Are endoscopic ulcers really surrogates of ulcer complications?

[Slide.]

Actually, it seemed to make sense. NSAIDs reduce mucosa prostaglandins, and we know thereby causing ulcers. Ulcers can result due to erosion through a vessel or erosion through the wall of the stomach of the duodenum, and bleeding perforation or outlet obstruction, but we couldn't be sure that the endoscopic ulcers really did predict this.

Where we really found that to be true was in the development program for misoprostol, which is a synthetic prostaglandin, and based on this program, we were able to show a relationship between endoscopic ulcer data and ulcer complications.

[Slide.]

I would first like to show you the results of an endoscopy trial using misoprostol. This was a one-year study in patients with osteoarthritis or rheumatoid arthritis.

All patients were endoscoped at baseline and then endoscoped at various points during the trial. Half the patients received an NSAID plus placebo, whereas, the other patients received the NSAID plus the synthetic prostaglandin.

[Slide.]

This slide shows the results of that study. Over a one-year period, the incidence of ulcers in patients who received the NSAID plus placebo was about 30 percent. The patients who received the NSAID plus the synthetic prostaglandin was reduced in half to 15 percent, so a 50 percent reduction.

[Slide.]

We then conducted the MUCOSA trial, and this was to look at the effects of the synthetic prostaglandin on clinically relevant outcomes. It was a prospective, randomized, double-blind trial where the primary endpoint now was ulcer complications defined as bleeding, perforation, and obstruction.

[Slide.]

It was designed to parallel normal medical practice in that scheduled endoscopies were not performed, they were only performed for cause.

[Slide.]

This slide shows that we prospectively formed a GI Events Committee that provided definitions of what an ulcer complication would be in the MUCOSA trial, and these definitions really became the basis of definitions we use in the celecoxib program.

[Slide.]

Here, we show the results of the MUCOSA trial.

Over time, the incidence of ulcer complications in the NSAID-treated group increased, and those who received misoprostol plus the NSAID, the rate was reduced by approximately 50 percent.

[Slide.]

So, these prospective studies taught us that endoscopic ulcers and ulcer complications really are reliable endpoints for investigating GI safety, and endoscopic ulcers are indeed predictive of ulcer complications. The most important information that confirms this is that exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by approximately 50 percent.

[Slide.]

Now, I would like to follow up on what we knew about the upper GI safety of celecoxib in the NDA in 1998 using endoscopic ulcers, as well as ulcer complications as endpoints.

[Slide.]

At that time, we had performed endoscopies in over 4,700 arthritis patients. The results of the trials showed us that the incidence of upper GI ulcers was similar to placebo, and this was replicated, and statistically lower compared to traditional NSAIDs, such as naproxen, diclofenac, and ibuprofen.

[Slide.]

This slide shows the results of two of the studies, one of which Dr. Needleman previously described. There were three-month endoscopy trials. One was in OA patients, one was in RA patients, and each involved over 1,000 patients.

We compared the incidence of ulcers in placebo to celecoxib and then the NSAID naproxen. Celecoxib was similar to placebo at all doses even at the high dose of 400 mg twice a day, which is much higher than the approved therapeutic doses for OA and RA, and was statistically lower than that seen with naproxen.

[Slide.]

This slide shows one of the studies that was submitted at that time, which was a six-month endoscopy trial, comparing celecoxib to diclofenac. Once again, we showed a lower incidence of upper GI ulcers with celecoxib compared to diclofenac.

[Slide.]

In the program for celecoxib, we also looked at analysis of upper GI ulcer complications. Let me describe the methodology for collecting that data briefly.

We formed an external GI Events Committee that established criteria or definitions for upper GI complications, and this was defined prospectively.

The data then came from 14 randomized controlled

trials and one open-label trial, all of whom involved OA and RA patients. Patients who the investigators thought might be having an ulcer complication were then submitted to the GI Events Committee, who based on their definitions determined whether or not a complication really had or had not occurred.

In this whole process, the GI Events Committee was blinded to the trial and blinded to the study drug that the patient was on.

[Slide.]

The definitions of ulcer complications were similar to MUCOSA and are shown here.

[Slide.]

Also, these controlled trials were actually very extensive. They involved over 11,000 patient. The open-label trial involved over 5,000 patients. The controlled trials were 12 weeks in duration, the open-label two years, and the doses of celecoxib ranged from 200 to 400 mg per day.

[Slide.]

This slide shows the results of this analysis. From the controlled trials, in the NSAID-treated patients, the ulcer rate, the annualized ulcer rate was about 1.7 percent, with celecoxib it was only 0.2 percent, again, about a 7-fold reduction and similar to what was seen in

placebo and similar to what was seen in the literature for the background rates.

In the open-label trial, we also showed an incidence or an annualized incidence of about 0.2 percent.

[Slide.]

So, our conclusions at that time were that the incidence of endoscopic ulcers with celecoxib were similar to placebo and lower than NSAIDs, that endoscopic ulcer data were, in fact, predictive of the ulcer complication data, and that there was a lower incidence of ulcer complications with celecoxib compared to NSAIDs.

[Slide.]

However, the generalizability of the ulcer complication data was uncertain at that time because in the 14 randomized trials or controlled trials, many of these trial were endoscopy studies in which the patients were proven to be ulcer free by endoscopy at the start of the study.

So, about 40 percent of the patients in the analysis were really ulcer free, and the question was, well, is that data generalizable to the entire population, and in addition, most of the studies were three months in duration.

[Slide.]

So, this became the rationale for conducting the CLASS trial. We wanted to step forward and do a rigorous

assessment of the upper GI safety of celecoxib using clinically relevant outcomes in a patient population that fully represents the intended population and also to observe this with chronic exposure of celecoxib.

[Slide.]

Therefore, in brief, the design was a large prospective study. We wanted it to mirror normal medical practice, that is, endoscopies were performed only for cause. We wanted it to include a broad spectrum of patients, OA and RA patients.

We included high risk patients, that is, those who had comorbidities and those who were using low dose aspirin. As Dr. Needleman pointed out, we used the dose of celecoxib which was 400 mg twice a day, 4 times the OA dose and 2 times the highest RA dose, and the duration of the trial extensive. Patients were allowed to participate for up to 15 months.

I would now like to turn the podium to Dr. Lefkowith, who will review the trial in more detail and the results.

Safety Profile of Celecoxib:

CLASS, Long Term Safety Trial

DR. LEFKOWITH: Good morning.

[Slide.]

The celecoxib long-term arthritis safety study, or

CLASS for short, was performed to further explore the GI and general safety attributes of celecoxib.

[Slide.]

Before sharing with you the results of this landmark clinical trial, I would like to review for you the elements of study design. As the speakers before me have indicated, this was intended to be a "real world" study in that clinical practice conditions were reproduced as closely as possible.

Accordingly, the full spectrum of arthritis patients were enrolled, patients with OA, as well as RA. Moreover, patients were allowed to use low dose aspirin. Cardiovascular disease is a common comorbidity within the arthritis patient population.

Moreover, this was a stringent test of safety in that celecoxib was administered at 2 times to 4 times the RA and OA doses that were shown to be maximally effective, and compared to both ibuprofen and diclofenac, widely used NSAIDs. Again, ibuprofen has been regarded as one of the safest of the conventional NSAIDs.

[Slide.]

In discussing the design elements of the trial, I would like to review for you briefly the study objectives, the protocol design, the analytic plan, as well as the oversight committees and their function, these oversight

committees supervising the trial performance.

[Slide.]

The objectives of the trial were 3-fold. Celecoxib was to be compared with NSAIDs consisting of ibuprofen and diclofenac with respect to the incidence of ulcer complications and symptomatic ulcers. Moreover, the study intended to examine for risk factors for such outcomes, and for the effect of such risk factors on outcome.

Specifically included was an analysis of aspirin as a risk factor. Finally, the study was intended to compare the general safety and tolerability of celecoxib to the NSAID comparators.

[Slide.]

Turning now to the study design, the CLASS study was double-blind, randomized, parallel group study that was separated into two protocols that were performed contemporaneously, which were identical save for the comparator employed. They were designed to be analyzed in a pooled fashion. All patients were to be allowed an opportunity to participate for at least six months.

The inclusion and exclusion criteria were constructed in a way to replicate clinical practice. Accordingly, patients who had a clinical diagnosis of either OA or RA could be enrolled and were only excluded if they

presented a contraindication for the use of the study drugs, specifically a history of recent or active GI disease or any other comorbidities, such as serious renal or hepatic disease.

[Slide.]

In keeping with this being a real world study, low dose aspirin use was permitted. Again, cardiovascular disease is common in the arthritis patient population. In addition, patients were allowed to use antacids on a limited basis, predominantly calcium supplements for osteoporosis.

They were prohibited, however, from using any anti-ulcer drugs, either H2 receptor antagonists or proton pump inhibitors because of their propensity to either mask symptoms or alter the outcomes of interest. In addition, patients were also not allowed to take NSAIDs during the trial.

The treatments employed were celecoxib at the dose of 400 mg twice daily, again, 2 times the RA dose and 4 times the OA dose, which were maximally effective, and the doses of the comparators were 75 mg twice daily of diclofenac, a commonly used dose for the indications in the trial, and ibuprofen, 800 mg three times daily, again a commonly used dose of ibuprofen for OA and RA.

[Slide.]

The trial power calculation was based on ulcer

complication rates of 0.3 events per 100 patient years for celecoxib and 1.2 events per 100 patient years for NSAIDs.

Additional assumptions were that these incidence rates would remain constant over time and that aspirin use would approximate that seen within the context of the NDA, approximately 12 percent.

The trial was powered to include a total of 40 events, requiring the enrollment of 8,000 patients, 4,000 on celecoxib and 4,000 on the NSAIDs, 2,000 per each comparator.

[Slide.]

In terms of the analysis plan, the endpoints to be analyzed were ulcer complications, as well as symptomatic ulcers and ulcer complications. The statistics were based on an intent-to-treat analysis and included all patients who took at least one dose of study medication.

The principal statistical test was the log-rank test of time-to-event, and a step-wise comparison was planned in which celecoxib was compared to the NSAIDs combined and then to each NSAID separately.

[Slide.]

Risk factors prespecified in the protocol included aspirin use, as well as the risk factors defined by the previously performed MUCOSA trial, as well as a variety of other risk factors which Dr. Geis discussed.

[Slide.]

There were three oversight committees which supervised the performance of the trial.

[Slide.]

The committees and their membership are shown in this slide. They consisted of the GI Events Committee chaired by Dr. Goldstein and his colleagues, the Data Safety Monitoring Board chaired by Dr. Faich and his colleagues, and the Executive Committee chaired by Dr. Silverstein and his colleagues.

[Slide.]

Their charters are simplified in this slide. In brief, the GI Events Committee was to review all potential GI events reported during the conduct of the trial.

The Data Safety Monitoring Board monitored the accrual of such events and in addition performed the safety oversight function looking at general safety during the execution of the trial.

The Executive Committee was the main oversight body and administered study conduct.

[Slide.]

I would like to review for you in some detail now how information was funneled into the GI Events Committee and then judged by the committee.

Investigators were asked to monitor for the signs

or symptoms of ulcer complications, which included but were not limited to such symptoms and signs as dyspepsia, abdominal pain, the presence of anemia or melena.

If any were present, they were asked to evaluate the patient according to their ordinary clinical care patterns, but they were required or asked to obtain at a minimum stool testing for occult blood, hematocrit and hemoglobin, as well as perform vital signs for determination of volume status, and if indicated, they were to perform an endoscopy or contrast radiographic study.

Clinical care was dictated as appropriate for the work-up and the results obtained.

[Slide.]

All the information obtained by the investigators was reported to the GEC or GI Events Committee.

[Slide.]

The GI Events Committee reviewed all such reports and either diagnosed them as an ulcer complication, a symptomatic ulcer, or assigned to them some other diagnosis other than those two.

[Slide.]

Ulcer complications were prospectively defined in the protocol as either bleeding ulcers, perforated ulcers, or ulcers causing gastric outlet obstruction, and in this trial, all ulcer complications required hard documentation,

that is, endoscopic or radiographic proof of an evidence of an ulcer or a large erosion.

[Slide.]

Upper GI bleeding ulcers were the most common complication and were subcategorized into four categories again as prespecified by the protocol. Each category required the presence of a lesion.

There was either hematemesis with the lesion or the lesion demonstrated either active bleeding or evidence of recent bleeding, the presence of melena with the lesion, or the presence of blood in the stool by hemoccult testing along with some clinical evidence of substantial blood loss.

[Slide.]

Symptomatic ulcers were also defined in the protocol as any mucosal break with unequivocal depth found on a "for cause" work-up, that is, a work-up performed to investigate either a sign or a symptom of a potential ulcer complication. Again, all ulcer complications required hard documentation, that is, either endoscopic or radiographic documentation.

[Slide.]

I would like now to share with you the results of the trial, and I would like to direct my remarks first to GI outcomes and then to general safety outcomes.

In discussing with you the GI outcomes, I would

first like to describe the study population, the GI outcomes, and then potential sources of bias that may arise in assessing ulcer complications.

After discussions with the agency, we will focus today's discussion entirely on the entire study results as opposed to the six-month analyses that have been presented in the briefing documents.

[Slide.]

The demographics of the study population are shown here. Patients averaged 60 years in age and were predominantly female with the ethnic distribution as shown. Seventy percent of the patients had a primary diagnosis of OA and 30 percent a primary diagnosis of RA. No differences were seen between the treatment groups.

[Slide.]

In terms of the risk factors as defined by the MUCOSA trial, approximately 11 to 12 percent of patients were either 75 years or older, 1.5 percent had a prior history of GI bleed, and approximately 8 percent had a prior history of ulcer disease. Forty percent of the patients had a history of cardiovascular disease, again reinforcing my comment that cardiovascular disease is a common comorbidity in the arthritis patient population. No differences between treatment groups were observed.

[Slide.]

Aspirin was used by approximately 22 percent of the trial population, steroids were used by approximately 30 percent of the trial population, and anticoagulants, which were permitted, were used by approximately 1 percent of the trial population. No differences between treatment groups again were apparent.

Although over-the-counter NSAIDs were prohibited during the trial, approximately 5 to 6 percent of patients in each of the treatment groups used such over-the-counter NSAIDs, and in keeping with this being a real world clinical trial, such patients were not removed from the protocol, but were analyzed and kept within the study.

[Slide.]

Patients participated for a mean of approximately 7 months with a maximum exposure ranging between 12 and 15 months. Total exposure in the trial approximated 4,500 patient years split equally between celecoxib and the two NSAID comparators.

[Slide.]

I would like to characterize for you individually now the demographics of both the OA, as well as the RA cohort contained within this trial. OT patients on average tended to be slightly older than the overall study population and were predominantly female. These patients had long-standing OA of approximately 10 years in duration

and most had been on prior NSAID therapy up until the inception of the trial. Again there were no differences between treatment arms.

[Slide.]

The RA population within the trial tended to be younger, was still predominantly female, but had long-standing disease of approximately 10 years in duration. Most had used NSAIDs prior to the trial, and approximately 50 percent used steroids and/or methotrexate during the trial, and again there were no differences between treatment arms.

[Slide.]

In terms of the disposition of patients, approximately 50 percent or actually slightly less than 50 percent of patients completed the trial. Significantly, fewer patients assigned to the ibuprofen arm completed the trial compared to celecoxib patients.

More patients on diclofenac withdrew for adverse events compared to the celecoxib-treated patients, and more patients withdrew from the trial for treatment failure assigned to ibuprofen relative to celecoxib. No patients were lost to follow up that is, their medical status was ascertained at the time they exited from the trial, so no information is lacking because of lost to follow up patients.

[Slide.]

So, to summarize, this was a representative cohort of arthritis patients. Aspirin use was substantial, approximately 1 in 5 patients used aspirin. No information was lost because of lost to follow up patients.

Exposure to the study drugs was substantial and ranged up to 15 months. Moreover, there was a higher incidence of withdrawals seen from the study compared to celecoxib, in ibuprofen-treated patients for treatment failure, and diclofenac-treated patients for adverse events.

I would like now to discuss for you the GI outcomes of the trial.

[Slide.]

During the trial, 1,500 cases of potential ulcer complications were reported and each was evaluated by the committee. Forty-four of these cases were diagnosed as ulcer complications, 67 as symptomatic ulcers which did not meet the definition of ulcer complication, and the balance were assigned other diagnoses.

[Slide.]

In terms of the incidence of ulcer complications, there was no difference in comparing celecoxib to the NSAIDs combined as a group.

[Slide.]

In terms of the combined endpoint or the extended

endpoint, symptomatic ulcers and ulcer complications, there was a significant difference observed between NSAIDs and celecoxib with approximately a 40 percent reduction with a p-value as shown.

[Slide.]

The Kaplan Meier curves which form the basis of the prior bar graph are shown here. Again, there was a linear accrual of events throughout the duration of the trial with a p-value as shown here. This p-value is obtained from the log-rank test of the time-to-event.

[Slide.]

Because the comparison with NSAIDs was significant, we next compared with the individual comparators. There was no significant difference between celecoxib and diclofenac, but there was an approximately 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications associated with celecoxib compared to ibuprofen with a p-value as shown.

[Slide.]

The Kaplan Meier analysis of this bar graph is shown here. Again, events accrued in a linear fashion throughout the trial in both treatment arms with the treatment difference being relatively easily apparent with a p-value of 0.017.

[Slide.]

So, in sum, comparing celecoxib to NSAIDs as a group, there was a lower incidence of symptomatic ulcers and ulcer complications associated with celecoxib, and this was also specifically true of the comparison of celecoxib to ibuprofen

[Slide.]

I would like to turn now to consideration of the risk factors for such events.

[Slide.]

The prespecified risk factors are shown here and are related either to the patients' characteristics, their underlying disease, their concomitant medications, or prior medical history.

[Slide.]

Risk factors which were significant in terms of being associated with the outcome are symptomatic ulcers and ulcer complication were age greater than or equal to 75 years, a prior history of ulcer disease or upper GI bleeding, and cardiovascular disease.

Cardiovascular disease was a risk factor only by virtue of its association with aspirin use. In addition, aspirin use was shown to have a significant effect on treatment outcome.

[Slide.]

Risk factors which were not significant are shown

here and included gender, alcohol or tobacco use, or disease type or duration, or steroid use.

[Slide.]

So, this trial actually confirms the MUCOSA study risk factor analysis, and additionally indicates that aspirin use has an important effect on treatment outcome.

[Slide.]

Accordingly, we next analyzed the effect of aspirin use by examining the outcomes in both the aspirin-treated patients and the non-aspirin-treated patients.

[Slide.]

As shown here, there was no difference in the incidence of symptomatic ulcers and ulcer complications in patients on aspirin with the p-value as shown. There was, however, a 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications in patients on celecoxib as compared to NSAIDs combined with a p-value of 0.02.

[Slide.]

Turning now specifically to the comparison of ibuprofen to celecoxib, there was no difference in the incidence symptomatic ulcers combined with ulcer complications in aspirin users, but there was an approximately 2- to 3-fold reduction in non-aspirin users, this value being significant with a p-value of less than 0.001.

[Slide.]

This Kaplan Meier curve shows the analysis of the non-aspirin users comparing celecoxib to ibuprofen. Again, events accrued linearly with time over the course of the trial, and the treatment difference is readily apparent with a p-value based on the log-rank test as shown.

[Slide.]

The profound effect of aspirin in terms of the analysis of GI outcomes is shown in this graph. If one looks at the primary outcome, that is, ulcer complications, and compares celecoxib to ibuprofen, there is a 2- to 3-fold reduction in the incidence of such comparing the two treatment arms, the p-value for this comparison being 0.037.

[Slide.]

So, in conclusion, among non-aspirin users, there is a lower incidence of symptomatic ulcers and ulcer complications in patients on celecoxib compared to those on NSAIDs and ibuprofen specifically, whereas, there is no difference apparent within the context of aspirin use.

[Slide.]

Part of the robustness of this trial is that it allows us to look at both RA and OA separately, and this is a question, of course, which is of interest to practitioners, that is, how do these drugs perform in these different patient populations.

[Slide.]

In separating out the results for RA and OA, comparing NSAIDs to celecoxib, two conclusions can be drawn here. One is that the overall rates for each of the treatment arms is similar between the two arthritides.

Additionally, the treatment effect within each type of arthritis is similar. This was statistically significant within the context of RA with a p-value of 0.04 and approached statistical significance within the context of OA.

[Slide.]

We can also look at this comparison within the context of patients not using aspirin. As shown here, in RA patients not using aspirin, there is an approximately 2-fold reduction in the incidence of symptomatic ulcers and ulcer complications, this value being significant, and an approximately 2-fold reduction in OA, this p-value approaching significance.

Again the incidence of ulcer complications and symptomatic ulcers between the two types of arthritis is relatively similar.

[Slide.]

Turning now to a specific comparison between celecoxib and ibuprofen, one sees similar results. The OA and RA results for symptomatic ulcers and ulcer

complications for each of the treatment arms is quite similar between the two different types of arthritis, and the treatment differences or treatment effects are similar. This approached statistically significance within the OA cohort with a p-value of 0.11, and was significant within the RA cohort with a p-value of 0.017.

[Slide.]

Among non-aspirin users, there was a 2- to 3-fold reduction in the incidence of symptomatic ulcers and ulcer complications in OA patients with a p-value as shown, and a 3- to 4-fold reduction in the context of RA with a p-value as shown.

[Slide.]

This last bar graph is shown as a Kaplan Meier analysis. Here again, for the non-aspirin cohort of RA patients, as you can see here, events accrued literally over time during the trial, and the treatment effect is readily apparent with a p-value of less than 0.001.

[Slide.]

So, in sum, in comparing OA to RA, the incidence of symptomatic ulcers and ulcer complications is similar between the two types of arthritis. Moreover, the treatment differences between celecoxib and NSAIDs, or celecoxib and ibuprofen, are similar in the two types of arthritis.

[Slide.]

This trial taught us a lot about outcome trials and potential sources of bias in assessing the endpoint of ulcer complication.

[Slide.]

One such source of bias was the use of low dose aspirin, and that I have outlined for you in detail previously. Another potential source of bias that can enter into such trials with respect to determining the rate of ulcer complication is the withdrawal of patients with symptomatic ulcers.

[Slide:]

Now, GI outcome trials, such as CLASS, assumed that after treatment initiation, the patients would go on to develop an ulcer complication and be withdrawn from the trial as an event.

[Slide.]

However, if patients develop an earlier form of the disease, which can be found by investigators, and identified, leading to their removal from the trial, they will lower the rate of ulcer complications observed.

Now, this source of bias will only be important if there is differential withdrawal for symptomatic ulcers between treatment arms, and as you can see in the next graph, withdrawal for symptomatic ulcers alone was significantly greater among patients treated with NSAIDs

than celecoxib. This differential withdrawal then can introduce bias in the assessment of ulcer complication incidence.

[Slide.]

So, in sum, celecoxib is associated with lower incidence of symptomatic ulcers alone compared to NSAIDs, and the withdrawals for such may bias the analysis of ulcer complications in a trial such as this.

[Slide.]

I would like to turn now to consideration of general safety and summarize my comments into either a consideration of overall safety, an analysis of safety specifically focused on the four body systems shown here, an analysis in aspirin users, and an analysis of patients of all ages particularly focusing on patients who are over 65 years of age.

[Slide.]

In terms of overall safety, deaths occurred uncommonly during the trial and were large due to cardiovascular disease because cardiovascular disease is a common cause of morbidity and mortality in this patient population.

Serious adverse events, those leading to hospitalizations, occurred in approximately 10 cases per 100 patient years of exposure. There were no differences

between treatment groups either in deaths or serious adverse events.

That was also specifically true of cardiac serious adverse events or all-cause GI serious adverse events, which includes a large subset of events not restricted to the outcomes of the trial, such as esophageal, colonic, or pancreatic serious adverse events.

There were no serious dermatologic adverse events noted in patients assigned to celecoxib, and they occurred infrequently among the other treatment arms. Renal serious adverse events were also rare and consisted largely of renal calculi.

[Slide.]

The common adverse events which occurred during the trial are shown in the following two slides.

Common adverse events were significantly more common in patients assigned to diclofenac than to celecoxib, principally for those related to the GI system - dyspepsia, abdominal pain, diarrhea, nausea shown here.

[Slide.]

Rash was more common among patients assigned to the celecoxib-treated arm, but anemia, and peripheral edema were more common among patients assigned to the ibuprofen-treated relative to celecoxib.

Again, constipation as a GI side effect was more

frequently seen in patients assigned to diclofenac, and elevated transaminases in specific ALT was seen more frequently in patients assigned to diclofenac.

[Slide.]

Adverse events causing withdrawal were significantly more common in patients assigned to diclofenac compared to celecoxib. This difference was largely driven by withdrawals due to GI events, such as abdominal pain and nausea or, or hepatic events, such as elevated transaminases as shown here.

[Slide.]

So, in summary, celecoxib appeared to be well tolerated at this super-therapeutic dose as compared to the NDA database that has been reviewed previously. In addition, no dose- or duration-related increases in adverse events were seen with the exception of non-serious rash during the course of the course of the CLASS trial.

[Slide.]

I would like to now focus on the GI system. In terms of GI adverse events, any cause adverse event was significantly more common in patients assigned to diclofenac compared to celecoxib, and this difference was largely driven by the common GI adverse events shown here - dyspepsia, abdominal pain, nausea, diarrhea and constipation.

The clinical relevance of this difference in tolerability is shown by the significant difference in withdrawals. Withdrawals were significantly more common in patients assigned to diclofenac as compared to those assigned to celecoxib.

[Slide.]

The protocol also prespecified a definition of what was considered to be a clinically significant decrease in hematocrit or hemoglobin. Any decrease in hematocrit of greater than or equal to 10 percentage points, or hemoglobin greater than 2 grams per deciliter, was defined as being clinically significant.

In terms of the incidence of such decreases, they were significantly more frequent on both treatment arms as compared to patients assigned to celecoxib, that is, they are more frequent among NSAID-treated patients.

This was not simply a function of overt bleeding due to ulcer bleeds because if you remove patients with ulcer bleeds from the analysis, the incidence of such significant changes in hematocrit and hemoglobin were still significantly more common in patient on NSAIDs as compared to patients on celecoxib.

[Slide.]

These decreases in hematocrit and hemoglobin were associated with decreases in iron stores as indicated by the

iron/iron binding capacity. As shown here, these ratios tended to decrease in diclofenac- and ibuprofen-treated patients relative to patients on celecoxib.

[Slide.]

So, in conclusion, celecoxib appeared to be associated with a lower incidence of GI adverse events and withdrawals for such relative to diclofenac, and a lower incidence of clinically significant reductions in hematocrit and hemoglobin relative to both NSAID comparators.

Moreover, the decrease in iron stores that were associated with such decreases suggests and are consistent with chronic GI blood loss occurring with the NSAID comparators.

[Slide.]

In terms of renal adverse events, overall renal adverse events were significantly more common in patients assigned to ibuprofen compared to celecoxib. This difference was attributable to a significantly higher rate of hypertension, generalized or peripheral edema in patients on ibuprofen.

[Slide.]

Also, in the protocol, there was predefined definition of clinically significant renal lab abnormalities. That consisted of any patient who exhibited serum or urea nitrogen or BUN of greater than or equal to 40

mg percent, or a creatinine greater than or equal to 1.8 mg percent.

Such clinically significant abnormalities were significantly more common in patients assigned to diclofenac as compared to patients assigned to celecoxib.

[Slide.]

So, in sum, celecoxib appeared to be associated with a lower incidence of hypertension and edema compared to ibuprofen, and a lower incidence of clinically significant increases in creatinine and/or BUN than diclofenac.

[Slide.]

In terms of hepatic issues, this graph show the protocol-defined clinically significant elevations in hepatic transaminases, those that were 3 times the upper limit of normal.

Such elevations occurred in approximately 3 1/2 percent of patients treated with diclofenac consistent with the known hepatotoxic potential of diclofenac. This was significantly and substantially greater than the rates seen in patients assigned to celecoxib.

Withdrawals for such transaminase elevations were commensurate, that is, approximately 3 1/2 percent of patients withdrew from the trial for such elevations in patients assigned to diclofenac, and that was commensurately reduced in the patients assigned to celecoxib.

[Slide.]

So, celecoxib was clearly associated with a lower incidence of clinically significant increases in transaminases relative to patients assigned to diclofenac.

[Slide.]

Turning to the cardiovascular system, thromboembolic events in the trial were seen with equal frequency on all three treatment arms. That was true for any arterial or venous thromboembolic event or specifically true for the four major cardiac thromboembolic events - MI, angina, coronary artery disease, or unstable angina.

Stroke actually was seen significantly less commonly among patients assigned to celecoxib compared to those assigned to ibuprofen.

[Slide.]

Now, in consideration of patients not treated with aspirin, of course, is important because these represent patients potentially at risk for such complications, however, no treatment differences were observed between the treatment arms in the CLASS study even among this cohort for any thromboembolic event or specifically for MI, angina, CAD, or unstable angina.

Stroke again was significantly less common in patients assigned to celecoxib relative to diclofenac.

[Slide.]

Atrial dysrhythmias are shown in this slide. Atrial fibrillation was the most common atrial dysrhythmia observed in this patient population, again consistent with this being an older patient population. No treatment differences were observed for this arrhythmia or any of the other atrial arrhythmias observed or shown eh re.

Congestive heart failure was rare during the trial and it occurred with equal frequency in all three treatment arms.

[Slide.]

Looking specifically again at patients not treated with aspirin, the incidence of atrial fibrillation was low and not different between treatment arms, and other atrial dysrhythmias were rare.

Congestive heart failure also was rare within the study, and not different between all three treatment arms, but withdrawals for congestive heart failure were significantly more common in patients treated with ibuprofen compared to patients treated with celecoxib.

[Slide.]

So, overall, comparing celecoxib to both the NSAID comparators, there was no difference in thromboembolic events observed and no difference in the incidence of atrial dysrhythmias or congestive heart failure.

The GI protective effect in terms of the GI

outcomes of the trial were predominantly seen within the context of non-aspirin users. It is an important issue for clinicians and an important aspect of this trial to analyze what the safety profile is in the context of aspirin use.

[Slide.]

As shown here, selectively in aspirin users, any GI adverse event and withdrawals for such were more common among patients treated with diclofenac compared to those with celecoxib, this difference being significant for withdrawals.

Renal events again were significantly more common in patients treated with ibuprofen relative to celecoxib. Again this is within the aspirin using population.

[Slide.]

Although aspirin increased the incidence of clinically significant changes in hematocrit and hemoglobin in all three treatment arms, the treatment differences were preserved, that is, there were fewer such decreases in patients treated with celecoxib as compared to those treated with either diclofenac or ibuprofen.

[Slide.]

In terms of clinically significant renal abnormalities, that is, increases in renal function tests, they tended to be higher among aspirin users consistent with this patient population having a higher incidence of

cardiovascular disease, but the treatment difference between diclofenac and celecoxib was preserved and was significantly different between these two treatment arms.

[Slide.]

Hepatotoxicity was evident regardless of the use of aspirin, and the treatment differences between diclofenac and ibuprofen were preserved and substantial.

[Slide.]

So, in sum, even among aspirin users, the general safety profile is quite similar to the patients not on aspirin with respect to GI, renal, and hepatic safety.

[Slide.]

It is particularly important to look at safety within the context of the older patient, because the arthritis patient population tends to be older, and this slide summarizes for you in very brief form the safety in patients who are 65 years or older.

[Slide.]

GI adverse events again occurred significantly more commonly in patients assigned to diclofenac. Decreases in hematocrit and hemoglobin were also significantly more common in patients assigned to either of the two NSAIDs comparators compared to diclofenac.

Overall renal adverse events were significantly more common again in patients treated with ibuprofen, and

increases in renal function tests were significantly more common in patients treated with diclofenac. Hepatotoxicity was even more apparent within this older patient population, and again, there was a significant and substantial difference between patients treated with diclofenac and celecoxib.

[Slide.]

So, the safety profile of celecoxib appears to be maintained even within the older population.

The following two slides will then summarize all the comments that I have made in graphical form.

[Slide.]

The GI safety advantages of celecoxib, which are largely mechanism, that is, COX-2 based, are shown here. Celecoxib was associated with a significantly decreased incidence of symptomatic ulcers and ulcer complications versus NSAIDs combined and ibuprofen specifically.

Celecoxib was associated with less chronic GI blood loss versus NSAIDs combined or either of the two comparators, and associated with fewer GI adverse events versus both NSAIDs combined and diclofenac specifically.

Blood loss and tolerability differences were also evident within aspirin-using patients.

[Slide.]

In terms of general safety attributes, which may

be largely molecularly based, not mechanism based, celecoxib was associated with less edema and hypertension compared to ibuprofen, and fewer increases in creatinine and BUN compared to diclofenac, and again, less hepatotoxicity compared to diclofenac, these results being similar in the aspirin-using patient population.

Moreover, the safety profile appears to be similar in all age groups, and the CLASS trial does not substantiate that celecoxib is associated with an increased risk of cardiac or thromboembolic events.

Thank you.

I would like to now turn over the podium to Dr. Fred Silverstein who is the Chair of the Executive Committee for the CLASS trial to make some concluding remarks.

Summary

DR. SILVERSTEIN: Thank you very much, Dr. Lefkowith. Those really were three outstanding presentations.

I sit here, stand here as a clinical investigator who has worked in the field of GI bleeding for almost 30 years, and I am absolutely astounded by how much more we know now about why people bleed and who is bleeding than we knew when I started.

In 1974, I was asked by the head of the School of Biomedical Engineering at the University of Washington to

develop methods to control bleeding using lasers and heated monopolar and a variety of techniques.

I spent about a decade of my life doing that with Dr. David Auth, but then I realized in the early eighties that I didn't really know who was bleeding, and so we did a large study with the ASGE looking at the demographics of what patients were bleeding.

It was just at this time that this association with NSAIDs was becoming clear and then I got involved in understanding that and in looking at protective agents and specifically prostaglandins. Then, we did the MUCOSA trial, which kind of put these things together a big, and then I was privileged to be able to work with the COX-2 inhibitors, but I am telling you we know so much more now than we did in 1963, when I started in medical school about what causes ulcers.

Almost everything we thought then was wrong, what caused them, how to diagnose them, what to do about them, and things have really progressed with the H. pylori hypothesis and with the understanding of the importance of nonsteroidal agents. So, I think it has just been a truly remarkable advance in our knowledge, and I think the advantages of the COX-2 inhibitors are really pretty apparent.

Could I have Slide 1141, please.

[Slide.]

So, I would just like to briefly summarize what I take away from what I just heard as a consultant clinical investigator from Seattle to Searle.

The first has to do with the trial design. This was a truly rigorously designed trial. It was blinded. I chair the Executive Committee. I guarantee the blind was never broken, not once. We had no idea what groups patients were in or what medication the patients were on.

It was a randomized, blinded trial, and really the people who deserve the most credit are the patients who donated all of their effort to being part of the trial, along with the physicians, the nurses, the clinical research associates, et cetera, but I think it was a remarkable effort, and it has resulted in a huge database of very robust data, and I think the agency's analysis of the study agrees with that, that this is a very well done study with some really good data that we can use.

Of interest to me, we designed the study using the safest NSAIDs as comparators with ibuprofen and diclofenac at doses of celecoxib which were higher than at 2X or 4X, the approved dose of celecoxib for the intended population, whereas, the NSAIDs were used at the routine dose.

We didn't allow proton pump inhibitors or H2 blockers which might have masked symptoms, and kept people

in the trial until they developed a complication as opposed to saying, hey, she is symptomatic, she was endoscoped, she had an ulcer, she is coming off the trial before she developed a complication.

And we allowed aspirin, which I think is critical because you have already seen that it has a dramatic effect, and I think it is an important part of a study of this type.

So, I think it is an excellent trial design.

To look at the clinical results of the trial, I would like to turn to Slide 257, please.

[Slide.]

So, what was presented here was the ulcer complication rate in all the patients, had a trend in the right direction, but was not quite statistically significant. When the patients who were taking aspirin were taken out of the analysis, the change was more apparent.

What I am going to address in the next just few minutes is what happened, you know, what happened to the way we planned the trial versus the way the trial turned out, and one of the key things is that nothing happened to the celecoxib group.

The celecoxib group basically did what it was predicted to do. It had, off of aspirin, it had about a 0.4 percent complication rate. That wasn't the issue. The issue was why did the comparator nonsteroidals have a lower

rate, which is what created this question about why the primary endpoint wasn't quite achieved.

Could I have 256, please.

[Slide.]

So, when we look at the primary endpoint was this ulcer complication endpoint, and then as you heard in Dr. Lefkowith's presentation, the symptomatic ulcers were added to that. This was an endpoint, a secondary endpoint, which was identified prospectively in the protocol, and it seems to me to make sense to combine them.

Now, Dr. Geis, in that lovely tutorial on ulcers and NSAIDs, showed us that the difference between a complicated ulcer. So, when we combined the symptomatic ulcer, the question is should we be looking at a meaningful endpoint of combining the symptomatic ulcers, and from my clinical standpoint, I would say absolutely we should.

Steve showed us that the difference. I have endoscoped thousands of patients and hundreds, as many of you have, of bleeding patients, and the difference between a patient who has a ulcer and a patient who has a bleeding ulcer, a complicated ulcer, is really a temporal phenomenon in some cases, and I think it does make sense from a clinical standpoint to combine those two as another endpoint, an alternative endpoint.

Now, could I have Slide 124, please.

[Slide.]

Now, the question then is, well, what happened. I mean this was an evidence-based trial in terms of design. We took this huge amount of data from the MUCOSA trial, from the literature, et cetera, and designed the trial.

The question was, well, what happened. Well, things happen, and what happened was that there were changes in several aspects of the way patients were entered into the trial and managed on the trial.

What do I mean? Well, in the MUCOSA trial, as Dr. Lefkowith pointed out, we identified four risk factors as being important for increased likelihood of a complication, and you can see the incidence of each of those factors.

But look what happened in the CLASS trial. They went down. There were fewer people with these risk factors entered in the CLASS trial, and that just reflects clinical practice. Practitioners are smart, they read the literature, they know these people are at risk, and they tend to change the nature of the people they will put on a clinical trial.

So, the first factor was that there was a change in the underlying risk of the patients in the CLASS trial, which had not been prospectively anticipated.

May we have 126, please.

[Slide.]

Now, the second factor was the use of aspirin, and here I am comparing the NDA database in which 12 percent of people were on aspirin, as I believe Steve mentioned earlier, and in the CLASS trial, where 22 percent of patients were on aspirin, and this probably, once again, reflects changes in clinical practice, more people in the older population being put on aspirin prophylaxis. Whether that is the right thing to do or not for primary prophylaxis is yet another issue.

But clearly, again, the CLASS trial had this factor, which was almost twice as large numerically as the NDA data, and as we have seen from the data that Dr. Lefkowith showed us, had a very significant impact on outcome.

Can we have 126, please.

[Slide.]

The third factor I want to show you, of multiple factors we could talk about, has to do with how many patients were worked up from a GI standpoint.

In the MUCOSA trial, which was a huge body of work, about 2.7 percent of people were worked up for abdominal symptoms to determine if they had an ulcer, et cetera, but in the CLASS trial, this almost doubled to 4.8 percent.

Now, what that means clinically is that patients

were presenting with symptoms, they were being endoscoped for cause, and if they had an ulcer, they were being taken off the trial as a symptomatic ulcer, and for the reasons that Steve showed you, I believe, as he does, that ulcers become complicated ulcers. If you take an ulcer out of the trial, that ulcer cannot become a complicated ulcer. So, that is another change that occurred that could not have been discerned from the MUCOSA trial, but did occur in the CLASS trial.

122, please.

[Slide.]

The final slide is looking at the data using the combined endpoints saying ulcer complications are important, we told you what happened with that, but symptomatic ulcers are important, too, and when you combine then and you look at all patients, you see the difference that occurred with celecoxib, and especially when you take the aspirin patients out, you see an even more remarkable difference in the reduction from NSAIDs to celecoxib for the combined endpoint.

Once again this is what we expected. We did expect this type of data with celecoxib. It was rather the comparators that were the issue.

So, can we go back, please, to Slide 1141.

[Slide.]

And so in conclusion, I would say that there is a large body of data about celecoxib and the GI tract. There are about 60 controlled trials in about 25,000 patients. There is a large body of data that I think suggests that there is improved GI safety in terms of GI symptoms, withdrawal for GI symptoms, complications symptomatic ulcers, et cetera.

I think that, therefore, the CLASS trial actually confirmed the antecedent trials with the notes that I made about why there were some differences.

The safety data from the CLASS trial, which is also a large body of data, also found no new signals. There was not evidence of cardiovascular or renal effects, and it looks as if celecoxib is not any worse than NSAIDs, and in some ways may be somewhat better.

So, again, we have expanded this large safety database, and we are not finding any signals of unanticipated adverse events.

[Slide.]

So, in conclusion the NSAID problem is a large problem. The gastroenterologists and the rheumatologists didn't agree about this for a couple of decades because they were saying, hey, it's only 1 percent, I have 300 in my panel, and only seen one or two events a year.

The gastroenterologists were saying that is crazy,

half the people I see coming in bleeding are on NSAIDs.

So that has become resolved as we have understood these numbers, but if there are 15 or 17 million people on NSAIDs in the United States, and a 1 percent incidence of that is 150,000 to 170,000, it is a lot of people, and if we can cut that in half, then, you have saved 50- or 100,000 of these bleeding episodes.

So, even though the incidence is small, because of the population exposed is so large, it is a major problem. So, what I would include is that the data from the CLASS trial supports the fact that celecoxib is a safe and effective drug and is well tolerated, and I think is a real addition to our armamentaria for patients with arthritis.

Thank you.

DR. HARRIS: Thank you very much, Dr. Silverstein.

I am going to just ask now if there are any questions of clarity that one may want to ask any of the sponsors by any member of the committee? Yes.

DR. PINA: I have a whole series of questions actually.

Of the whole 40 patients that had a cardiovascular history, how many of those were the aspirin users? You have 22 percent on aspirin at entry and 40 percent of patients with a cardiovascular history, are the 22 percent part of that 40 percent?

DR. LEFKOWITH: In using the guidelines, the FDA guidelines for what is appropriate secondary prophylaxis, approximately, 16 percent of the patients, that is 16 percent, not of the 22 percent, but 16 percent were taking it for secondary prophylaxis and 6 percent were taking it for other reasons.

DR. PINA: But were those part of the 40 percent that had the cardiovascular history at entry?

DR. LEFKOWITH: Cardiovascular disease was defined as any instance of cardiovascular disease. All patients given it for secondary prophylaxis would have met that definition of cardiovascular disease.

DR. PINA: I have another question if I may. You don't talk about other concomitant use of drugs, and if you have such a high number of patients with cardiovascular disorders, I would think that among them, and many of them hypertensives, there is a high use of ACE inhibitors in this group.

Did you set aside the ACE inhibitor patients, do you know how many patients were on ACE?

DR. GEIS: As part of the normal course of the study, we did collect concomitant medications, and we can provide you that data.

DR. LEFKOWITH: In terms of the use of ACE inhibitors specifically, in incidence of patients who

entered the trial using ACE inhibitors is shown here. The incidence of those starting ACE inhibitors during the trial is shown here.

Does that answer your question?

DR. PINA: Well, it answers my question as far as entry drug criteria, but I again start wondering about the interactions of these drugs with patients on these inhibitors, particularly with the renal effects, and I am sure we will get to this a little bit later.

DR. HARRIS: Dr. Wolfe?

DR. M. WOLFE: I had a similar question. I was really surprised at the number of patients on ibuprofen, taking ibuprofen over the counter, as well, as well as naproxen over the counter, and even though they were instructed not to take H2 blockers or PPI's, were they taking it either in prescription form or over the counter?

DR. GEIS: We can present that data. Dr. Lefkowith.

DR. LEFKOWITH: Prescription or over-the-counter H2 blockers or PPI's?

DR. M. WOLFE: Prescription PPI's.

DR. LEFKOWITH: Prescription PPI's.

DR. M. WOLFE: Over the counter or prescription, both.

[Slide.]

DR. LEFKOWITH: This is for NSAID use. You were asking for PPI's or H2 blockers? I am sorry. You wanted the PPI's and the H2 blockers. We will get that up in a second.

Such use obviously did occur during the trial, and patients were not excluded if they used it over the counter. Prolonged use that was discovered during the trial of PPI use or at prescription doses, however, did lead to patients being removed from the trial as a protocol violation.

Could we have the slide, please.

[Slide.]

As you can see, this is an overwhelming list of medications which taxes my visual acuity at this distance, but maybe we can cone down in terms of H2 receptor antagonists, the use was approximately 5 percent in the trial population. I don't believe we show here any use of PPI's. PPI's were used predominantly in the treatment of events, but H2 receptor antagonists were used during the trial by the patient population.

DR. HARRIS: Yes.

DR. WOFSY: I also have two questions relating to thrombotic events, one in aspirin users and one in non-aspirin users.

What was the thrombotic event rate in the aspirin users? It seems that we had a lot in the non-aspirin users.