemed like there was a high number -- I
21 guess it wasn't broken down in your musculoskeletal
22 complaints, but I was assuming that the back pain may

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1 have been a significant number. Were some of the
2 patients who were successful also complaining of back
3 pain? Did that --

4 DR. ZUCHERMAN: Were successful? No.

5 DR. RUDICEL: Were those mutually
6 exclusive?

7 DR. ZUCHERMAN: No. I would say no,
8 that's not the case. If they had much back pain, they
9 would fail on the questionnaires.

10 DR. YASZEMSKI: Dr. Doyle, do you have a
11 comment on this?

12 DR. DOYLE: This is a question that's
13 related to it. Am I understanding you to say that
14 then the group that had X STOP had a higher incidence
15 in musculoskeletal and neurologic problems going in?
16 That there wasn't a real increase, that it was just
17 the distribution?

18 DR. ZUCHERMAN: They actually did have a
19 higher incidence going in. But there were several
20 factors that resulted in, we believe, more
21 musculoskeletal events in this patient population. In
22 addition to the fact that more of them, quite a few

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1 more, I think it was 34 versus 20 percent had
2 musculoskeletal comorbid conditions going in. In
3 addition though, if you look at the patients with the
4 stenosis, like the two that we heard earlier today,
5 during the time they had their stenosis they're
6 basically inactive. They can't do anything. And any
7 comorbid issues they have with joints and so forth or
8 tendencies toward tendonitis are going to be latent
9 because the individual is fixated on the main problems
10 preventing them from walking which is their spinal
11 stenosis. So when the X STOP group, when that effect
12 is removed, and all of a sudden after not doing
13 anything for quite awhile patients become active, they
14 now activate these problems in their joints, which are
15 very common in this age group of patients.

16 And in addition, the patients that were in
17 the X STOP group were probably followed more closely
18 by their surgeons than the patients in the control
19 group. The injections were often done at other
20 centers, and in a lot of cases, the non-surgical
21 treatment was also participated in by other doctors,
22 either medical doctors or a physiatrist and so forth.

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1 So it's probably a combination of closer scrutiny on
2 the people that had the X STOP, the unmasking effect
3 of them being inactive then allowing themselves
4 activity, and overdoing it essentially, and the higher
5 incidence of comorbid events -- comorbid issues in
6 these patients that had the X STOP, which was
7 coincident.

8 DR. YASZEMSKI: Thanks. Ms. Lysakowski,
9 do you have additional data to answer Dr. Doyle?

10 MS. LYSAKOWSKI: Yes, thank you.
11 Actually, what I was providing to Dr. Zucherman was a
12 listing of some of the lower back adverse events that
13 were asked about so that he might comment on that
14 specifically.

15 DR. ZUCHERMAN: Yes. So this is the --
16 looking at the low back unspecified events, there's 21
17 events in 16 patients. Eight of them were pain. And
18 eight of them were unspecified. There was three were
19 due to arthritis. And every other case is an isolated
20 event. Bursitis, sacro-iliac joint, disc herniation,
21 disc degeneration, popping sensation in lower back,
22 sciatica, back and buttock pain, stenosis pain. These

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1 are all the sort of thing that you'd see in this
2 elderly population.

3 The largest group among the
4 musculoskeletal group was the hip. And there was
5 actually five cases of severe hip degenerative disease
6 that required surgery. And that's obviously not
7 related to the device. There was also a group of
8 musculoskeletal events in the upper extremity,
9 Depuytren's contracture, superspinous ligament pain,
10 which is shoulder bursitis. One case of avascular
11 necrosis. One case reported as slipped capital
12 femoral epiphysis, which is interesting in this age
13 group. And there was also a group of upper back and
14 upper extremity symptoms, all of which are just the
15 general thing that you'd see in the patients average
16 age of 70 in your office.

17 DR. YASZEMSKI: May I ask Dr. Rudicel, has
18 this answered your question?

19 DR. RUDICEL: Yes, it was just actually
20 the back pain that I was interested in in terms of
21 trying to decide whether there was any relationship of
22 the device, or if it was a progression of their

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1 disease. And that was more what I was trying to get
2 at.

3 DR. ZUCHERMAN: Certainly all the failed
4 cases are going to be included in the back. It's
5 going to come out in the data.

6 DR. ZUCHERMAN: Dr. Andersson?

7 DR. ANDERSSON: It's actually very rare
8 that you eliminate all back pain with any type of
9 spinal surgery. If you look at the reported results
10 of disc herniations, more than 50 percent have back
11 pain. If you look at operations for spinal stenosis,
12 more than 60 to 70 percent have back pain. And it
13 probably has to do with the fact that there are so
14 many other reasons for back pain which are not
15 eliminated by the surgical procedure.

16 DR. YASZEMSKI: Thanks Dr. Andersson. Dr.
17 Rudicel, additional questions? Ms. Lysakowski?

18 MS. LYSAKOWSKI: Yes, thank you. I just
19 wanted to clarify one point or question that was asked
20 earlier, and that was that there didn't seem to be a
21 breakdown by the categories of adverse events. And
22 there actually is a table provided in the PMA, and we

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1 do have that data, but it does break it down by the
2 number of adverse events that are in the back, hip,
3 lower extremity, et cetera. So we do have that data.

4 DR. KIRKPATRICK: What table number?

5 MS. LYSAKOWSKI: Excuse me?

6 DR. KIRKPATRICK: What table number,
7 please?

8 MS. LYSAKOWSKI: In the PMA clinical
9 report I believe it's Table 50. If someone could
10 verify that for me? Yes, it's Table 50. It's Page
11 170 of your first binder.

12 DR. YASZEMSKI: Dr. Kirkpatrick, do you
13 have a comment on that now?

14 DR. KIRKPATRICK: If I could follow up.
15 Do you have the same breakdown in the pre-study group?
16 In other words, the selected patients pre-
17 intervention?

18 MS. LYSAKOWSKI: Yes, we do. It's a table
19 of comorbidities. And if you give me a moment, I
20 could let you know what the table number is.

21 DR. YASZEMSKI: How about if we do this.
22 How about if we give you a moment to get that ready,

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1 and Dr. Kirkpatrick a moment to think about, and when
2 we come around to him on the table I'll ask him to ask
3 that question to you.

4 MS. LYSAKOWSKI: Okay, great. Thank you.

5 DR. YASZEMSKI: Thanks. Dr. Diaz?

6 DR. DIAZ: I don't have a lot to add to
7 what Dr. Finnegan said. I think she was very eloquent
8 in the way she described the process. I just have a
9 couple of comments. One that really disturbed me just
10 now, something Dr. Zucherman just said was that the
11 follow-up of the control patients was not as good as
12 the follow-up that was of the study subjects. And
13 that to me just basically puts in question the entire
14 study. There should have been no difference in
15 follow-up on either side of the equation.

16 Also, what Dr. Andersson said I think is
17 critical. Patients with spinal stenosis who have back
18 pain are patients who will continue to have back pain.

19 Any type of inclusion of back pain as part of the
20 spinal stenosis assessment, in my mind, does not
21 really add up to anything. Because back pain is not
22 one of the primary components of spinal stenosis.

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1 Spinal stenosis is a neurological manifestation
2 syndrome.

3 DR. YASZEMSKI: Thanks Dr. Diaz. Ms.
4 Maher?

5 MS. MAHER: Nothing at this time.

6 DR. YASZEMSKI: Thanks. Dr. Doyle?

7 DR. DOYLE: I guess I'm still confused
8 about this comorbidity. Then the X STOP had a
9 preexisting comorbidity that's significantly higher,
10 43 percent as opposed to 17 percent? I realize that
11 that's adverse events unrelated to treatment, but
12 you're telling me there's that vast difference in the
13 baseline? I'm still not sure I understand.

14 DR. YASZEMSKI: Does somebody from the
15 sponsor care to address that? Dr. Zucherman?

16 DR. ZUCHERMAN: In the additional
17 presentation, the entry pre-comorbid data showed that
18 there was some increase in the X STOP group. I think
19 it was a 14 percent increase, 20 compared to 34. And
20 then after the -- during the course of the study, the
21 X STOP patients had higher musculoskeletal events that
22 was significantly higher than the control group.

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1 DR. DOYLE: What you're telling me --

2 DR. ZUCHERMAN: So what I'm saying is that
3 they started out a little bit higher but there
4 certainly were more musculoskeletal events in the
5 treatment group.

6 DR. DOYLE: And which you say is because
7 of the unmasking, that they're able to do more
8 physical things, so this is why it becomes?

9 DR. ZUCHERMAN: Yes, and I listed the
10 reasons as being the unmasking effect, and that these
11 problems are ordinarily seen at a high incidence in
12 people of this average age group. And that I think
13 that there was probably -- although the patients were
14 seen in the same time periods and so forth, and
15 received the same treatment in the two groups, there
16 was probably greater scrutiny in the people that had
17 the X STOP for the reason that they had the procedure
18 done. And number two is because they felt better,
19 they came in and they're going to complain about
20 what's bothering them now. If their main problem is
21 that their back is acting up all the time, they're not
22 going to come in and complain about their ankle which

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1 hurts as they walk six blocks.

2 DR. DOYLE: But they didn't have that back
3 pain before.

4 DR. ZUCHERMAN: The --

5 DR. DOYLE: The X STOP patients.

6 DR. ZUCHERMAN: Well, no. Well, having a
7 lot of back pain without the leg pain, that wouldn't
8 be attributable to the stenosis in the investigator's
9 mind, would not have included in this study.

10 DR. DOYLE: I guess I'm thinking as the
11 potential patient. Am I going to trade my lower leg
12 pain for upper back pain?

13 DR. ZUCHERMAN: No. But if you look at
14 the breakdown of the pains, most of the pains are in
15 the lower extremity and hips. And there is some pain
16 in the back, and we think it's consistent with what
17 you see in this age population. So it's a combination
18 of all the musculoskeletal events that was more
19 frequent.

20 DR. DOYLE: I guess that seeing the
21 difference in the adverse events of 17 percent in one
22 group and 43 percent in another group to me is a very

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1 big difference, and would concern me as a patient,
2 that I'd be better off in the control group as far as
3 musculoskeletal events went then.

4 DR. ZUCHERMAN: Well, yes, you'd be better
5 off sitting at home watching TV all the time. You'd
6 have less musculoskeletal events.

7 DR. YASZEMSKI: Ms. Maher?

8 MS. MAHER: I think I'd like to clarify a
9 little bit, or ask the sponsor to clarify. I mean, we
10 have seen, and they've brought out, the difference in
11 the musculoskeletal adverse events. But in fact, did
12 you continue to track adverse events in patients in
13 the control group who were discontinued or become
14 failures because of laminectomies? And/or did the
15 patients in the treatment group do further activities,
16 and were they followed further?

17 DR. YASZEMSKI: Ms. Lysakowski.

18 MS. LYSAKOWSKI: Thank you. In answer to
19 your question with regard to tracking the control
20 patients, for those patients who had reached what we
21 referred to as the defined failure endpoint, or in
22 this case a laminectomy, that was considered the end

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1 of their study participation. So no, we did not
2 follow them. So that meant that there were far fewer
3 patients in the control group by the time we reached
4 the 24-month end period.

5 DR. YASZEMSKI: Thank you. Dr. Doyle, has
6 that adequately answered your questions? Thank you.
7 Dr. Kim.

8 DR. KIM: I'm wondering if we can get at
9 this question another way. The unmasking event is a
10 reasonable explanation. If that's the case, I wonder
11 if you were to look at the control patients that did
12 well and compare them to the X STOP patients that did
13 well, they should both be more active and therefore
14 unmask those symptoms. Is it possible to do an
15 analysis like that to get at this question?

16 DR. ZUCHERMAN: In this case I don't think
17 it would be because there was only four patients that
18 were successful in the control group.

19 DR. YASZEMSKI: Thank you Dr. Zucherman.
20 Dr. Kim, additional questions?

21 DR. KIM: No.

22 DR. YASZEMSKI: Dr. Naidu.

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1 DR. NAIDU: I am concerned about this
2 increased back pain in the X STOP group. And I'm not
3 sure that I can dismiss that. I mean, Dr. Diaz has
4 said that it can be dismissed, and Dr. Andersson has
5 addressed also that it could be dismissed in this kind
6 of population. But nevertheless, the X STOP in all
7 the studies, pre-clinical studies showed that the bony
8 diameter is actually increased in the cadaver
9 specimens. Now, there's also a significant component
10 from the ligamentum flavum effect from what I
11 understand. It is also part of the claudication
12 process. If it buckles, and if it has been buckled
13 for a long time, and you tend to stretch that tissue,
14 did you ever consider soft tissue effects with this
15 distraction at that segment leading to back pain?

16 DR. YASZEMSKI: Dr. Zucherman.

17 DR. ZUCHERMAN: The -- In the entire
18 study, I only know of one patient that seemed to have
19 back pain that was a problem in relation to the
20 device. In our own series, which involves about 50
21 patients, including the continued access, there's no
22 patient that has significant back pain. There's

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1 obviously some soreness initially after the procedure
2 from the wound and so forth. So as far as pain at the
3 level of the device, it isn't a problem. And only, as
4 I said, one device was removed because it was painful
5 out of the six cases in which the device was removed.

6 So as far as the device causing problems, it's not an
7 issue. And we actually didn't expect that in the
8 beginning. We expected some people might have some
9 pain from having this device in there, but it seems to
10 be a silent area.

11 DR. NAIDU: Okay, thank you.

12 DR. YASZEMSKI: Thanks Dr. Naidu. Dr.
13 Kirkpatrick?

14 DR. KIRKPATRICK: May I clarify with the
15 sponsor that Table 19 would be the pre-intervention
16 comorbidities?

17 MS. LYSAKOWSKI: This is Yvonne
18 Lysakowski. Yes, it's Table 19.

19 DR. KIRKPATRICK: So then am I correct in
20 interpreting that back pain in the upper, lower, and
21 unspecified categories, for the X STOP was 14 percent
22 before the intervention?

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1 MS. LYSAKOWSKI: That sounds about right,
2 but forgive me, I did not bring that table to the
3 podium with me. If you'll allow me a moment, I'll
4 check that.

5 DR. KIRKPATRICK: Okay. And if I could
6 confirm, that would be the physician's reporting of
7 back pain on a data collection form, not the patient's
8 complaint. So there's no qualitative measure of that
9 back pain.

10 MS. LYSAKOWSKI: That would be correct.

11 DR. KIRKPATRICK: Okay. Then, as I
12 interpret Table 50, we have a 23 percent incidence
13 after the intervention. And I assume Table 50 is at
14 two years? Twenty-four months?

15 MS. LYSAKOWSKI: No, that's the total
16 number of events throughout the course of the study.

17 DR. KIRKPATRICK: So included in that 23
18 percent could have been somebody that had back pain at
19 six months, but not at 12 and 24?

20 MS. LYSAKOWSKI: That's a possibility. Or
21 it could include that same patient with perhaps a
22 repeated episode, for example.

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1 DR. KIRKPATRICK: Okay. Thank you. In
2 light of that, to answer the FDA's question, I think
3 with the higher comorbidity of the study group coming
4 in, and with the fact that we're not seeing a very
5 large increase in the number of patients that are
6 having back pain, the only question I would have with
7 relation to that is did the quantity of back pain
8 increase in patients that had back pain when they went
9 into the study. Did it get worse after the X STOP.
10 If it did, I think it'll be a small number of patients
11 that had that, and as such, I don't find it a
12 significant concern that the long-term results had a
13 different comorbidity for back pain in the study
14 group.

15 DR. YASZEMSKI: Thanks Dr. Kirkpatrick.
16 Dr. Li?

17 DR. LI: I have one more testing question,
18 if I may. If I understand it, the very first version
19 of this device had a problem with the screws backing
20 out that you subsequently welded so that wouldn't
21 happen again?

22 DR. YERBY: That's correct.

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1 DR. LI: That's correct? Did you -- When
2 you redesigned the device to have the welded portion,
3 and tested that device, was the test carried out in
4 such a way that if you put the original unwelded
5 device that in fact the screw would have backed out?
6 In other words, what I'm trying to get is trying to
7 get a feel for the robustness of your testing. In
8 other words, could the testing -- did the testing that
9 you conduct actually duplicate the clinical failure of
10 that screw backing out?

11 DR. YERBY: Yes, it did.

12 DR. LI: It did, okay. Thank you.

13 DR. YASZEMSKI: Thanks Dr. Yerby.

14 DR. LI: So in answer to your question, I
15 guess I'll defer to the clinicians as far as the
16 clinical consequences of this. I think in general,
17 from where I sit, the answer is you can't tell. Pain
18 is such a -- it's just kind of an amorphous entity,
19 and sometimes the pain is not exactly where the
20 problem starts from. So I think with those missing
21 parts, I'm not exactly sure how you tell exactly. For
22 instance, you know, Dr. Zucherman, that the device has

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1 no effect on the post-operative pain that results.
2 You can say clearly that the pain doesn't seem to be
3 at where the device is, but I'm not quite sure you
4 could absolve it of all responsibility of pain
5 anywhere else. And I don't know how anybody tells
6 that. So as far as the biomechanical testing was
7 adequate, I think pre-clinically the testing was
8 adequate. I think the question now is given that
9 these other questions arise, and I keep harping on
10 this fact that there's such a wide range of success
11 rates between the institutions, I think there's a big
12 missing question of just exactly how is this device
13 performing. And given that, I think there are a
14 series of tests one could now additionally perform.
15 But certainly I think the tests up until the clinical
16 results, I feel, was adequate.

17 And just to kind of throw my two cents in,
18 with all due respect to Dr. Kirkpatrick and everybody
19 else that measures the effect of motions away from a
20 level where you do surgery. It seems to me it's a
21 simple matter of energy in, that when you put energy
22 into a spine by flexing or extending, you put energy

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1 into that system. And if you lock one or more levels
2 from motion, that energy has got to go somewhere. So
3 you may not be able to measure it, but it seems that
4 energy has got to go somewhere. So either it's
5 dissipated through everything else, in which case the
6 energy changes for any different levels are minute, or
7 it's happening in such a way that it kind of escapes
8 our attention. And I guess some evidences of where it
9 might be an escape or detection phenomena is for
10 instance that the younger patients seem to do better
11 than the older patients. The fact that two-level
12 procedures seem to be a little bit more effective than
13 one-level procedures. So there seems to be some kind
14 of effect that is beyond exactly just the simple level
15 that you're treating. So it seems inevitable that
16 you're somehow affecting the levels around it,
17 although it may not be directly biomechanically
18 measured.

19 DR. YASZEMSKI: Thanks Dr. Li. Dr.
20 Ellenberg?

21 DR. ELLENBERG: No questions on this
22 question.

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1 DR. YASZEMSKI: Thank you, panel, for that
2 thorough discussion. Dr. Witten, as you've seen
3 there's a wide spectrum of answers to this first
4 question that the FDA has asked us. Dr. Finnegan
5 raised some concerns about considering altered
6 biomechanics, and that there was no animal model to
7 evaluate the biomechanics. And Dr. Li underscored
8 that by stating that it's really hard to tell at
9 different levels what's going on. And we've heard
10 from Dr. Diaz that patients with lumbar spinal
11 stenosis are going to have back pain and continue to
12 do so, regardless of the treatment. Dr. Diaz also
13 brought up the concern that the control patients
14 weren't followed as closely as the study patients.
15 And I think the summary from the panel will be what
16 Dr. Kirkpatrick said, that he doesn't think that this
17 discrepancy asked of us in Question One is clinically
18 significant.

19 Have we adequately discussed Question
20 Number One from the FDA's perspective?

21 DR. WITTEN: Yes, thank you.

22 DR. YASZEMSKI: Thanks. I'd like to

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1 suggest now that we take lunch. It's a little after
2 20 minutes past 12:00. Perhaps we could try to come
3 back here say at 1:15. Take almost an hour, then
4 we'll get started up about that time. Thanks
5 everybody. See you after lunch.

6 (Whereupon, the foregoing matter went off
7 the record at 12:22 p.m. and went back on the record
8 at 1:15 p.m.)

9 DR. YASZEMSKI: We're going to first
10 welcome back everybody to the afternoon session.
11 We'll continue with the discussion of the seven
12 questions that the FDA has asked of the panel. And
13 then we'll go on with summaries from both the FDA and
14 the sponsor, and then we'll get on to voting. We'll
15 also have another open session this afternoon.

16 We finished the discussion with Question 1
17 just before lunch, and we'll move on with Question 2
18 now. Dr. Holden? Thank you.

19 DR. HOLDEN: The full question is as it
20 appears on the screen. Based on your knowledge of the
21 biomechanics of the spine and the nature of spinal
22 stenosis, please discuss whether there is a clinical

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1 basis for pooling the outcomes of the one- and two-
2 level patients.

3 DR. YASZEMSKI: Thanks very much. We're
4 going to start with Dr. Rudicel this time, then go
5 around clockwise with Dr. Diaz and Ms. Maher. Dr.
6 Rudicel?

7 DR. RUDICEL: I'm going to be speaking
8 more clinically than biomechanically. I think
9 certainly if the baseline characteristics of the two
10 groups are similar I would see no problem with that.
11 So I would just like a refresher on the baseline
12 characteristics. And I think the second question that
13 I have related to that is how the decision was made to
14 do one or two levels. I may have missed that earlier
15 on. But basically, if you can answer those two
16 questions, I don't have any other concerns.

17 DR. YASZEMSKI: Thank you. Maybe somebody
18 from the sponsor would like to take that?

19 DR. RUDICEL: The baseline characteristics
20 of the two groups.

21 DR. YASZEMSKI: So the summary is a
22 clarification of the baseline characteristics of the

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1 one- and two-level groups, and how the decision was
2 made --

3 DR. RUDICEL: Correct.

4 DR. YASZEMSKI: -- clinically to either
5 operate on one level or two levels.

6 MS. LYSAKOWSKI: Okay. With respect to
7 the question about the baseline data, we did not
8 conduct that analysis. With regard to the clinical
9 decision about one- versus two-level, I'd like to turn
10 that over to Dr. Hartjen.

11 DR. YASZEMSKI: Thanks Ms. Lysakowski.
12 Dr. Hartjen?

13 DR. HARTJEN: You wanted me to answer
14 about determining the levels?

15 DR. RUDICEL: Yes. Not the levels, but
16 whether or not to do one or two levels. How that
17 determination was made.

18 DR. HARTJEN: It was usually based on the
19 degree of the stenosis, and if the patient had any
20 signs or symptoms that would suggest a level was
21 symptomatic.

22 DR. RUDICEL: So it wasn't MRI correlated,

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1 or anything else?

2 DR. HARTJEN: It was a combination. I
3 mean, if a patient had a moderate to moderately severe
4 stenosis at a 3-4 level, and had a moderately severe
5 stenosis at 4-5, and they had symptoms that suggested
6 possibly some L4 radiculopathy, the 3-4 was done in
7 conjunction with the 4-5 level.

8 DR. RUDICEL: Do we know if the patients
9 who had two-level were more symptomatic? If there was
10 any difference?

11 DR. HARTJEN: I believe the numbers --

12 DR. RUDICEL: I know she's saying you
13 don't know the baseline characteristics, but I'm just
14 from a clinician's point of view.

15 DR. HARTJEN: I think they're
16 approximately the same.

17 DR. RUDICEL: Okay.

18 DR. YASZEMSKI: Thanks very much Dr.
19 Hartjen. Dr. Diaz?

20 DR. DIAZ: I intuitively don't have a
21 problem with the pooling of the data. I think if the
22 selection criteria used for doing this surgery were

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