Gastroenterology and Urology Devices Panel

Gastroenterology and Urology Devices Panel of the Medical Devices Advisory Committee

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P R O C E E D I N G S (9:45 a.m.)

Agenda Item: Open Public Hearing

DR. MELMAN: I would like to call to order this meeting of the Gastroenterology and Urology Devices Panel. I would like to remind everyone in attendance at this meeting that you are requested to sign in on the attendance sheets that are available outside these doors.

I would like to note for the record that the voting members present constitute a quorum as required by 21CFR, Part 14. And I would like each member to introduce him or herself, to designate specialty, and position title; we will start at my far right with Dr. Sadler.

DR. SADLER: Good morning. I am John Sadler. I am a nephrologist from Baltimore and the University of Maryland.

DR. DONATUCCI: Good morning. Craig Donatucci, urologist from Durham, North Carolina, Duke University.

DR. VERTUNO: Leonard Vertuno. I am a nephrologist from Loyola University School of Medicine in Chicago.

DR. FRANK: Barbara Frank from Allegheny University in Philadelphia. I am a gastroenterologist.

DR. EPSTEIN: Mike Epstein, I am a gastroenterologist in private clinical practice in Annapolis, Maryland, and Assistant Clinical Professor

Medicine Uniform Services University, Bethesda.

DR. HAWES: I am Rob Hawes. I am a staff gastroenterologist, Professor of Medicine at the Medical University of South Carolina in Charleston.

DR. BENNETT: I am Alan Bennett, I am a urologist. I am the industry representative to the panel and I am the Vice President of Medical Affairs for C.R. Bard.

DR. YIN: I am Lillian Yin with CDRY, FDA.

DR. JETER: I am Katherine Jeter, the consumer representative.

DR. STEINBACH: I am Joseph Steinbach. I am a research bio-mathematician at the University of California, San Diego.

DR. MELMAN: I am Arnold Melman. I am a urologist at Albert Einstein College of Medicine in New York.

MS. CORNELIUS: Mary Cornelius, Executive Secretary of the Gastroenterology and Urology Branch Panel.

DR. KALLOO: Tony Kalloo, gastroenterologist, Johns Hopkins University, Associate Professor.

DR. WOODS: I am Karen Woods. I am a gastroenterologist at Baylor College of Medicine in Houston.

DR. MELMAN: Now I would like to turn the meeting back to Mary Cornelius who will read the Executive Secretary's statement.

MS. CORNELIUS: Good morning. Before we begin, I

would like to read a statement concerning the appointments to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter (dated October 27, 1990, as amended April 25, 1995) Drs. Michael Epstein, Robert Hawes, Anthony Kalloo, John Sadler, and Karen Woods and have been appointed as voting members by Dr. Bruce Burlington, Director of the Center for Devices and Radiological Health for the April 30, 1998 meeting of the Gastroenterology and Urology Panel.

Dr. Barbara Frank is a special government employee and a voting member of the Gastrointestinal Drugs Advisory Committee, Center for Drug Evaluation and Research and has been appointed as a voting member by Dr. Michael A. Friedman, Deputy Commissioner.

All of these people have undergone customary conflict of interest review. They have reviewed the material to be considered at this meeting. The FDA is concerned about conflict of interest. The following announcement addresses conflict of interest issues associated with the meeting and is part of the record to preclude even the appearance of impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by committee participants. The Conflict of

Interest Statutes prohibits special government employees from participating in matters that could affect their or their employers' financial interests.

A full waiver has been granted to Dr. Joseph Steinbach for his financial interest in firms that could potentially be affected by the committee's deliberation.

A copy of this waiver may be obtained from the Agency's Freedom of information Office, Room I2A-15 of the Parklawn Building.

We would also like to note for the record that the Agency took into consideration other matters; Drs. Anthony Kalloo, Robert Hawes and Karen Woods. These individuals reported financial interests with firms at issue, but in matters not related to topics to be discussed by the panel. The Agency has determined, therefore, that they may participate fully in today's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion will be noted for the record.

With all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to

comment upon.

If anyone has anything to discuss concerning these matters, please advise me. FDA also has a conflict of interest policy regarding persons making public statements at advisory panel meetings.

Dr. Melman will ask all persons making statements either during the open public meeting or during the committee discussion portions of the meeting to state their name, professional affiliation, and disclose whether they have any financial interest in the medical device company.

DR. MELMAN: We are now going to proceed with the first Open Public Hearing session of this meeting. If there is anyone wishing to address the panel, please raise your hand and you may have an opportunity to speak. I do not see anyone's hands raised so we will now go to the next section of the meeting.

Agenda Item: Open Committee Discussion

I am going to call to order the open committee discussion. I would like to remind public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the Panel.

The first speaker as listed on the agenda is Dr. Barbara Frank. Dr Barbara Frank will present a synopsis of the 1989 Panel Meeting considering ExtracorporeaI Biliary

Lithotripters.

Agenda Item: Synopsis

DR. FRANK: Good morning. My purpose today is first, to provide an overview of the October 1989 presentations and panel deliberations that led to disapproval of the first two biliary lithotripters. And second, to describe the specific issues that relate to Medstone's PMA.

Limiting my discussion to the PMA from Medstone alone would be a disservice to both this Panel and to the company. You need to appreciate the setting in which the 1989 Panel meeting took place.

Laparoscopic cholecystectomy nine years ago was an attractive concept, but not yet a reality, so the only alternatives for patients with symptomatic gallstones were either an open cholecystectomy, or a long course of bile acid dissolution therapy.

Neither choice was terribly attractive. Meanwhile, the first renal lithotripter had just been approved less than five years before, and Medstone's about one year before, and they had revolutionalized the treatment of kidney stones.

The machine fragmented the stones and the patient's kidney or urologist just did the rest. So, if it worked for kidney stones, why not for gallstones? So, here

you have an estimated 20 to 25 million people in the United States with gallstone disease, including close to 750,000 with symptomatic stones in the gallbladder.

You had a machine potentially capable of getting rid of those stones, and you had a section of the FDA that had traditionally been much more lenient in device approval than the process for drugs ever was.

Controlled clinical trials were virtually unheard for device approval and in fact, were usually impossible to carry out because of the very nature of devices. Consequently, any company that did or could manufacture a lithotripter joined the race to market one, including, in some cases, selling machines prior to FDA approval on the assumption that approval would be forthcoming.

Indeed, had gallstones behaved like kidney stones, we would not be here today. That they do not led Dr. John Sadler, who is here with us today also, who was Chair of the 1989 panel, to introduce the session with the admonition that consideration of lithotripsy for gallstones places the technology in a different context, and different spectrum of disease space. So, it was our duty both to evaluate the technological performance of lithotripsy in the biliary tract, and the clinical significance of that technology performance.

To understand the clinical context, review of the

PMAs was preceded by a series of presentations on the evaluation of biliary lithotripsy and its envisioned role in the treatment of gallstones.

Speakers were Dr. David Ernest, who represented the American Gastroenterology Association Patient Care Committee; Dr. Stephen Fredd, representing the FDA Center for Drug Evaluation and Research; Mary Kaye Barrick, an FDA bio-statistician; Sam della Veccia from HCFHA; and physician investigators representing six manufacturers of lithotripters. Drs. Alan Stein from Diasonix; Les Schoenfield for Dornier; Hans Fromm for EDAP; Alan Hoffman from Medstone; Robert Zeeman for Siemans; and James Adlers(?) for Techno-Med.

Dr. Ernest expressed the AGA's concern, not just about the safety and efficacy of biliary lithotripsy, but about its clinical value; its potential for abuse by application to unwarranted clinical situations; and its potential to significantly increase the costs of health care.

These concerns stemmed from the pervasive sense of urgency being generated to start using these machines, plus recognition that more than 80 percent of patients with gallstones are asymptomatic.

The worry was whether lithotripsy might be applied indiscriminately to people with gallstones, whether or not

they had symptoms, and thus could lead to morbidity from the procedure and from further results from stone fragments that otherwise would not have occurred. But these were not issues traditionally considered during device evaluation. Nor was it traditional for a national society to propose criteria for the efficacy of a device, but propose them it did.

The AGA recommended that the goal for non-surgical therapy should be to, "completely and safely rid the biliary system of stones and stone fragments, and if possible, prevent stone recurrence."

They did not consider reduction of stone size or production of multiple small fragments not cleared by the gallbladder a satisfactory endpoint, since there is no evidence that that decreases or eliminates the risk of complications from gallstone disease.

They did acknowledge that the treatment itself might not achieve this goal, but could accelerate the effects of other treatments in achieving it.

The AGA Committee also noted the lack of inclusion of control groups in published studies of biliary lithotripsy, and they concluded that these studies did not demonstrate such a clear-cut advantage of lithotripsy over currently available treatments that a rush to approval was warranted.

Dr. Fredd then described the process that lead to the approval of chenodiol and ursodiol for gallstone dissolution. Approval of cheno in 1982 was based primarily on the results of the National Cooperative Gallstone Study, which was randomized and placebo-controlled.

Only about 13 percent of patients on the higher of two doses of cheno achieved the required endpoint of complete clearance. This was significant, though, because less than 1 percent of those on placebo demonstrated dissolution.

Actigall, which was Ciba-Geigy's urso was approved in 1987, based on eight clinical studies which were not done under a common protocol, or even in a single country. Drug doses varied between studies as well.

The result was a complete dissolution rate that varied between studies from 13 percent all the way to 67 percent. In every study, though, drug was significantly superior to placebo. Because of these variations, however, pooling of these studies to serve as historical controls for comparison with the results of combined therapy with lithotripsy and urso raised questions.

Ms. Barrick spelled out the difficulties of using historical controls, especially when they include disparate studies.

The question is, does addition of lithotripsy help

the patient without increasing his risk? To answer that question, the comparison group must be identical to those receiving the combined therapy, except that they only receive the drug.

A number of factors can contribute to non-comparability of results, including differences in patient populations, in drug dosage, or even in the study used to determine the size and number of gallstones pre-treatment, or the stone-free gallbladder after treatment.

Well, would it surprise you to learn that differences in all of these factors were found, either between the different Actigall studies, or between the studies of combined therapy and those with drug alone?

Ms. Barrick also alluded to the crux of the problem. If biliary lithotripsy was as effective as renal lithotripsy, there would have been much less concern about comparability, because the difference would probably be significant, anyhow. But since the results of combined therapy were not much different from those of urso alone, how closely the data, study design, and patient factors relate to one another, or are comparable, become critical issues.

Most of the speakers representing the lithotripter manufacturers emphasized the inverse relationship between stone size and rate of dissolution with oral bile acids.

The function of lithotripter-induced fragmentation is simply to convert larger stones to smaller ones, thereby increasing the surface area, and therefore the dissolution rate so the patient can become stone-free sooner.

In urso studies, complete disappearance of gallstones occurred in about 15 percent of patients in six months, and about 30 percent at one year.

When the stones were less than 5 mm in size, the dissolution rate doubled to about 30 percent in six months and 60 percent at a year.

The machine was simply supposed to make urso's job simpler and easier, by producing these tiny stones, which may be why the studies were planned without much concern about the use of historic controls.

The other issues that arose surrounded the use of ultrasound, including consistency in the equipment used and performance of the examinations; the challenging task of determining the size and number of fragments following fragmentation, and the presence of a learning curve that seemed to vary greatly from place-to-place and person-to-person, and had to be addressed to ensure the reliability of the results.

Those were the broad issues that occupied the morning. The afternoon was devoted to review and discussion of the PMAs of Dornier and Medstone.

Dr. Norton Greenberger presented the clinical data in support of the Medstone lithotripter in combination with Actigall for biliary lithotripsy. Their indications were radiolucent gallstones less than 20 mm in size in patients with functioning gallbladders who were Stage III surgical risks or refused surgery.

Dr. Greenberger reported on 312 patients; 33 patients from the pilot study performed at Baylor, the so-called GS-001 study, and 279 patients enrolled at nine U.S. sites in GS-002.

The only differences in the two studies were that in the second study, stone size for eligibility was reduced to 20 mm, and instead of pre-treatment of all patients with Actigall, the patients were randomized to receive either Actigall or placebo for one week prior to lithotripsy.

At the baseline, the stones were less than 20 mm in 242 patients, or 79 percent. And about half the patients had solitary stones and about half had multiple stones.

After treatment, 42 of 312 patients were stone- and fragment-free on three or more consecutive ultrasounds; 27 were stone-free on one or two ultrasounds and awaiting the others; 29 had had an urgent or elective cholecystectomy; 31 were lost to follow-up; and 182 were not stone-free and were still on Actigall therapy.

The mean length of follow-up at the time of the

presentation was only six months. Calculated stone- and fragment-free rates at six months were 36 percent for solitary stones less than 20 mm; 22 percent for solitary stones larger than that; 13 percent for multiple stones less than 20 mm; and 7 percent for multiple stones that were larger.

When the 312 patients in this study were compared to 230 in the U.S. Actigall studies, stratified by number and size of gallstones, only about 12 percent of the Actigall-treated patients with solitary or multiple stones less than 20 mm were stone-free at six months. So, maybe -- maybe there was some additional benefit from lithotripsy, at least for the solitary stones.

The Medstone study differed from the Actigall trials, though, in that the percent of women, mean body weight, and average dose of urso, were slightly higher, and the mean age was slightly lower. None of these differences was felt to be significant by the investigators involved.

What the panel thought was significant however, was the striking variability in stone-free rates; from zero at three study sites, to 66 percent at one site. Even in those with stones less than 20 mm, four centers had no stone-free patients, while 58 percent of patients were stone-free at one center.

Was this difference due to differences in size and

number of stones in the patients being treated at the different centers, or did it reflect a rather dramatic learning curve?

Dr. Greenberger attributed the site-to-site variation to a probable combination of different stone characteristics, differences in the expertise and diligence of the ultrasonographers, and perhaps even differences in gallbladder contractility.

Whatever the cause, it made the use of historical controls even more problematic, and it meant that a greater number of patients had to be treated at each center, to judge consistency and the duration of follow-up had to be longer.

In terms of adverse reactions, severe ones included at least one episode of severe pain in 24 percent of patients, which compares to 100 percent with severe pain prior to treatment; pancreatitis in four patients; and obstruction of the cystic duct in one patient, and of the common duct in two.

Among mild adverse effects, transient gross hematuria and skin ecchymosis were reportedly common. What were not discussed and seemed adverse to the panel were microscopic hematuria in 64 percent and 46 percent of patients in the two trials, in addition to the gross hematuria that had been mentioned; a fall in hemoglobin of

at least one gram in about 30 percent of patients, and up to four grams in some patients; and striking elevations in transaminase levels in a couple of people.

Medication used during the procedure was also questioned, including administration of verapamil and inderal to one patient each, and atropine to a number of patients, as well as rather high doses of IV sedation.

The presence of an anesthesiologist at every procedure accounted for the IV sedation doses, as well as the administration of other medications which, believe it or not, were given to speed up the procedure by increasing the heart rate.

Panel members also asked about re-treatment indications, since 28 percent of patients had more than one treatment, but we could not find criteria for the re-treatment. Apparently, re-treatment was indicated if residual fragments of more than 5 mm in size were present after three to six months in symptomatic patients.

Other issues were raised, but the PMA was voted not approveable, primarily on the basis of the problem of appropriate controls, the need for more data from each study center, to achieve greater site-to-site consistency, the need for additional evaluation of some of the side effects and medication use, and the desirability of longer follow-up.

The FDA agreed with this recommendation and sent a letter to Medstone in January of 1990, listing the problems and suggestions for their correction. Since the panel members received a copy of that letter, as well as a 1990 open letter to firms producing biliary lithotripters, I am not going to go into those now.

I would like to conclude though with a suggestion to Panel members that you take into consideration how much has changed since the last time this PMA was submitted, both within and outside of the PMA itself.

Over the last nine years, laparoscopic cholecystectomy, which did not require proof of safety or efficacy, or FDA approval, overpayments, growing pains, and learning curves, and became the treatment of choice in the treatment of symptomatic gallstones. In fact, I suspect that many patients with asymptomatic gallstones who belched, also lost their gallbladder.

Second, because of both lap choli and the limited efficacy of biliary lithotripsy, the issue has changed from potential abuse to potential use. The opportunity to conduct a controlled clinical trial of urso alone, versus combined therapy, has probably passed as well as the number of potential candidates for non-surgical therapy has shrunk.

In terms of the submissions from Medstone, there are differences between this PMA and the one we reviewed in

1989. For example, the number of patients being reported has increased 312 to more than 750.

Instead of a mean follow-up of six months, which meant much less than that in many cases, there is now 6- and 12-month follow-up.

Evaluation of data are now by intention to treat rather than life table analyses. Raw data from the Actigall trials have been used to improve the reliability of the historical controls, although I am not qualified to say whether it succeeds are not.

Finally, ten years experience with renal lithotripsy, addresses some of the safety issues raised in 1989, as well as the issue of expertise in ultrasonography. Thank you.

DR. MELMAN: Thank you Dr. Frank. I would like remind the panel members they may ask for clarifications of any point included in the sponsor's presentation, but discussion should not go beyond the clarification issues.

Now we will begin the review and discussion of the PMA application for the Medstone international STS Lithotripter, P970042, which was intended to fragment biliary stones, with an introduction by Anil Bahalani.

Agenda Item: Sponsor Presentation

DR. GARVEY: I am Tom Garvey, so there will be an introduction by Tom Garvey. I am a gastroenterologist

practicing here in the Rockville-Bethesda area, and a consultant to Medstone; in fact, I wrote the original Actigall NDA, as well as most of this current PMA.

Let me just show you who will speak. The people here from Medstone are David Radlinski, who is the President of the firm; Fred Ryan from Novartis Pharmaceuticals, Anil Bahalani, who is the Vice President for Regulatory Affairs at Medstone; I mentioned my own name; Larry Muntz, who is a consulting statistician; Jerry Salen, who is a Professor of Medicine and Chief of Gastroenterology at the V.A. Hospital in East Orange, is affiliated with the New Jersey College of Medicine and Dentistry. He has been important in the field of bile acids for many years; John Lachin, Professor of Statistics at GW and the Director of the Biostatistics Center at GW; and Hans Fromm, who is the Director of the Division of Gastroenterology and Nutrition and Professor of Medicine at the George Washington University Medical Center.

We will start off with Anil Bahalani, who will discuss the machine itself, give you some idea of what it looks like, how it works.

MR. BAHALANI: Good morning. I am Anil Bahalani. I work with Medstone International. I will discuss briefly the Medstone Shock Wave Therapy System. The Medstone Shock Wave Therapy System is also known as the Medstone STS Lithotripter, is currently approved and sold for the

treatment kidney stones.

This slide shows the Medstone STS Lithotripter in use. The major components of the lithotripter are the x-ray machine, which is mounted into the ceiling; the ultrasound, which is the primary localization method for gallstones; and the x-ray table.

Now, the shock wave generation system is mounted beneath the patient supporting table.

The shock wave generator uses a spark gap electrode, which when discharged in a fluid medium generates a shock wave.

The shock is deflected off of an ellipsoid and transmitted through a coupling system to the patient and onto the stone where the stone is fragmented.

This diagram shows the electrode or the spark gap inside the ellipsoid, which contains fluid. There is a fluid medium all the way to the patient.

The shock wave is generated by the spark gap and it is transmitted through the fluid to the patient, onto the F2 which is the secondary focal point of the ellipsoid.

The shock wave creates compressive and tensile stresses which results and fragmentation of the stone.

The procedure used to treat a patient undergoing treatment for gallstones is that the patient lies prone on

the table and is monitored using an ECG machine.

The gallstones are located using an ultrasound and then the patient table is positioned so that the gallstone is at F2. Then the shock wave is discharged at the peak of R-wave.

Ultrasound imaging is the mode of localizing stones for biliary patients.

The procedure used is, the physician locates the stone using a hand-held ultrasound probe. Then the physician uses a light pen to indicate the location of the stone on the ultrasound screen.

That screen is then transferred onto the computer screen and the computer triangulates the stone location. Once that is done, the operator moves the table top to the place, so that the stone is now at F2 and the shock wave treatment is begun.

This picture shows the physician using an ultrasound on the patient to localize the gallstone. The gallstone image is acquired and then transferred onto the ultrasound screen where the physician marks the location of the stone.

The ultrasound screen is then transferred onto the computer screen and the location of the gallstone and the cursor that marks the stone are verified. The cursor should the right on the gallstone.

The computer then triangulates the location of the gallstone versus the F2 position. The diagram on the left, which is the cross-hairs, the center of the cross-hairs is the location of the F2 on the x-y plane.

The diagram on the right which is a straight line, the center of that is the location of the F2 and the z-axis of the up and down the plane. The red dot that you see -- -- these two red dots indicate the location of the gallstone versus the F2 in the radius planes.

The operator then moves the tabletop or the patient so that the gallstone is now at F2, and this is verified with the red dots now at the center points of the two diagrams. Once that is done, the shock wave treatment is begun.

That is the end of my presentation. The next person is Dr. Salen. He is going to talk about biliary disease.

DR. SALEN: I am Dr. Gerald Salen, Professor of Medicine at the New Jersey Medical School, and I have had considerable experience in the non-surgical treatment of gallstones, participating in the studies dealing with the NDA application for ursodiol alone in the treatment gallstones, and later on in the combination of lithotripsy plus ursodiol.

My job today is to talk a little bit about

gallstones. The first slide tells us that in the United States today about 10 percent of our population -- at least ten percent of our population -- probably have gallstones.

That gallstones in the United States is a disorder of cholesterol metabolism, really hypocholesterolemia of the bile. In contrast to the blood where there are specialized proteins which transport and solubilize the cholesterol, bile has virtually no protein, and therefore depends upon the bile acid milieu to solubilize and transport the cholesterol, and that each day about 1000 mg of cholesterol is excreted by the liver into the bile, and this is an important mechanism by which cholesterol is eliminated, and of course, underlies the problem of gallstones, because cholesterol is insoluble in the aqueous bile, and therefore if there is either an excess amount of cholesterol or an insufficient amount of bile salt or phospholipid or other factors, can precipitate out.

Now each year, at least a million new cases of gallstone disease are discovered. Whether the patients at the ultrasound examination because of symptoms gallstones or just abdominal pain, the patient turns up in the doctor's office with gallstones, and really that is part of the challenge what to do. Because at least 500,000 cholecystectomies are performed for the treatment of gallstones.

Now, out of this group of 500,000 cholecystectomies, 150,000, at least a third, are performed because of the complications of gallstones on and emergent basis -- the development of cholecystitis obstructive jaundice -- so that these patients are clearly not the ones in competition for alternative treatments.

The remaining two-thirds of patients that have cholecystectomies, and now more than 90 percent of the gallbladder operations are performed by the laparoscopic technique, these are the patients who might be considered for alternative therapy. But, again, the alternative therapy is really specific for the patient who either can not have an operation safely, or for the patient who does not want the surgery.

Really, I am saying that is a treater of patients with non-surgical techniques, that we have already offered the patient surgery. We have already promoted the advantages of surgery. And that the patient has made the decision already to either wait, accept no treatment, continue to be symptomatic, or what we are asking, can we treat these patients alternatively with the hopes of improving their symptoms because they are not willing to undergo operation?

Now it is important to note that gallstone disease is a disorder that seems to be of increasing frequency. Not

only ultrasound a more sensitive and very specific diagnostic tool, but we know that certainly women are more likely to develop stones.

The older the population gets, the more likely that stones will develop. Certain cholesterol-lowering drugs like the fibric acid derivatives increase the incidence of gallstone. Certain populations, Native American especially, are prone to develop symptomatic gallstones.

Digestive diseases such as Krohn's disease where there is damage to the terminal ileum and malabsorption of bile salts, these are people likely to have increased incidence of gallstone, and of course the entity of rapid weight loss which we all know about and which is -- I mean weight loss is popular -- seems to increase the risk for the development of gallstones. So that, we seem to be in an environment where gallstone disease is a lot more common, and will be increasingly common, and therefore looking at non-surgical therapies may be very important as well.

Now, just to reemphasize, this is a gallbladder showing cholecystitis. The problem with gallstones is that if gallstones would stay only within the gallbladder, that would be okay and probably not produce very much in the way of stones, but as you can see, the stone has migrated in the infundibulum, blocked off the cystic duct here, caused

inflammation, interfered with the venous return, and this gallbladder has become engorged.

This is a situation of cholecystitis and a reason for immediate therapy and really only surgical therapy.

Here we show a little more in detail that the stones can migrate into the common bile ducts and cause obstructive jaundice. They can impact at the outlet of the pancreatic duct, and cause acute pancreatitis.

We also know that gallstones predispose to development of gallbladder carcinoma, and we also know that very rarely the stones can pass from gallbladder into the small intestine, and block off the terminal ileum; a situation called gallstone ileus.

The point is that we cannot predict who is going to develop those complications. As a matter of fact, the development of complications may be rather infrequent, and just to say that you need treatment, you need your gallbladder out because you are likely to develop a complication of that, is certainly not a recommended therapy -- although perhaps it happens more frequently than we would like to admit.

Now, it is important to emphasize that the stones that form in the gallbladder, form because the bile is abnormal. One of the important points -- and this is bile

from a patient who has gallstones. You can see that bit of pigment there, and you can see the large number of insoluble cholesterol crystals.

In order to get gallstones, one talks about abnormal bile, and in talking about abnormal bile, one is indicating the really the liver in some way is abnormal in the formation of this bile. So that there is a chain reaction. Although the stones form in the gallbladder, they form because the bile is abnormal and part of the mechanism of alternative with ursodiol is to correct this lithogenic bile situation.

It is also very important to emphasize that not all gallstones are cholesterol; only about 80 percent of them. But here is a situation in a patient with the hemolytic anemia, and you can see that the microscope tells you that these crystals are calcium bilirubinate, but as likely in most gallstones, even those were there is bilirubinate crystals, one can see in the background crystals of cholesterol, as well or mixed gallstone.

The problem of gallstones is that, even though cholesterol is the most common underlying component, that even in the bilirubinate stones, cholesterol is also involved. And this is important for selecting combination therapy, not just fragmentations, but to treat the cholesterol -- hypercholesterolemia of the bile -- with

ursodiol.

Now, just a emphasize the size of the stone, because really, the message here today is that we are talking about stones between 10 and 20 mm as being likely. And this is out of more than 800 patients, and one can see the high proportion of stones in this area. So that, although this represents both single and multiple stones, almost 40 percent of the stones will be in this area of large stones that are not suitable for medical treatment alone, but need the addition of the lithotripsy to fragment the larger stones so that they can be dissolved and eliminated more quickly.

Now, just a brief word about medical therapy. Here are the structures of cheno- and ursodeoxycholic acids; these were the two bile acids approved by the FDA for medical therapy. You can see that actually they have almost identical chemical formulas and chemical structures; the only difference is that in ursodeoxycholic acid, the hydroxyl group that is attached at carbon-7, is in the beta configuration, meaning that in the three-dimensional world that we live in, this hydroxyl group comes out towards us, whereas cheno, the hydroxyl group is in the alpha configuration. It is attached behind this screen.

Now this little difference in the geometry of the molecule has led to increase efficacy, greater safety of the

ursodeoxycholic acids, so now the only bile acid that is available for medical treatment is the ursodeoxycholic acid.

An important point again worth restating about ursodeoxycholic acid treatment, this graph shows the time it takes to dissolve the stone, versus the size of the stone. Here we have on the y-axis here, time; on the x-axis, the gallstone size. And as you would expect, the bigger the stone, the longer it takes to dissolve.

This is a study performed in our laboratory on our patients' stones, and this has been repeated, that if you calculate the regression line here that the stones dissolve at about a millimeter a month.

If your ultrasound tells you that you have a 10 mm stone, a 1 cm stone, you are already talking with medical therapy, alone a year of therapy. If it is a 20 mm stone, it is already two years or more, and this contributes to the lack of popularity of just medical treatment alone for these stones. It takes too much time, people aren't interested and so either the people will opt for the surgery, which they have already been offered, or more likely they will opt for no treatment at all, continue their symptoms, try to control their pain and discomfort by diet and be at risk for the development of more severe complications.

In any event the urso was supposed to work -- and it interesting -- by reducing the synthesis of cholesterol

in the liver. As I said, it corrects the liver part of the abnormality to reduce the absorption of cholesterol and not to interfere with the synthesis of the detergent bile acids. All three of these probably act, and contribute to the reduction of cholesterol in the bile, which underlies the dissolution of the gallstone fragments that are present in the gallbladder.

Now just to mention lithotripsy, here is just what Mr. Bahalani showed you, that a stone in the gallbladder is focused -- the shock waves are focused on it with the idea of transmitting the shock wave energy to the stone to fragment it.

I will end my talk by just showing case that we treated. Here is an oral cholecystogram showing a single stone in the gallbladder. Here is the ultrasound showing a single stone in the gallbladder of approximately 15 mm in diameter.

Again, if we used our formula and if we treated this patient's stone with just ursodiol alone, we are talking at least a year and a half of treatment, if successful.

Here is one day post-lithotripsy, and you can see instead of having a single stone, this is the ideal situation, that there are multiple 2 mm fragments. That eight months after the lithotripsy this gallbladder is

stone-free.

In summary, lithotripsy is an effective way of breaking stones up in a small enough fashion so that ursodiol therapy can dissolve them away. It is certainly not the ideal treatment. The ideal treatment, the preferred treatment, is surgery. But when a patient cannot be operated on because of a co-existing medical problem, or if a patient simply does not want to have the operation but still needs treatment, this represents, we believe, in our opinion, a reasonable, safe, and effective option. Thank you very much.

DR. MELMAN: Dr. Salen, could you just tell us if you have a financial relationship with the company -- and anyone else who is not an employee of the company should so state that also.

DR. SALEN: I have no financial relationship with either Medstone or Novartis Pharmaceutical which manufactures the ursodiol.

DR. GARVEY: I am Tim Garvey as I mentioned before. I want to step through the Medstone studies so we can all have an idea of the data we are dealing with. I want to start however by giving a regulatory chronology -- a regulatory history of this submission.

As you have heard, Actigall was approved in the December of 1987. In April of 1988 the Medstone STS

Lithotripter was approved for kidney stones. In December of 1988 Medstone submitted a PMA supplement to the approved PMA for kidney stones for combination therapy for cholesterol gallstones.

The panel meeting which Dr. Frank described was in October of 1989. The panel met, and as you have heard, considered the Medstone and Dornier submissions, turned them both down. A non-approval letter was issued to Medstone in January of 1990.

Between 1990 and 1995, several experts in the field of gallstone disease and bile acids pressed for new attempts to get the combination approved on the basis of the historical control. We had many meetings with FDA about this primarily with Dr. Stephen Fredd, who was at the time the Director of the Division of Gastrointestinal and Coagulation Drug Products at the Center for Drug Evaluation and Research, which I were referred to as CDER as we go on here.

I want to emphasize that the submission you are considering today was primarily investigator-driven. The prime movers were Dr. Salen and Fromm, who felt that combination therapy -- and still feel that -- that combination therapy has a place for cholesterol gallstone.

In February of 1996, Medstone, Novartis, and Garvey Associates met with HFZ 470 and HFD 180, which was

Dr. Fredd's division, to discuss the submission of our updated Medstone data compared to the Actigall historical control.

After that meeting at which it was agreed that such a submission was not out of the question, although of course no commitments were made with regard to approveability, a pre-PMA, including Dr. Lachin's comparative analysis, was submitted to the Agency in February of 1997. Subsequently we had a teleconference with HFZ 470 in the statisticians who reviewed that submission, and were encouraged to submit the PMA. Again, no commitments were made with respect to approveability, but at that point no comment was made about deficiencies.

The PMA was then submitted in September of 1997. On September 11, 1997 we were notified of a change in the reviewing branch at FDA. So we were going to be under the aegis of another group at FDA.

In October of 1997, at the request of FDA we met with the reviewing division to discuss deficiencies in the submission. This was before the submission was filed. A submission has to be filed before it is reviewed, and the Agency has an opportunity to make a decision about whether a submission is fileable.

Things that make submissions not fileable are facial deficiencies that make them unreviewable; for

instance, lack of a control group.

On that very same day October 17, a refusal to file letter was issued by the division. We appealed that decision. On December 11, we met with the Office of device Evaluation to discuss the refusal to file.

On January 12, 1998, this year, a letter confirming the refusal to file was issued by the Office of Device Evaluation.

March 5, 1998, surprisingly, and happily, the submission was filed for reasons that I am still having difficulty understanding, but I am very pleased.

Now, back to the data. I want to also -- Dr. Frank alluded to the prior submission and the numbers involved. On the left is 1998, that is the current submission; 1988 is the old PMA. There are several comments in the reviews that suggest that this is not a new submission and I contend that it is in fact a new submission, and I want to contrast the two, to try to make that point.

The prior submission had the 33 patients from 001 -- and I will describe the design of that later; 190 from 002; and no patients from 004.

The current submission has, as you see the numbers here, a total of 723 patients. The original submission was 223.

At the advisory committee meeting Dr. Greenberger reported a larger number patients, the original submission, though, was 223. So there were, as Dr. Frank pointed out, three-fold more patients represented in the Medstone database than there were in the prior submission.

The source of the data for the Actigall monotherapy comparison that was discussed in the prior PMA, and at the meeting, was the Deursil which is the original name of the drug. It was a drug made in Italy. It was called Deursil and the name was changed to Actigall -- with a Summary Basis of Approval for that drug, which is FDA's case for approval. It is a public document and is not very detailed.

The source of the data for the Actigall monotherapy comparison in the current submission was the original NDA for Actigall and the case report forms, the raw data, were not available for the prior submission.

For the comparison of Actigall to placebo pre-treatment, which was the burden of the large study 002, there was no inferential analysis of this comparison in the prior submission. In the current submission, there is an explicit inferential comparison for both safety and effectiveness to explore whether addition of Actigall pre-treatment has an effect on the safety or success of gallstone dissolution with the combination.

The method of the combination therapy versus monotherapy effectiveness comparison differed. In the prior submission, essentially what was done was an apposition of a pair of curves and crude rates. No inferential analysis.

In the current submission there is an epidemiologic technique applied. It is based on a Poisson regression model. It uses a so-called direct adjustment for significantly influencing variables, such as, stone size and number.

In the safety analysis, there was known detailed safety analysis in the prior submission. In the current submission it has been written as for a CBER Analysis. The analysis is done in a way that a safety analysis for a drug would be done. There is explicit detailed discussion of death, dropouts, serious adverse events, cholecystectomies, other morbidities possibly ascribable to lithotripsy, the disease, or the drug.

In the safety analysis, with respect to clinical adverse events, for instance headache, belly ache, so forth and so on, these were dealt with as in a drug submission. There was no inferential analysis.

In the current submission, for clinical laboratory and blood pressure results, these were organized and assessed for mean changes from baseline, treatment-emergent abnormality incidence rate -- those are abnormalities that

appeared newly on therapy. Clinically significant abnormality incidence rates; these are abnormalities that reached a certain degree, a predefined degree of severity. In the 1988 submission there was no such inferential analysis.

As for the non-clinical studies, I think the Agency and the sponsor agree that there are now outstanding issues. What was seen in this very truncated series of studies that was of some interest were pulmonary hemorrhage in two dogs; but as know the right lower lobe of the lung in the dog often overlies the gallbladder in the dog and this was felt to be irrelevant when the dog developed bleeding -- not dangerous -- bleeding after exposure to lithotripsy -- that this was not thought to be relevant to the situation in man.

There was a finding of hemorrhage in the gallbladder wall which after 30 days with reversible. It was considered that Actigall was an approved drug and a lot was known about lithotripsy for kidney stones and the program was allowed to proceed.

I apologize for these slides, we were a little rushed and many of them -- not this one -- are taken directly from the briefing book, and I will try to make them clear.

This summarizes the status and the numbers of

patients randomized, the objectives, and the designs for the four studies. There were actually four studies and I want to dispense with 003 quickly. That study was abandoned. It was a study designed to compare lithotripsy alone to combination therapy.

After two patients were brought into that study after a year or so of effort, because of the reluctance of the investigators to subject the patients to lithotripsy alone, it was abandoned. So that study was never completed. So we were left with three studies: 001 which randomized 33; 002 which I have mentioned before and which involved an Actigall placebo pre-treatment comparison which randomized 637 patients; and 004, a later study which involved 99 patients.

The design of these, the objectives for these studies:

GS-001 was an open, single center and as with any trial historically and baseline control; there was no concurrent control. And I want to point out to you that all trials implicitly have both baseline and historical controls

GS-002, as I have said, involved one to two weeks of pre-treatment with either placebo or Actigall. There was random, double blind, balanced assignment of patients to one or the other pre-treatments, subsequent to which there was lithotripsy, as I will describe, and all patients were

treated with Actigall. This was an open, randomized, placebo-controlled multi-center parallel study.

GS-003, I have discussed; and

GS-004 was very similar in design to 001, but it used a mobile lithotripsy unit on the back of a flatbed truck.

The accession criteria for the three studies were essentially the same. Consenting male or female candidates for cholecystectomies were considered for entry. The age limits were 18 to 75 and inclusive. Patients with any number of radiolucent stones, at least 4 and less than 30 mm in diameter in a oral cholecystographically documented functioning gallbladder qualified for admission.

These are the central accession criteria. There were a number of others with respect to concomitant medications and conditions. There were not to be any confounders on the basis of history, physical examination, and clinical laboratory evaluation.

Studies were conducted in the following way. The patients were screened, underwent a history, physical examination, electrocardiographic evaluation, had an ultrasound and an oral cholecystogram of the gallbladder. CBC, urinalysis, liver test, as detailed there. Amylase, a CPK and renal test, BUN and creatinine.

Pre-treatment described the dose of Actigall. In the pre-treatment for all the studies it was 8 to 10 mg/kg/day in divided doses, as described in the approved labeling for Actigall.

Lithotripsy in all the studies was either under general inhaled or intravenous anesthesia, it was 2000 shock and 24,000 volts each.

Immediately following with lithotripsy, the patient underwent under ultrasound re-evaluation and this was repeated 24 hours after lithotripsy. Subsequently, there was a monthly interview and ultrasound and clinical laboratory re-evaluation for six months.

Subsequent to that there was ultrasound monitoring as well as clinical laboratory monitoring for up to 22 months in the patients, although the original studies were to be limited for a maximal scrutiny of outcomes to six months.

A repeat lithotripsy could be carried out at the investigators's discretion after 30 days for persisting fragments, defined as stones or fragments of 4 mm or greater, in greatest diameter. Subsequently, some patients underwent yet a third lithotripsy.

Here I have summarized the results of the three studies. Here's the obligatory disposition table, a little

hard to read.

Here is study 002; here is study 022 and the two subgroups, Actigall pre-treatment, placebo pre-treatment; here is study 004. Numbers of patients randomized. Withdrawn before lithotripsy for a variety of reasons. Here are the patients who underwent lithotripsy. This is the so-called intent-to-treat group, the primary analysis groups. You have 33, 307 in the AP groups; 302 in the PP groups of 002, and 81 in 004.

The patient protocol violators were identified and the evaluable subset or protocol correct analysis group is listed here -- 29 in 001; 257 in the Actigall pre-treatment group; 244 in the placebo pre-treatment group. And 55 out of 81 -- or out of 99 actually in 004.

The reason that there is such a drop-off here is that this study was abandoned when the drug was turned down.

Here are the overall -- and we can discuss the inter-center rates when Dr. Lachin speaks. It will be more relevant then.

Here are the overall results for the three studies. This again is a complicated slide; it is in the briefing book.

Here, at 6 months; here are 12 months. Here are the three studies 01, 02, and 04. Here are the Actigall pre-treatment group. The placebo pre-treatment group. Here

are the crude cross-sectional proportions of stone- and sludge-free -- this is a completely empty gallbladder as best we could tell by ultrasound.

Here are the Kaplan-Meier estimates of SSF stone- and sludge-free rates, and as you can see, at 6 months, the rates for 01 and 04 were quite similar, both crude and Kaplan-Meier estimates. Both estimates were somewhat lower in 002.

Here is the Actigall pre-treatment group which was treated the same way as the patients in this study and this study. The rates here, the crude rates, are about 18 and 20, compared to, for instance, 27 and 31 here; 24, 35 here.

What is interesting, to me at least, in these data, however is the disparity between the stone- and sludge-free rates between the Actigall pre-treatment group and placebo pre-treatment group.

The crude differences are around 18 and 20 -- that is intent-to-treat and effectiveness subset; that is versus about 12 and 14. A similar disparity in the Kaplan-Meier estimated rates.

These differences are much less apparent at 12 months, suggests that we see acceleration of clearance of the gallbladder by Actigall pre-treatment.

These are the Kaplan-Meier, the life table estimates, of the stone- and sludge-free rates in the big

study 002, in which there are four lines here. The top line is Actigall pre-treatment in the effectiveness subset; these are protocol correct patients. You would expect a higher estimate of effectiveness in this group. Here we are going up over 40 percent at about 20 months.

The solid blue line is Actigall pre-treated or the -- excuse me -- the solid green line is the placebo effectiveness subset. The dotted lines, which are difficult to see, are the intent-to-treat groups. They are both lower, topping out at about 40 percent for the Actigall pre-treated patients.

That is months after lithotripsy on the x-axis. And percent stone- and sludge-free on the y-axis.

Here we have the number of patients remaining in the analysis by time, according to these time points.

Here is a similar, less colorful display for the results of Study 001, the solid line is the effectiveness subset. The dotted line here is the intent-to-treat subset. Again, effectiveness subset protocol correct does better, obviously, but it is up around 45 percent for Study 001.

Here is Study 004, a similar relationship up above 40 out at 15 or 16 months in this study with, of course study the intent-to-treat groups having a lower estimate.

This is the results by quartile of stone size in

the big study. As you can see, this is for the first quartile with stone size, the smallest stone. Again, this is hard to see.

The Actigall pre-treatment group is on the top in red, and that goes up to close to 60 percent at 18 months. The placebo group, estimated 12 months is about 40 percent, so that is for the smaller stones, topping out at about 60 percent.

Here is the second quartile of stones. These go up to about 50 percent, 30 percent, for the placebo group.

Here are larger stones, around 40 percent, both estimates. And the largest stones, the y-axis is changed here, it goes up to 16 and at about 16 to 18 months, we are 12 to 14 percent stone- and sludge-free rates. So, size of the stone has a great deal to do with success.

The predictors of stone-and sludge-free gallbladder in these studies were summarized in this table; 02 was the large study; the following were predictors and clearly showed in this study. Age. Young patients had a higher stone-and sludge-free rate than old. Females did better. Short patients did better. Like patients did better. Patients with a low body mass index did better. Patients with a low stone overall did better.

Patients with fewer stones did better. Patients with small stone diameter did better, and, above all,

fragmentation was a very important predictor of success -- fragmentation and lithotripsy.

These predictors were evident spottily in the other study. Age, height showed in one, these were smaller studies. Number of stones, larger stone in both 001 and 004. But these are the primary predictors that we have identified.

Dr. KALLOO: A question before you go on.

DR. GARVEY: Well, sure.

DR. KALLOO: How many patients got better?

DR. GARVEY: How many patients got better?

DR. KALLOO: Yes.

DR. GARVEY: In how many patients were the symptoms that precipitated their arrival into the study, abolished?

DR. KALLOO: The indication for treatment was patients who had symptoms. Your endpoint have been clearing the stones, but how many patients were pain-free?

DR. GARVEY: I can not answer that directly. I will have to look into the slides -- we have the information.

DR. MELMAN: Did you participate in the -- I do not really know what your relationship is here with the company. Did you participate in the studies?

DR. GARVEY: No.

DR. MELMAN: You were summarizing the data for the company is that --

DR. GARVEY: Analyzing, summarizing, wrote the submission. Originally designed the protocols.

DR. STEINBACH: Another question I have is, when a patient is reported stone-free at six months, even though in some cases he was listed as leaving the study after three months -- and it happened in a few cases -- for the six months stone-free, was he brought back and verified?

DR. GARVEY: The original protocol required verification of stone freedom by ultrasound at two subsequent visits. This was largely observed in the breach. It was not done very often.

Of 187 patients, as I remember, who were stone-free in the three studies at any point, first, on study; they had a first stone-and sludge-free evaluation, I think 147 had a subsequent ultrasound.

Among those patients, there was evidence of not stone-free in 17. Among those patients, on subsequent examinations, a total of seven were again stone-free. So there were 10 patients, who about 6 to 7 percent of the population on patients declared stone-free, who might have been false-positives; that is, in the sense called stone-free, but perhaps not --

DR. STEINBACH: Or perhaps recurrence.

DR. GARVEY: Or perhaps recurrence. They do -- these cholesterol gallstones as we know do recover.

DR. SADLER: Dr. Garvey, about a third of the patients were noted on your graph as remaining on Actigall. Was that done systematically out to 18 to 20 months for those who still had stones, or was it done for those who tolerated the drug?

DR. GARVEY: It was done for those who still had stones. The dropout rates were actually low; the drug with well-tolerated.

DR. SADLER: But I noticed only about third of them were still taking it at the --

DR. GARVEY: Yes. A number of these patients were referred for surgery; had symptoms, intercurrent symptoms related to the gallstones disease, or other diseases, and we can go back to those numbers if you wish, but --

DR. MELMAN: Why don't you finish your talk, and then we will ask those questions.

DR. GARVEY: Yes. I think we need to deal with the questions, we ought to do that.

In summary, then, for effectiveness, male and female candidates for cholecystectomy, as described in the accession criteria, treated with a does Actigall of 8 to 10 mg/kg/day, and started one to two weeks before and continued after lithotripsy, carried out as described.

The intent-to-treat complete emptying rates were about 18, 30, and 35 percent after 6, 12, and 18 months, respectively. Those are unadjusted for stone size or any other relevant parameter

The predictors of success with combination therapy included reduction of gallstones present to fragments less than at least 3 mm or less; a smaller number of stones; small stones, small overall stone burden; female gender relative use, low body weight and short stature.

I will bring you quickly through safety results. We can discuss them in the question session later. There are a number of details.

The length of follow-up, the median lengths of follow-up in the three studies are summarized in this slide. The 50th percentile of follow-up was about eight months in 001; nine months in the Actigall pre-treatment group in 002; and nine months in the placebo pre-treatment group in 002; five months in the truncated study, 004.

This slide is very hard to see, I am sorry about it. It summarizes deaths, withdrawals, serious adverse events, and cholecystectomy on study. There were three deaths in the study, among patients shortly after leaving the study. All those deaths occurred in the Actigall pre-treatment group in 002, and I will discuss all three of them in detail in a minute.

With respect to withdrawals. There were a total of 7 withdrawals for lithotripsy-related problems; for other problems, there were 12, and these were considered treatment-related in 10 cases. Excuse me; 7, 12 and 10; there are 19 withdrawals there.

Serious adverse events were encountered in 45 patients; 23 of these within one month of lithotripsy; 21 of these were considered possibly related to treatment, lithotripsy or Actigall; 22 of these occurred between one a six months after lithotripsy; the majority of these as well, 15 were considered treatment-related.

For cholecystectomy, 90 of the patients in the study, about 13 percent -- 12 or 13 percent -- underwent cholecystectomy. Of these, 13 were urgent. There were no emergent cholecystectomies. Nine of these were within six months of therapy; 77 of the patients underwent cholecystectomy -- elective cholecystectomy -- within six months of lithotripsy. And this 36, within six months; 13 after six months.

Another group, 25 or so patients, were told to have lithotripsy, and we have no information on them, whether they did or did not. That is 90 cholecystectomies, about 12.5 percent. None of these patients had complicated courses -- or complications of their cholecystectomies.

The deaths in the program. There were three, as I

mentioned. One of them was a 81 year old woman, 189 days after lithotripsy, she died of complications of Parkinson's disease.

A second one was a 58 year old woman who had a cardiac arrest following a myocardial infarction 34 days after lithotripsy.

The third one was a 65 year old white man who had end stage renal disease at study entry. He died of the complications of end stage renal disease 365 days after lithotripsy.

In these patients, we found an increase in SGOT immediately after -- and I will show you that if you ask me later. I do not want to show you now. Anyhow, patients typically had an increase in OT and PT immediately after lithotripsy, and sometimes seen at 24 hours. These all regressed to the normal range. Occasional patients would have intercurrent OT or PT elevations. No patient developed serious liver injury.

The same was true for BUN and creatinine and hematocrit, hemoglobin, white counts; no significant changes, except among the patients who ultimately had complications of gallstone disease that precipitated cholecystectomy.

One thing that was seen consistently, as mentioned by Dr. Frank, was post-lithotripsy hematuria, both by

dipstick and microscopic, and an interesting disparity between the two here, possibly happening because not all patients had both examinations.

This tended to regress; this was at the 24-hour point. This slide is very difficult to understand; I know these are the studies listed across the top; here is dipstick, microscopic; here are the months along the left.

The frequency, the incidence of hematuria, tended to decline -- in some cases did not decline, but only small numbers of these patients were followed, so it is hard to tell what this really means.

What we do know is that, for renal lithotripsy, when the device is focused on the kidney or upper ureter, gross hematuria is par for the course, and has not been associated with persistent abnormality or a significant renal damage.

The safety summary, in general, then; combination therapies associated with transient hematuria. It is not associated with persistent adverse effects on blood pressure; this was also an issue with renal lithotripsy, and a post-approval study was done with renal lithotripsy, and no evidence of a persistent adverse effect on blood pressure was found in a study of about 500 patients.

It is not associated with potentially serious liver, pancreatic, renal, and pulmonary injury. We did see

any increased risk of stone- or gallstone fragment-related morbidity. It was not associated with an increased risk of adverse outcome in patients who undergo cholecystectomy for failure of gallstone clearance, or intercurrent complications of gallstone disease.

The conclusion that we draw is that, when it used -- when the lithotripsy/Actigall combination is used as in these studies, it is safe and effective for treatment of cholesterol gallstones.

DR. MELMAN: Before you go to the next speaker, maybe -- because you presented a lot of information --

DR. GARVEY: Sure did.

DR. MELMAN: Are there any other questions from the Panel at this time? Clarification.

DR. DONATUCCI: Could you clarify for me, the original submission had 200 and some patients in the -- was it the 002 study -- and now --

DR. GARVEY: 190 in the 002 study.

DR. DONATUCCI: 190, and now it is 600?

DR. GARVEY: It is 630 or so.

DR. DONATUCCI: 630. Did those patients enter the study after the original submission, or were they -- I mean, when did those patients --

DR. GARVEY: They entered after the original submission.

DR. DONATUCCI: You mean, after the Panel meeting?

DR. GARVEY: Yes.

DR. KALLOO: Question. Do you have follow-up data on those patients who originally entered into this study, meaning, your length of follow-up has remained the same, even though this is ten years ago. Do you know what has happened to those patients that were treated in the original submission? How many of them did well; how many had cholecystectomies and -- this is a ten-year follow-up.

DR. GARVEY: We do not have a ten-year follow-up, no. We know up to about two years.

DR. MELMAN: They presented mean data of eight months. The chart that you showed us showed the same eight months mean --

DR. GARVEY: Oh, these patients were followed systematically for about eight months, yes. But, they were kept track of for longer, but none for ten years; and none for much more than about 18 months or 20 months.

DR. KALLOO: So we do not know what happened to those patients after 18 months --

DR. GARVEY: No.

DR. KALLOO: -- in the original submission.

DR. GARVEY: No,.

DR. WOODS: And the data you presented on cholecystectomies, what is the denominator in terms of the

number of patients you actually had information on, that entered the study, that you were able to gather information, and out to how far? You said, after six months, but is that just through the 18 months that you mentioned, or how long are we getting information on?

DR. GARVEY: That is out to 18 to 20 months, yes.

DR. WOODS: How many patients are you talking about that you were able to track, all 600 in the --

DR. GARVEY: All 700 or so -- let me go back --

DR. WOODS: So, out of all 700 patients, truly, in that 18-month period, only 12 percent had cholecystectomies?

DR. GARVEY: 12.4 percent, yes.

DR. MELMAN: What did you say the age inclusion criteria were?

DR. GARVEY: 18 to 75.

DR. MELMAN: And the woman who died aged rapidly at 81?

DR. GARVEY: Yes, the woman should not have been -- should not have been in the study.

DR. MELMAN: So, how many other people might not have been in the study? You know, that is the --

DR. GARVEY: There were some -- there were protocol violations throughout. We included them, however, in the intent-to-treat analysis. The effectiveness subset excluded protocol violations.

DR. MELMAN: Why was one to two weeks of pre-treatment chosen as the time for pre-treatment?

DR. GARVEY: Well, it is not clear. As we all know, gallbladder bile becomes saturated in bile acids, only after three to four weeks. You reach steady state at that point, and one to two weeks was all I could get in that protocol.

DR. MELMAN: The only number of patients you could get into the --

DR. GARVEY: No, no. One to two weeks was what the sponsor wanted.

DR. WOODS: Do we only have ultrasound data for recurrence of stones out to six months on patients and thereafter, the 18-month follow-up was simply symptom follow-up?

DR. GARVEY: No. The patients were studied by ultrasound out to -- a lot of them -- out to 18 months. Not all, there were drop-outs as there are with any study.

DR. MELMAN: Do you have a slide that shows -- even if it is historical data -- the effectiveness of stone dissolution, if you just give drug treatment, compared to the --

DR. GARVEY: Well, that -- Dr. Lachin will discuss this at length in his presentation. We do, indeed.

DR. MELMAN: Okay. Any other questions?

DR. JETER: I have one. I just have one question. As the consumer representative, I would like to go back to Dr. Kalloo's question. Does anybody, from the company or anybody else, know how many patients got better?

DR. GARVEY: Do you want to try to --

DR. SALEN: Yes, because we were -- we continued to follow those patients who were willing to come in. The frequency of cholecystectomy as a complication was very, very rare. We did more than 100 lithotripsies, and in our patients, we might have had only one or two cholecystectomies in the follow-up. That does not mean that later on, people did not continue over the entire ten years, but certainly, for patients that continued to see us, to report to us, that I know of only two cholecystectomies out of the 100 patients that we performed this treatment on.

DR. MELMAN: That is not the question.

DR. JETER: Never mind cholecystectomy. How about what they ate? How about how often they had pain and so on and so forth?

DR. SALEN: Oh, the quality of -- the quality of life was much improved. I mean, here you are talking about patients that had serious pain that needed treatment, that had a restricted diet. Very often, these people had associated medical conditions and the quality of their life was made miserable by the superimposition of the gallbladder

diet.

After their treatment, they had a much more liberalized food intake. One could see that by the fact that these people were gaining weight. But, their restrictions were limited. They could go out to restaurants.

I think you are dealing with patients who were treated and the treatment was effective, and it was reflected by an improvement in the quality of life. The point is that the removal of the gallstones was our endpoint, but to the patients, it was how they felt. And the fact that they felt better was really what was the indication to us that this treatment was a successful and effective treatment.

DR. EPSTEIN(?): But you collected no quality of life data?

DR. WOODS: That is right, do you have any of that?

DR. EPSTEIN(?): You have no quality of life data to present?

DR. FRANK: They do have data for the occurrence of post-lithotripsy biliary pain; you considered that a complication, didn't you -- I mean, an adverse effect. Don't you have that rate?

DR. GARVEY: But you are talking about pain the

first month; that, or within 24 hours. That was common in the patients -- at least a third of the patients had pain after the lithotripsy reflecting the break-up of the stones and passage of some of the fragments in the bile. But, afterward -- remember, all of the patients were started on ursodiol Actigall at that time, and continued through that period, and throughout the treatment period and often beyond the treatment period, because the patients felt better while they were taking the Actigall. There was an elimination of this pain, so that the initial pain associated with the fragmentation of the gallstone, and passage of the fragments, was very short term, and was almost abolished, and the patients felt quite well during their treatment, and there is data with Actigall showing that long before the stone fragments are completely gone and successful medical dissolution, that the patients are feeling much, much better. So that that part, I think seemed to be well-documented.

DR. EPSTEIN(?): I think that is one of the points, isn't it, Jerry? I mean, people get better on Actigall alone, so we do not really know whether the lithotripsy helped them feel better, if indeed, they really did, since we do not have very good data there. But it might be drug alone, is that not the case?

I mean, people who are treated with monotherapy,

Actigall alone, studies support the fact they do better symptomatically, don't they?

DR. SALEN: The Actigall might improve the bile, but the Actigall does not dissolve these big stones. We felt that the improvement --

DR. EPSTEIN: But, does it make symptoms better?

DR. SALEN: Well, I think we have to -- we believe that the symptoms are in part related to the stones in the gallbladder -- in other words, these were all symptomatic patients who came to us, and that we felt that the treatment required the elimination of the stones for completeness in therapy.

If you go back to the chenodeoxycholic acid study, where they had very careful symptom follow-ups, their patients were not completely symptom-free until after the gallbladders were free of the stones. So that there is a symptom relationship to the stone component, as well.

DR. SADLER: But the stone- and sludge-free percentage is less than 50 percent, at the most optimistic, and yet you are painting us a fairly glowing picture of improved quality of life for your patients.

DR. GARVEY: No, I think Dr. Salen is not. I am certainly not. Don't forget, these are ten year old studies. The principle objective was to assess the presence or absence of stones, the effect on the presence of stones.

Symptoms were assessed, and we do have some data, and can probably address, to a certain extent, this question.

I cannot paint a glowing picture because I really do not know the answer. But do not forget, these were ten years ago. We did not even know the term, quality of life at that point.

DR. MELMAN: Well, it wasn't -- we knew quality of life, didn't we? Don't say that.

DR. GARVEY: No, how to measure it.

DR. MELMAN: Wait. Dr. Donatucci asked when the extra patients were added, and you said after the last submission, but now you are saying it is ten years old. So, when were the additional patients added, above the last submission?

DR. GARVEY: These studies were designed more than ten years ago. The last accessions for these patients were about a year after the advisory committee meeting. So, it is perhaps nine years or eight years.

DR. MELMAN: Let's go on to the next speaker and then we will --

DR. GARVEY: Sounds like a good thing. Okay. The next speaker will be Dr. Lachin, who will address the issue of the combination therapy versus Actigall comparison.

This is obviously very important, because the central issue here is actually not whether this combined

intervention is effective; it is clearly effective. Gallstones do not disappear by themselves for more than one or two percent over two years.

The question is, whether the data allow one to conclude that the FDA's combination policy has been satisfied; that is, whether we know that both of these interventions contribute significantly to the wanted outcome.

DR. LACHIN: As Tom showed, I am Professor of Statistics at George Washington University, and I do not have any interest, either in Medstone, or in Novartis. I am doing this as a consultant.

I would like to start my presentation with a brief summary of the issues that one faces in conducting an assessment of treatment effectiveness, based upon either a randomized study, or an epidemiologic approach.

Now, the randomized clinical trial provides the principle benefit that the results are expected to be free of patient selection biases. By tossing a coin, we construct two groups of patients that we expect to be similar, with respect to characteristics, both measured and unmeasured. However, randomized clinical trials are not in and of themselves free of bias.

In order to say that a clinical trial -- a randomized clinical trial -- is free of bias, there are

additional criteria that must be met. So that randomization is necessary, but alone is not sufficient.

These additional criteria relate to the completeness of the data, and the unbiasedness with respect to the outcome assessments. And in every randomized clinical trial, there are some missing data in that missing data may introduce a bias. The idea that randomized clinical trials are always unbiased does not apply.

Now, an epidemiologic assessment, does not have the advantage of starting with a randomized. And one must start this process by recognizing that the results will be open to biases that may be due to differential patient selection -- by that, I mean, differences between the cohorts with respect to the patient characteristics. They may differ with respect to various aspects of the treatments applied; the way that the outcome assessments were conducted, among many other possible factors.

Now, over the years, there have been a number of statistical approaches that have been developed to control for biases due to differences in patient selection. This is biases due to differences with respect to the distribution of the patient characteristics. But we are now adjusting for only one of the possible sources of bias. And after one does an analysis, adjusting for these differences as best one can, we must then consider whether other, uncontrolled

biases could explain the differences observed. That is the basic issue in evaluating the results of a non-randomized study. Is it possible that some other remaining biases could have produced the treatment differences that are observed?

What I will do today first is show you the results of the adjustment for the differences in patient characteristics as best we can, and then we will address concerns related to other possible sources of bias.

Now, what about methods of adjustment? There are two basic classes of statistical procedures that can be used to conduct an adjustment. The first is what is called an indirect adjustment.

Many of you may be familiar with the idea of a Mantel-Haenszel stratified adjusted analysis. Another approach is to pool the data from all the subjects together, and to then use a regression model to obtain an adjusted assessment of the treatment effect.

Now, basically, this approach assesses the differences between the treatment groups, or the treatment group effect, after accounting for the influence of other covariates in the combined population. And because we are using a model to do this, the model assumes that each covariate has the same effect in both treatment groups, which does not always apply. And it is possible to, in

fact, conduct a statistical test of this assumption.

Now, if the covariate effects differ between the two cohorts, then this approach -- the most likely outcome is that this approach will lose some sensitivity. You will lose power. It may not, in fact, result in any difference in the estimate of the treatment group effect, but it may be less powerful than other approaches.

On the other hand, direct adjustment takes a different approach. In direct adjustment, what we do is we estimate the probabilities of the outcome from one group, and then we apply that to the subjects in the other group. And by doing so, we can then obtain an adjusted estimate of the expected number of events, had the patients in the experimental group actually been treated with the control treatment.

Now, this is a much older approach than indirect adjustment. This in fact predates indirect adjustment. Some examples are the use of age standardization to look at differences in cancer rates over time. The National Cancer Institute has been using direct adjustment methods going back to the 1940s, to look at age-specific cancer death rates.

This is also widely used by the National Center for Health Statistics, that publishes a number of monographs on the use of direct adjustment methods, in their monitoring

of the health of the nation.

Now, the use of regression models as a direct adjustment approach, dates back to Jerry Cornfield's reanalysis of the results of the University Group's Diabetes Program in 1971. To my knowledge, that is the first time a regression model was used to estimate these probabilities.

More recently, Gastwirth and Greenhouse in an article in Statistics in Medicine in 1995, described the statistical properties of using a regression adjustment with logistic regression.

Now, if you are interested, I have some very simple slides that can show you the difference between a direct versus an indirect adjustment, but I will leave it up to you if you would like for me to show that later.

Now, let's talk about the Actigall database. There were eight studies that were conducted in the United States, the United Kingdom, and Italy, during the period 1976 to 1984.

All total, 816 patients received Actigall treatment, some of them in combination with other diet therapies in one of the studies. There were 799 patients that received Actigall alone.

Now, these studies included patients with common duct stones, and also patients with non-functioning gallbladders, whereas for the Medstone/lithotripsy studies,

patients with functioning gallbladders were required, and patients should not have had any calcification of stones, although some were enrolled who did.

This leaves 715 patients that meet the same eligibility criteria as in the Medstone studies. Of those, 671 had complete information on the reduced set of covariates that we required for the direct adjustment analysis, and of these, 622 had complete covariate information on all of the covariates.

Now, these patients received Actigall doses ranging from 4 to 15 mg/kg/day. Patients were followed for up to 24 months in some studies, and in all of these studies, oral cholecystography, or OCG, was used to assess gallstone size and number at six-month intervals.

To do the adjusted analysis compared to the Medstone combination therapy experience, it was required that we construct a regression model that would allow us to conduct a comparison of life tables. And to do that, we developed this methodology using a Poisson regression model.

The outcome is stone- and sludge-free at any point in time up to 18 months of follow-up. The potential covariates that were included in these analyses were age; gender; body weight; percent ideal body weight; the country in which the study was conducted -- the United Kingdom or Italy versus the United States); the dose of Actigall

received, which was grouped into three broad categories; single versus multiple gallstones; and then categories of maximal gallstone diameter -- less than 5 mm, 5 to 10 mm and greater than 10 mm.

It was not possible to use the exact gallstone diameter because many of the studies in the Actigall database only reported the category of gallstone size, so this is a categorization that is being imposed on us by the actual Actigall data.

Alright, now, this is just a summary of the regression model that was used to conduct these analyses. The covariates that entered into this model were single stones versus not; gallstone size using the medium or 5 to 10 versus small, or less than 5; large versus small stones; whether the subject was from the United Kingdom versus the United States; and then the subject's role treated as though they had received the highest mg/kg of greater than 9.4 mg/kg.

All of these effects are highly significant, and we had a different effect for some of these, over the 7- to 12-month period, from the 1- to 6-month period, and the 13- to 18-month period, which is what we call statistically a time-dependent covariate analysis.

In this Actigall cohort, the basic idea is that the patients with single stones have a 57 percent greater

risk, or likelihood of becoming stone-free. As the size of the stone increases, the risk of becoming stone-free decreases.

Patients from the United Kingdom had a somewhat lower risk of becoming stone-free than patients in other countries; and those with the highest mg/kg dose had a higher risk of becoming stone-free.

Alright, now, let's talk about the Medstone studies. As Dr. Garvey indicated, there were three studies conducted in the United States from 1988 to 1990, n = 769, all total.

The bulk of these were enrolled in the GS-002, which was a randomized comparison of no Actigall pre-treatment versus pre-treatment.

We defined an intention-to-treat cohort, and of these, I looked at 689 patients who were free of calcification of gallstones on entry. As I indicated, that was one of the original eligibility criteria, but there was a fraction of patients that were enrolled with calcified gallstones, so they have been excluded from these analyses.

We also identified the efficacy subset cohort, which contained 585 subjects again, with the same covariate information that I just showed you that was used in the Actigall analysis. And these patients were followed for up to 18 months with ultrasound assessments as frequently as

monthly in most patients.

DR. KALLOO: Question. Why were the patients with calcification treated, included?

DR. LACHIN: Included in what?

DR. KALLOO: In the intention-to-treat?

DR. LACHIN: Why were they enrolled?

DR. KALLOO: Yes.

DR. LACHIN: I have no idea, but it was clear that they should not have been enrolled and the indication that is being requested is for treatment of non-calcified gallstones in a functioning gallbladder.

This is a summary of the differences between the cohorts. Looking at the subset of patients -- as I just indicated -- that have covariate information, roughly 60 percent were female in both cohorts. The age distributions were very comparable; however, there was a major difference with respect to the distribution of body weight and percent ideal body weight, both among males and females. Those in the Medstone cohort were significantly bulkier, if you will.

50 percent of the patients in the Medstone cohort had single stones versus 31 percent in the Actigall cohort, and the distributions of gallstone size also differed; roughly a third of patients in each category in the Actigall cohort, only 2 percent in the smallest category in the Medstone cohort, and 65 percent in the largest category of

gallstone size. Because of this small fraction here, in the comparative analyses, we have lumped those less than 5 with 5 to 10, so the comparative analyses will compare all those less than 10 versus greater than 10 in the two cohorts.

This slide describes the way the direct adjustment works. And for this purpose, I selected the data from one of the clinics in protocol 002, and all of these patients received Actigall pre-treatment. I am showing you here, two patients in this site.

This data is represented where a 0 means no and a 1 means yes. So, the first patient does not have a single stone -- meaning the patient has multiple stones. There is a 1 in this category, which means that the patient has a maximal gallstone diameter greater than 10 mm. The patient is treated as though the patient came from the United States, and received a dose of greater than 9.4 mg/kg/day. This patient was followed for eight months.

Now, based on that information, I can use the Actigall regression model to ask, what is the probability that this patient, over eight months, would have become stone-free, if treated with Actigall alone?

Had this patient been treated with Actigall at a dose greater than 9.4 mg/kg, there is a 9 percent chance that the patient would have become stone-free.

Now, the second patient has a single stone that is

from 5 to 10 mm in diameter; and again we say, what would happen if this patient were treated in the United States at a dose greater than 9.4 mg/kg? And this patient was followed for 18 months. So we asked, what would the probability be of becoming stone-free at some time during that 18-month period? Based on the regression model, we estimate that it is 72 percent.

We can do this for every single patient in this clinic. Of the 16 patient in this clinic, 8 patients became stone-free. However, had those 16 patients, with their characteristics, received the Actigall monotherapy, we estimate that 3.3 would have become stone-free.

Now, this 3.3 is the expected number to become stone-free, had this group of 16 patients been treated with the Actigall monotherapy.

Now, statisticians do not worry about fractions. If you take a coin and toss it ten times, what is the expected number of heads? It is five.

If you toss the coin nine times, the expected number of heads is what? 4.5. You see, it is a fraction. That does not bother us at all.

DR. KALLOO: It is 3.3 for what length of time?

DR. LACHIN: I am sorry?

DR. KALLOO: You said you expect 3.3, but what period of time?

DR. LACHIN: If I have 16 patients with these characteristics, followed one for 8 months, one for 18 months, one for 10 months, then it is 3.3. So, it is for the average period of time. I did not compute the average for this subset, but in all of the tables in the analysis, I show the average period of time.

DR. WOODS: Is this the raw data from the study?

DR. LACHIN: This is the raw data from the Medstone studies.

DR. WOODS: So, the months followed column indicates when the patient fell out of the study; they were not followed any further beyond that period of time.

DR. LACHIN: Precisely. Right. Alright? So that is the basic idea behind the direct adjusted approach. And that is central. Are there any questions about this?

DR. HAWES: Just, again, one question relating to the follow-up. So, the estimated 3.3 patients that were going to dissolve on -- be stone-free on monotherapy, is that for the same amount of time as what they were followed, which --

DR. LACHIN: Precisely. Precisely.

DR. HAWES: So most of those patients were followed only for a month, or a lot of them were followed only for a month.

DR. LACHIN: Well, but they became stone-free.

DR. HAWES: So that --

DR. LACHIN: So, that is what they contribute to the analysis.

DR. HAWES: So, 3.3 would become stone-free, but four of them would have only gotten one month worth of monotherapy.

DR. LACHIN: Precisely. Right.

DR. HAWES: And only, what, two, three -- like five of them would have gotten a full 18 months of --

DR. LACHIN: Right. Right. Basically, what you want to do is to say, for each individual patient, over the period of time that they were observed, what would be expected had they received the Actigall monotherapy?

Any other questions about this? As I said, this is the fundamental idea behind doing this.

DR. MELMAN: You are estimating that it is 2.4 percent per month on Actigall will become stone-free, according to your analysis, right?

DR. LACHIN: I am sorry, 2.4?

DR. MELMAN: Yes. Because after one month, you expect that someone who is on Actigall alone, that 2.4 percent of those people will be stone-free.

DR. LACHIN: Where is that?

DR. MELMAN: Patient 33, for example.

DR. LACHIN: Well, this is a patient who would be

followed for one month, with these characteristics.

DR. MELMAN: Right.

DR. LACHIN: If I have a patient with a different characteristics, then the probability would be different. So, this particular patient has a gallstone in the 5 to 10 mm range as a maximal diameter, but the patient has multiple stones.

The patient with single stones would have a different probability.

DR. HAWES: Question for you. If you readjusted those figures so that they all had uniform follow-up, what would then be your expected Actigall probability?

DR. LACHIN: I did not do that, and that would -- to me, would not be a fair basis of comparison, because what we want to say is that, you know, if I take, for example, this patient who was followed for eight months, and say, what would happen had that patient received Actigall monotherapy for 18 months?

I do not know what would have happened to that patient had the patient received the combination therapy for 18 months. All I can say is that, after eight months, this patient still had stones.

DR. HAWES: It is not a fair statistical test to adjust out --

DR. LACHIN: Every patient at 18 months because I

do not -- no, that to me does not make sense, because I do not have 18 months of data for every patient that received the combination therapy. So now you are comparing apples to oranges. Do you see what I mean?

I mean, this is the fundamental idea --

DR. KALLOO: If you look at patient 24, who was treated, followed up for eight months, his probability was 20 percent.

DR. LACHIN: Right.

DR. KALLOO: And if you look at patient 33, with the identical characteristics, who was treated for one month, his probability is 24 percent?

DR. LACHIN: That is right. And the reason --

DR. HAWES: 2.4 percent.

DR. LACHIN: 2.4 percent.

DR. KALLOO: 2.4 percent.

DR. LACHIN: The reason for that is that the effects of the covariates over the first six months are different from the effects of the covariates during the second six months. And so, the probabilities will differ, depending on how long a patient was followed, when the patients had the exact same configuration of characteristics at baseline.

Alright, well, let me go on. We can come back to this, but this -- I hope that everybody understands the

basic idea. We are using the probabilities estimated from the Actigall data, and applying them to every subject in the Medstone cohort, assuming that those subjects were treated in the United States at a dose greater than 9.4 mg/kg/day. That is the central concept.

DR. HAWES(?): You had the U.K. on the slide, was that a typo?

DR. LACHIN: No, the patients in the United Kingdom have a lower probability, so I am treating them all as though they came from the United States.

DR. HAWES: Okay.

DR. LACHIN: The same way patients who received a lower dose of Actigall had a lower probability, but I am treating them all as though they received the highest dose of Actigall. Okay?

From this, we can then summarize the data as follows: 16 patients; an observed stone-free rate of 50 percent; an expected stone-free rate of 21 percent. I did not put the average number of months exposure on this slide, although the tables that are in my reports do include that.

From this, we estimate a relative risk or a relative effectiveness, of 2.4, meaning that the patients who received the combination therapy had 140 percent greater likelihood, in this clinic, of becoming stone-free.

I can then compute the lower and upper 95 percent

confidence limits, p-value from that comparison, although with a sample size of 16, the p-value would be somewhat unreliable. But when we are dealing with hundreds of patients, the p-values are highly reliable.

Now, in the report, we perhaps overdid this, but we did lots and lots of analyses. We did analyses looking at all subjects, and we did this by study, using the combined groups in 002 in each of the two treatment groups in 002. And then by 004, and then, most importantly we did this for all patients who received the Actigall pre-treatment.

This would be patients in GS-001, Group 2 of GS-002, and GS-004. We did an analysis in the intention to treat cohort for up to 18 months, using all subjects, and then subjects with stones less than 10 mm, and then greater than 10 mm in size. This is in Table 6 of the original report.

We then did likewise for the evaluable subset; that is presented in Table 8.

Now, because many of the studies were designed to follow all patients for at least six months, we also did analyses in intention to treat and the evaluable subset, looking only at stone-free rates over the first six months, and those are presented in Tables 10A and 10B, respectively, in the report.

Now, I am only going to focus on the analysis of the all pre-treatment subjects combined, because that is the group that directly relates to the requested indication.

The indication is for use of the combination therapy in conjunction with a period of pre-treatment. So, I am only going to present the results using the Actigall pre-treatment combined.

This is a summary of the relative effectiveness over an 18-month period for the intention to treat cohort. There were 402 subjects that received the Actigall pre-treatment, 28 percent became stone-free in the Medstone studies, using the combination therapy.

Using the same technique I just showed, if we apply the Actigall regression model to every one of these 402 patients, we estimate that 18 percent would have become stone-free; the relative effectiveness is 1.6, or 60 percent improvement in effectiveness with the combination therapy, which is highly significant.

Among those with smaller stones, the effectiveness rates are increased, more so with the combination therapy, so that the relative effectiveness increases; again, it is statistically significant.

Among larger stones, the relative effectiveness with both treatments is somewhat reduced; however, the relative risk is still meaningful at 1.48, and is also

statistically significant at the .05 level.

This shows the actual life tables giving the cumulative incidence of becoming completely stone- and sludge-free, or having an empty gallbladder. And see that for month one, there is an increase in the stone-free rate, and that this difference persists for up to 18 months, based on the observed cumulative incidence in the combination therapy, from the Medstone studies and the estimated cumulative incidence based upon the regression model from the Actigall monotherapy studies.

DR. MELMAN: Could I ask a question there? Could you put that back? How is the difference of about, what looks to be 10 percent proportion, translated into a relatively effectiveness of 62 percent greater? So, if you look at the graph, the people that had combination therapy at any time are about 10 percent -- it looks like 10 percent more of those people were stone-free --

DR. LACHIN: That is right. That is right.

DR. MELMAN: The number that we are looking at is 62 percent more people, so --

DR. LACHIN: Well, I --

DR. MELMAN: -- how does that come about?

DR. LACHIN: Well, in life table analyses, there is no single measure of relative effectiveness. The measure of relative effectiveness that I computed in the tables is

just a simple ratio of the proportion of patients, it is a mixture of patients with different periods of follow-up.

Whereas here, you might say, well, gee, what is the relative effectiveness at six months? Or, what is the relative effectiveness at 18 months? In which case I would take this point divided by this point. Right? Those relative effectiveness, you know, it will depend where you are along the curve.

As I recall, the average period of follow-up was about nine or ten months, and so the relative risks that were computed, just based on the average proportion, should be pretty close to the relative risk computed at the midpoint of these curves. I have not done the comparison, but that is what I would estimate.

DR. KALLOO: But isn't that a more important indicator?

DR. LACHIN: Isn't what a more important indicator?

DR. KALLOO: Of actually, the contribution to the monotherapy?

DR. LACHIN: What is more important?

DR. KALLOO: The question is, how much of a role is the monotherapy playing in the elimination of stones?

DR. LACHIN: You mean, in terms of the combination therapy?

DR. KALLOO: In terms -- yes, what is -- how important is it? Isn't that the crux of the question?

DR. LACHIN: Well, compared to what?

DR. KALLOO: Monotherapy, what is the -- to what extent does monotherapy affect the complete clearance -- to what extent does the Actigall effect clearance, as opposed to combination therapy?

DR. LACHIN: What I think you are asking -- and this is the reason why I asked, compared to what -- I think that you are asking is -- and correct me if I am wrong, because I do not want to answer the wrong question -- is, what is the contribution of the Actigall, compared to patients who did not receive Actigall, but still received lithotripsy?

DR. KALLOO: Correct.

DR. LACHIN: Well, we do not have data to address that, because we do not have a cohort of patients that were treated with lithotripsy alone.

DR. FRANK: Can I make a comment here? I think that some of our Panel members are looking at a straight line, say, at 10 months or at 12 months. If you would look at the proportion of patients who are stone- and sludge-free, at the same proportion, you see that the difference between the two curves is about three months. So, for the same amount of success, it takes three months less to

achieve it when the patient has initial lithotripsy.

DR. LACHIN: Right. That is another good way of looking at this. And in fact, for the relative risk, the way I computed it, the relative risk can be interpreted, or the reciprocal of that relative risk can be interpreted as the reduction in the fraction of time it takes. So, I mean, those two concepts are related. I could have presented the data that way.

DR. MELMAN: Any other questions? Do you have other information you want to present?

DR. LACHIN: Oh, yes, we -- I am afraid I have a lot more that I plan to present.

DR. MELMAN: You had 15 minutes in our schedule, so --

DR. LACHIN: Yes, I know that. I am sorry. I will cut out a couple of slides as we go through this. This is now the effectiveness among those with smaller gallstones, and we see a huge increase in effectiveness over the first six months of those with the combination therapy that then stabilizes over time, which is a rather remarkable increase in effectiveness during the immediate post-lithotripsy period.

DR. EPSTEIN: Dr. Lachin, a question again and that is, not with idealized Actigall therapy, but with the Actigall monotherapy that was given related to the

historical controls from the Actigall --

DR. LACHIN: No, this is assuming that every one of the Medstone patients would have received greater than 9.4 mg/kg.

DR. EPSTEIN: But, over that variable period of time, or all --

DR. LACHIN: Over whatever period of time that patient was treated.

DR. EPSTEIN: So it is not idealized therapy with Actigall --

DR. LACHIN: I would say it is idealized therapy. Idealized therapy is greater than 9.4 mg/kg.

DR. EPSTEIN: But the time variable is anywhere from one month to 18 months.

DR. LACHIN: That is right. But, I mean, now we are back to the issue of, what do you compare? And that is the reason why I think with this approach, you can now do a valid comparison at each month, because the patients that are contributing to the analysis at, say, six months, are the ones actually followed for six months. And now, I have compared those treated for six months with the combination therapy, versus those that -- what would have been expected, had those patients been treated for six months with the monotherapy.

DR. EPSTEIN: But is not a comparison with

patients who would be treated with monotherapy according to the recommended course of treatment.

DR. LACHIN: Which is up to two years?

DR. EPSTEIN: Yes.

DR. LACHIN: Right. That is a different question.

DR. EPSTEIN: Okay.

DR. MELMAN: Why don't you finish your presentation and we will hold questions until after you are finished.

DR. LACHIN: Okay, that is fine. This is larger stones. We see here that there is a different pattern. Here, the increase in effectiveness increases a little bit with time, and on average -- as I pointed out -- there is about a 45 percent increase in effectiveness with those with larger stones.

This is the relative effectiveness over 18 months in the Medstone evaluable cohort. The estimates of the effectiveness rates are increased in the Medstone patients, so that the relative risks are also increased and are also highly significant.

I have figures which describe the actual life tables, but for the sake of time, I will skip over those. They show the same pattern in these groups of patients. I think I will show this one, which is the larger stones.

This shows a rather increasing rate of

effectiveness, much more so in this evaluable subset, than was observed in the intention to treat cohort.

Now, as you saw in the briefing books, there were a number of criticisms that were raised by the FDA in their refusal to file letter. We also responded to those criticisms and our response is also included in the briefing book; I believe that is in part three of your document.

I would like to simply summarize the additional analyses that we conducted to address these considerations, because as I said, in this epidemiologic approach, it is important to try and address every other potential source of bias that could affect the data, and the Agency has identified a number of very valid points that we need to think about.

Now, they start out by saying that the Actigall database is not an appropriate historical control for a number of reasons, and the first reason that is stated is the fact that there are differences in the imaging techniques.

Now, as I pointed out, Actigall, in those studies we used OCG at baseline and follow-up, whereas the Medstone studies used ultrasound at baseline and follow-up.

Well, there are two issues here. One is the impact of the difference in imaging in the baseline assessments, which are used to determine the covariate

characteristics of each patient; and the second is the differences in imaging characteristics in the follow-up values. Let's focus on the baseline differences first.

Now, as Dr. Garvey pointed out, OCG was conducted at screening of all of the Medstone patients to document a functioning gallbladder. So we have an OCG at baseline in all patients in the Medstone study.

It was possible to then go back and re-do the analysis, using the OCG assessments of single versus multiple gallstones, and the OCG assessments of gallstone size, in the Medstone patients.

I should point out that there was about 80 to 85 or even 90 percent agreement between the characteristics as assessed by ultrasound and OCG at baseline in these Medstone patients.

As a result, one would expect there to be little difference in the results. The original analysis that I showed you had a relative risk of 1.6. Using the OCG baseline assessments provides a relative risk of 1.57. So, conducting the analysis using the OCG baseline assessments has no effect on the assessment of effectiveness.

What about the follow-up assessments? Again, the Actigall database used OCG; the Medstone studies used ultrasound. OCG is less sensitive to detect stone-free.

It is possible that the Actigall effectiveness

rate is overestimated; meaning, there are some patients that Actigall, in the Actigall studies, were declared to be stone-free, where had we conducted an ultrasound, small stones or stone fragments might have been detected.

As a result, we have over-estimated the effectiveness of Actigall, relative to what would have been expected, had the Actigall cohorts also used ultrasound.

As a result, the Medstone combination relative effectiveness is underestimated because of this difference. So, we can be confident that this does not explain the 60 percent increase in effectiveness; in fact, had the studies both used ultrasound, we would expect an even greater increase in effectiveness.

The second concern that was raised is that differences in the dosage in the treatment regimen of Actigall, between the two databases, may have biased the results.

Now, the label recommendation for Actigall is 8 to 10 mg/kg/day. Now, in the direct adjustment that I just showed you, every patient is assumed to have been treated at greater than 9.4 mg/kg/day, which is clearly using a dose within the recommended range.

Now, we also did analyses that I will show you in a second, using indirect adjustment, where we compared the Medstone cohort versus the subset of 244 Actigall subjects

who were actually treated at greater than 9.4 mg/kg/day. In that analysis, the relative risk is 1.66, and again, is highly statistically significant. So, the dosage differences have no effect on the assessment of the relative effectiveness.

The third criticism is that statistically significant differences exist in the physical characteristics between the Medstone and the Actigall study populations.

Now as you recall, I showed you the regression model that was used as the basis for these analyses, and it showed that the major predictors of becoming stone-free with Actigall, are the gallstone number and size. Body weight was not an important predictor of success with Actigall. In fact, the p-value for body weight is .79 when added to the model that already contains gallstone size and number. Likewise, percent ideal body weight is not an important predictor. So, one would expect that adjusting for the differences in body weight would have little if any effect on the estimate of the relative risk. Nevertheless, we went ahead and redid the analysis, using an adjustment for body weight and percent ideal body weight as well.

We did the analysis adding two more columns to that table I showed you earlier, where we now had the actual body weight of each subject, and the percent of ideal weight

of each subject. And that was then factored to compute the estimated probability of becoming stone-free with Actigall.

When we do this, we find that there is a slight increase in the estimated relative effectiveness, after adjusting for these differences in body weight. The relative risk is now 1.72 and again, is highly statistically significant.

I will come to using indirect and other direct adjusted analyses in a minute, and in those analyses we also adjusted for body weight, and they also show that the adjustment for body weight has no meaningful effect on the estimate of the relative effectiveness.

Now, the fourth consideration that was raised by the Agency is that there are significant differences in the time periods of collection for the Medstone and the Actigall data -- we have already talked about this -- which may introduce an historical bias, based upon improvements in overall patient care.

Now, to our knowledge, there is no evidence that there has been a change in the natural history of untreated gallstone disease over the past 20 years. Or is there any evidence of a change in the on-therapy course of non-invasively treated gallstone disease.

There have been no new drugs or devices introduced since the approval of Actigall for the treatment of

gallstones.

The fact that we have a period of perhaps five to eight years here separating these studies, to us does not mean that the historical data is on the face of it, invalid.

Now, the one factor that could have affected this comparison is the emergence of laparoscopic cholecystectomy. Laparoscopic cholecystectomy became available during the Medstone studies, but was not available during the Actigall studies.

As one might expect, this lead to -- presumably led to -- an increased incidence of cholecystectomy in the Medstone studies; 13 percent of the Medstone patients underwent cholecystectomy versus only 3 percent of the Actigall patients.

Now, again, we do not think that this can explain the difference in effectiveness that we observed. The reason is that, in our analyses, any patient who underwent cholecystectomy was analyzed as a treatment failure. And in fact, in the life table analyses, we assume that any patient who had cholecystectomy would still have stones through 18 months of follow-up. So, the patients were not simply removed from the analysis and treated as though they were, say, missing for random causes. So we actually assigned a penalty for patients who had cholecystectomy.

Now, if 13 percent of these Actigall patients had

actually undergone cholecystectomy, there would have been a higher percentage of patients in the Actigall analysis that would have been assigned a penalty. And again, what would happen is that the effectiveness rate with Actigall has been over-estimated in these analyses, rather than underestimated.

Again, the Medstone combination relative effectiveness has been underestimated due to this possible difference in the appearance of laparoscopic cholecystectomy. It certainly does not explain the increase in effectiveness.

The next statement in the FDA refusal to file letter was that there are concerns regarding the poolability of the Medstone data, and the letter includes a quote from our submission that says, "the likelihood that a pooled analysis of the studies would allow detection of treatment effects not clearly apparent in the studies analyzed individually seems low.

Now, the intended point that we were trying to make is that, 83 percent of all of the Medstone subjects were enrolled in GS-002. So when you look at a combined analysis, the combined analysis is principally going to reflect the result of GS-002. That is all we were trying to say in that sentence. However, we agreed that poolability could be an issue and as a result, we conducted a number of

additional analyses.

The original submission included an assessment of the differences between the pre-treatment and no pre-treatment groups in GS-002, among the ten sites in that study. And in the life table comparisons of the pre-treated versus no pre-treated patients, there is no significant heterogeneity among sites.

In my supplement that was just completed a few weeks ago because of the time pressures that we have been under, I did conduct an assessment of the poolability of the results from GS-001, Group 2 of GS-002, and GS-004, in the comparative analysis.

When you look at this in terms of the overall relative effectiveness in each of these three studies, again, there is no significant difference in the relative effectiveness from these three studies; p-value .882.

I took this one step further and then looked at the poolability of all the sites in all of the studies, looking at the patients that had received the Actigall pre-treatment. And here we do find a significant difference in the effectiveness rates among sites.

Now, what this means is that the following. Let me give you a simple example. Suppose I wanted to estimate the mean cholesterol level of the -- how many do we have here -- 13, 14 patients sitting at this table?

Now, I can do this one way. I can assume that every one of you had exactly the same cholesterol. Alright? Now, in some cases, that may be plausible. I may have a very homogeneous collection of individuals, in which case, it might make sense to say, gee, I expect all of you to have the same cholesterol. But, I really do not, in this instance.

In most instances, people have different values of their cholesterol. Does that mean I cannot compute the average? I cannot say, well, gee, the average does not have any meaning anymore? Certainly, the average cholesterol in one of these 15 people has meaning. The question is, how you compute the average and how you estimate the variance of the average.

This is a problem that is faced in conducting what is called meta-analyses. You have all read papers in the JAMA and the New England Journal presenting meta-analyses of the results of different studies. And this is a very common technique, and it is called a random effects analysis among studies, where you recognize that there is going to be a collection of studies, and this collection of studies will have some inherent difference in their effectiveness over studies.

Then you use an appropriate methodology to estimate the overall average, and estimate the p-value for

that overall average.

If you conduct a random effects analysis over the sites of the different studies where the patients received pre-treatment, the relative effectiveness is now estimated to be 1.72, with a p-value of .001. So, the fact that there was some heterogeneity among the sites still provides a meaningful and statistically significant estimate of the overall average relative effectiveness. And if you like, I can show you a slide with the results by clinic, but that was not included in the original submission, so I am not going to include it in my presentation.

The final point that was raised in the critique by the Agency, is the fact that the Poisson regression direct adjustment methodology is novel, and other statistical approaches might yield less favorable results.

Now, I did not set out when we first talked about this, to use a life table adjustment. As Dr. Garvey indicated, we had a meeting with the Agency in 1996 to discuss the general strategies of using the Actigall database as a basis for our comparison. And Dr. Stephen Fred at that time felt that it was important to use an approach that allowed the comparison of life tables, rather than effectiveness at a given point in time.

My original recommendation was that we use a logistic regression model to look at the effectiveness rates

at six months. And I recommended that, because Gastwirth and Greenhouse had just published a year before their paper showing how to do this, using logistic regression.

My original recommendation was to use the Gastwirth and Greenhouse technique to assess the relative effectiveness at six months, comparing the Medstone experience versus the Actigall experience.

It was at Dr. Fred's suggestion that we adopted the Poisson regression methodology to conduct a direct adjustment comparison of life tables, rather than the effectiveness at a particular point in time.

If you go back in and actually apply this logistic regression direct adjustment, using a published methodology, the relative risk over six months now -- this is just over the first six months -- is 1.83, and again, highly statistically significant.

Well, another question might be, well, gee, is this direct approach at all plausible? What would happen if we were to employ the more standard, or the more common at this point in time, indirect adjustment?

For this purpose, I conducted an analysis using the Cox Proportional Hazards regression model, where we lumped the data from all subjects together, and then used this to estimate the treatment group difference in effectiveness, over the 18-month period. And again, this is

using the complete set of covariates.

In this analysis, if we look at the Medstone cohort versus all Actigall subjects, the relative risk is 2; however, that analysis does not take into account the range of doses of Actigall that were used, and if you redo the analysis using only the 244 subjects who actually received an Actigall dose of at least 9.4 mg/kg/day, the relative risk is 1.66; and again, is highly statistically significant.

In summary. In summary, this is what we have done. We have done a whole series of additional analyses that adjusted for body weight and percent ideal body weight, using the baseline OCG assessments; looking at a logistic model over the first six months.

We have conducted tests of homogeneity, and in the one instance I showed you, we had a random effects analysis. We also did an indirect adjustment using the Cox Proportional Hazards model. By the way, we did a test of the covariate by cohort interaction and it was statistically significant, which means that this indirect adjustment analysis is going to lose some power, but as we saw, the effect is trivial.

This then is just a summary of all the relative risks that I just showed you. The original analysis showed a relative risk 1.62. All of these adjustments for other

possible confounding or biasing factors failed to reduce significantly or meaningful this estimate of the relative risk.

Our conclusion is as follows. The Medstone lithotripsy plus Actigall combination therapy, when used in conjunction with Actigall pre-treatment, is at least 60 percent more effective than the Actigall monotherapy, at a p-value less than .01.

This result is consistent over studies. It is consistent over different analytic methods. And it is not due to differences between the two cohorts, with respect to known patient characteristics.

Thank you.

DR. MELMAN: Okay, are there questions now for this -- let me ask a question, then. Is it fair to interpret what you said, that is that what you are doing is shifting the curve to the left with this lithotripsy and that, therefore, what you are doing is you are improving the end result by three months? And that is, if you did -- waited there months without the therapy, you would end up with the same result?

DR. LACHIN: Well, again, the relative effective -- and this depends on patient characteristics --

DR. MELMAN: No, assuming on a patient-by-patient basis.

DR. LACHIN: On average, on average, yes. You are shifting the curve to the left.

DR. MELMAN: By three months.

DR. LACHIN: Now -- by -- well --

DR. MELMAN: That is what you said, three months. About.

DR. LACHIN: Well, by three months, yes. Now, let me ask you this. In many diseases, in many diseases, a relative effectiveness of 60 percent is a huge effect. In things like treatments that reduce the risk of mortality with a 60 percent reduction, they are doing likewise. They are shifting the curve, you know, some fraction to the left. Proportionately, it is the same fraction.

DR. MELMAN: But the implication here is that if you -- because you are giving patients an anesthetic -- I am a urologist; I like lithotripsy -- but if you give the patient -- you have to give the patient an anesthetic, and have a procedure, and that what you are saying you are accomplishing is that you are saving them three months of taking a pill every day. I want to make sure that is what you are saying, because it is important to the --

DR. LACHIN: Well, that plus, also increasing the likelihood that they will ultimately achieve success. Just shifting it to the left is alone only part of the picture.

DR. MELMAN: Any other questions?

DR. JETER: Well, yes, you said ultimately achieve success and yet, I asked a little while ago, but you do not know about ultimate, because the patients were not followed, ultimately.

DR. LACHIN: Well, we are talking about achieving success over the period of 18 months that they were followed. I mean, we do not have data beyond that, you are right.

DR. JETER: If they were.

DR. LACHIN: You are right. You are right.

DR. MELMAN: Okay. Then I think, as exciting as statistics is to listen to for an hour and a half, that what we should do is take a lunch break. It is now 12:15 and we will resume at 1:00 p.m.

[Whereupon, at 12:15 p.m., a recess was taken until 1:00 p.m. that same day.]

A F T E R N O O N S E S S I O N (1:00 p.m.)

DR. MELMAN: I think perhaps we should go on to FDA's presentations at this point. Unless, as Dr. Lachin points out, there are further questions at this point.

DR. WOODS: I have some simple questions. Do you want to save those for later, or --

DR. MELMAN: Questions that are related to this morning's presentation?

DR. WOODS: Well, to the lithotripsy itself. I can wait.

DR. MELMAN: No, why don't you ask him, go ahead.

DR. WOODS: Can you just give me an idea how long it takes to do the procedure?

DR. SALEN: Yes, the actual -- it is done as an outpatient procedure, at least in our unit. We did not require the services of an anesthesiologist. We required some sedation, because the shock wave is focused on the gallbladder and we did not want the patient to be moving out of the focus in this part of the procedure; we would stop every 300 or 400 shocks and reposition to be sure that we were -- that the shock wave was focused on the gallstones.

It was real time, during the procedure, as opposed to the renal lithotripsy; we used ultrasound to follow the stones being shocked, or broken up, and it took approximately an hour to give the 2000 shocks -- plus or

minus, depending upon how many times we would stop and reposition, but as you know, as Mr. Bahalani told you this morning, that the shock waves are coupled to the electrocardiogram, the R-wave of the electrocardiogram, so that we were able to do this within an hour.

DR. WOODS: And you used conscious sedation for the vast majority.

DR. SADLER: Conscious sedation, and it was not --

DR. WOODS: So, general anesthesia is clearly not required for this.

DR. SADLER: Was not -- in our unit, was never required. The same type of sedation that a gastroenterologist would provide during endoscopy would be about what we would use.

DR. WOODS: Do you have any idea what the estimated cost of the therapy combined with Actigall out to 18 months would be?

DR. SADLER: Well, because it was a research procedure, the lithotripsy did not cost the patient anything. The Actigall, I think, was estimated -- for a year of Actigall, was about $1,200.

DR. BENNETT: So, it is done like renal, then, as far as the anesthesia, but the other nine sites -- The other nine sites also were done under sedation?

DR. SALEN: That I am not -- I think that they

were consistently done the same way, but initially, some of the sites had an anesthesiologist available to provide --

DR. BENNETT: Well, that is okay, but the question of anesthetic is --

DR. SALEN: It was unnecessary and at the end, I think, virtually all of the sites were done the same way, with conscious sedation.

DR. BENNETT: Is that correct?

DR. WOODS: Can you also -- can you estimate -- if we assume that cholecystectomy is the gold standard, and that we are going to offer this type of procedure to patients who cannot undergo surgery, what percent of patients that are presenting, say, the 500,000 a year that we might do cholecystectomies on, about what volume do you think per year we might actually offer this procedure to?

DR. SALEN: Well, under the best circumstances -- in other words, we have learned a lot about which stones are the most suitable, and I would strongly recommend that we limit this treatment to the single stone, say, between 10 and 20 mm, which might represent about 15 percent of the gallstone patients that are there.

I think that out of the million patients that are discovered each year, at least 150,000 patients might be suitable for this treatment, having the right kind of stones for the lithotripsy treatment.

Now, out of that, obviously, most might opt for the surgical treatment, but the point is that this does represent an effective alternative treatment, especially in patients who need to be treated, and if they have coexisting medical problems, especially, that might make an operation or the induction of general anesthesia necessary, which is necessary for the laparoscopic cholecystectomy, here we do have an option available that is effective and that can treat the patient.

Out of that 150,000 patients, if 30,000 patients were treated this way, I think we would have accomplished something -- or, 25,000 patients, assuming that this is a group of patients who in the high risk, or who does not want to have the surgery. This would be a reasonable number of patients that might be treated effectively.

DR. KALLOO: A question for you, please. No, Dr. Salen.

DR. SALEN: Okay. I am sorry.

DR. KALLOO: Yes, a question. In your slide -- you showed a slide of a stone in the cystic duct causing acute cholecystitis and clearly these patients get pain. Why do you think patients with gallstones have pain?

DR. SALEN: Well, I also showed a slide of what the bile looks like from a patient with gallstones. And the multiple crystals in the bile and the sludge, and the

passage of this particulate material through the biliary system, I believe, is work, and is an explanation for the pain.

DR. KALLOO: Then why is it that most of the 20 million Americans who have stones have no pain?

DR. SALEN: Well, I mean, I would like to know the answer -- that answer -- too.

DR. KALLOO: So, then why do you think that just taking this -- getting rid of the stones only would be adequate therapy for the pain?

DR. SALEN: Well, I think it has to -- I mean, you ask questions that really, we do not have answers. I can give you thoughts and speculation, obviously, but one of the observations that I have made during the Actigall treatment is that the Actigall treatment may not dissolve the stone mass away, but it very often will dissolve the crystals and this affects the viscosity of the bile; this affects the flow rates of the bile.

I think that a lot of the pain that is associated with biliary stones relates to the sludge, the crystals in the bile, and I think that the crystals in the bile might be affected by the amount of dehydration of the bile in the gallbladder, and things like that.

Although I do not know the answer to the question, I think that the sludge in the bile is an important

component of the pain; also, I think it is important to state that this is intermittent; that the sludge depends upon the amount of dehydration -- in other words, the amount of fasting.

For example, there may be some advantages to feeding patients more frequently with the idea that feeding empties the gallbladder more rapidly, as opposed to the person that eats just a single meal during the day, and so for 22 hours, simply allows that gallbladder to contain all of this bile with sludge in there. So, there are other factors that probably contribute as well.

DR. KALLOO: I am sure there are, because -- so, therefore, you would not be surprised that if a patient, even though you cleared his stones, would continue to have pain. Would you be surprised by that?

DR. SALEN: Yes, that is a very important point. If that patient did have pain, I would want to look for another reason for the pain. Just because you have gallstones, does not mean that you could not have a coexisting ulcer, or spastic colon.

I think the ability to be comfortable with the diagnosis, being sure that you have the right diagnosis, is important. You know that after cholecystectomy, that about 20 percent of our patients still have pain after the gallbladder surgery, and we question whether those stones

were the cause of that patient's pain. So that I think that that is a very important point, of being sure what is causing the pain.

DR. MELMAN: Dr. Epstein, then Dr. Frank.

DR. EPSTEIN: Shorter question. Doctor, in your estimation, what is the risk of recurrence of stones in the gallbladder per year, after the patients have completed their course of Actigall therapy and the stones have been dissolved, what is the risk of recurrence per year?

DR. SALEN: Well, you know that after medical therapy, for example -- especially in multiple stones -- that the stones recurred at a rate of about 10 percent per year, so that after five years, almost half of the patients who had multiple stones dissolved medically, had recurrent stones.

On the other hand, the patients that we are talking about are single-stone patients, not multiple-stone. The single-stones, according to our German colleagues, apparently occur less frequently, and I think that they have a rate of recurrence after three years of 14 percent or so, so that what it suggests to me, is that multiple stones versus single stones may have formed at different times under different conditions.

The risk of recurrence with the treated single stone apparently is much less than with the multiple stones

just with dissolution therapy.

DR. EPSTEIN: And in your experience, beyond the studies, how many patients, in your estimation, have had cholecystectomy two years, three years, four years down the road, following this treatment? In your patient cohort.

DR. SALEN: This has been infrequent, because if a patient responded to medical therapy -- in other words, their stones dissolved, and they had a recurrence, they often had small stones, and especially if the recurrence was symptomatic, we simply put them back on the medical therapy.

The point is that, having stone recurrence did not mean that they necessarily presented with cholecystitis. We were able to treat them medically, again, so that the number of patients that we have had to treat with cholecystectomy has really been quite small in our center, which is a center that for more than 20 years has been treating these things by medical means.

DR. MELMAN: Dr. Frank?

DR. FRANK: Just in reference to that, the German group also seemed to indicate that if you had a solitary stone to start with, and had a recurrence, it was usually a solitary stone the second time as well.

The other thing is that as far as pain is concerned, the -- again, the studies of the German group, who did follow their patients longer-term, they found that

the patients who had recurrent stones, chances are they probably had sludge, because very shortly, they also got recurrent stones, in many cases. So, the stone and/or sludge and pain are very closely related, I think.

DR. SALEN: And you know, it sort of suggests that the people who have recurrence -- I mean, the question of, is this real recurrence, or is this simply part of the process that these people really never got rid of the tiny, small, nidus of insoluble material in their gallbladder?

The nidus of most stones is some pigment, some deoxycholic acid, in other words, and they never really were able to empty their gallbladder completely, and so that recurrence was simply -- not a new recurrence, but a continuous formation of stones once say, the ursodiol was discontinued.

DR. HAWES: A couple of things, or, two parts to a question. One is, I appreciate the difficulty in this data being old, but it does strike me as being a little bit deficient that we did not get better follow-up data.

You have a list of these patients; you know who they are; and it seems to me -- and I think the Panel shares this -- that we are interested in what happens after the lithotripsy is performed.

For example, if you take a case scenario, a hypothetical case scenario, that you have a patient. You

intervene with lithotripsy and Actigall. They, say, clear their stones, let's say, in a year, but if 100 percent of them get their stones back with symptoms within a year, then it would make this intervention not very appealing.

It seems to me that the follow-up data is really very important and that that is, at least, potentially retrievable.

The second part of my question is, is --

DR. SALEN: Can I answer just that question?

DR. HAWES: Yes, I am sorry.

DR. SALEN: I think what you say is absolutely right, and this is something that we wanted to do. There were no resources, you know, for this. And that was one of the reasons. Also, most of these patients were referred to us, they were not our patients, in the sense of asking patients that do not belong to you to keep on coming back, the referring doctors sometimes get very upset by that. So, these were some of the reasons. But, you are absolutely right. We missed at least an opportunity that -- it still would be possible to go back and try and answer these questions, and we have at times, had G.I. fellows and tried to get a little bit of resource to actually answer that question.

I think that the data now would be even more interesting to get, and that should be something that we

should, you know, be required to do to look at what is the outcome of this treatment?

DR. HAWES: The second part of my question is, is right now the labeling is for stones, 4 to 20 mm stones. Are you sort of imply -- you keep mentioning the solitary stone as being the best one. Is there a plan to apply for a relabeling for lithotripsy to include only --

DR. SALEN: I think -- I think this -- I think Dr. Garvey is going to specifically speak on that, but the answer is, yes. I think we would want to use the data that we have to be most effective.

DR. MELMAN: Dr. Jeter?

DR. JETER: That's alright.

DR. MELMAN: No?

DR. FROMM: [Comment away from microphone.]

DR. MELMAN: Would you use the microphone, please?

DR. FROMM: I am Hans Fromm from Gastroenterology at GW, and I certainly appreciate the opportunity to say a few words.

I was actually part of a group of investigators, investigating a different technology, electric lithotripsy, and we were actually for a number of years, extremely frustrated to do the investigations which you suggested -- especially, Dr. Hawes also, in terms of follow-up and obtain further data.

Actually, what we encountered very quickly after the disapproval, was -- and with the arrival of and wide use of laparoscopic cholecystectomy, that actually, no company was willing to put any money into lithotripsy, because it was basically considered to be not a money-making venture.

We had actually at least three meetings with the FDA investigators in trying to somehow come to an agreement to move forward. And the problem has always been, the lack of any support by a company, by a lithotripter company, and therefore, we are very, very happy to see that there is a company, and especially an American company, which has taken up this, and believe me, it has taken us investigators a lot of lobbying, a lot of pushing, to get Medstone interested in this again. And so, we are very happy that we are at this point.

We see many deficiencies and problems with the data, but I think one should not lose sight of a few facts. First of all, the device is safe, because it has been used for many years for renal lithotripsy.

Secondly, the data we have, as deficient as they may be in some aspects, we have shown that the device is safe for gallstone lithotripsy.

Thirdly, if you look at the data very carefully, you will see that in the group for which we would like lithotripsy to be approved; that is, 4 to 20 mm, single

stones, that the efficacy is not as high as one sees it generally in the literature. One has to consider, however, the various factors which -- the restrictive analysis which was used.

Basically, the machine is safe, the machine is effective, and what we are asking for, and hoping for, is that this technology is not going to be -- because I am afraid if the Panel decides to vote it down, it is going to be very difficult to move forward in this field, and I think it is an important field.

There are patients who would benefit from this treatment. This is not for every patient; this is for a selected patient population. And I just hope that we can some way in a constructive way, move forward, to move this technology forward.

DR. SADLER: I would like to ask you, and perhaps Dr. Salen as well, to define for me the population who would need this, because obviously, laparoscopic cholecystectomy has been so very widely used and is effective and is well-tolerated. So that, when I try to think -- not being a gastroenterologist -- when I try to think about the population of patients I serve who have a great deal of co-morbid disease, who still have procedures such as this with a high level of success and tolerance, I am not sure who is left, who needs this procedure. And so, I would like to ask

you to be as explicit as possible just to help me focus on that.

DR. FROMM: I can tell you that I have a number of patients who now, for several years, are waiting to be treated. These are patients that mildly have had symptoms in the past, have occasional attacks, and are very reluctant to undergo surgery. So, it would be, obviously, patients who fulfill the relatively restrictive criteria we mentioned; that is, single stones up to 2 centimeters in diameter, and patients who decline -- who do not want surgery -- or, patients who represent an increased surgical risk.

It is to some extent -- or, actually, to a major extent -- a patient's decision, and I will tell you the truth. From all I know about treatment of gallstones, if I have a single stone, I would not -- laparoscopic cholecystectomy would not be the first choice for me. And I think patients should have the option to make that choice, and that choice is in this country not available.

I should also mention that, in Europe and in Japan, lithotripsy is still used for the indications I mentioned.

DR. SADLER: But even there, the enthusiasm seems to have waned, somewhat.

DR. FROMM: This is not a treatment for everybody.

this is not standard treatment. We are talking about treatment for a selected patient population, so that there is a menu, so to speak, of treatment options available, and I think that patients deserve to have a choice.

DR. MELMAN: Did you -- first a statement. I need you to state your name and whether or not you are a consultant for the company.

DR. FROMM: I am a consultant for the company --

DR. MELMAN: And say --

DR. FROMM: But I have no -- I have no financial, no stocks, no financial interest in the company.

DR. MELMAN: And your whole name is what? Say your name.

DR. FROMM: Hans. H-A-N-S. Fromm. F-R-O-M-M.

DR. MELMAN: Okay, thank you. And in these patients that do not want surgery who have lithotripsy unavailable to them, why didn't you put them on Actigall?

DR. FROMM: Actually, I put them on Actigall, but this was actually discussed over many meetings with the FDA, because the data are available, one actually does not need a sophisticated analysis to really make that point.

A stone which is 10 mm in diameter, the chance of dissolving this stone is not more than 10 percent. So if you have a stone which is 10 mm or larger, your chance of dissolving this stone with Actigall is about 10 percent.

And that is exactly where lithotripsy would come in, if the patient declines surgery.

DR. MELMAN: So, the data that we were looking at for an hour and a half that implied that, really, we were just shifting the curve to the left, is not the case.

DR. FROMM: Actually, that I think is a very good point you are making. Basically, you are not just diminishing the time for success, you are increasing the success, the percentage of successful treatments, exactly.

DR. MELMAN: Okay.

DR. JETER: Dr. Melman.

DR. MELMAN: Yes.

DR. JETER: Let me see if I can go back to where I think I need to go, as a consumer representative.

It was my understanding that, in the past, it was thought that stones caused gallbladder disease, but the prevailing theory is now that gallbladder disease causes stones.

You said, Dr. Fromm, that the machine is safe and the machine is effective, but is the machine, and is the therapy, is that effective treatment for gallbladder disease?

DR. FROMM: Okay, let me make sure that we fully understand each other. Gallstones are not caused initially by gallbladder disease. Gallstones are caused -- as Dr.

Salen pointed out -- by an abnormality of cholesterol metabolism, which manifests itself by increased secretion of cholesterol into bile. And this actually has been studied very extensively in many animal models.

If you put more cholesterol crystals into bile -- into the gallbladder -- first, there were gallstones formed, but also, there were crystals. There is some irritation of the mucosa and inflammatory response --

DR. JETER: But the machine is not going to change that.

DR. FROMM: Actually, if you dissolve or eliminate the stones from the gallbladder, you basically remove the source of irritation and the source of problems with the gallbladder, because the gallbladder, in the vast majority, will not become inflamed; no complication will occur if the gallstone is absent.

DR. JETER: But you have not changed the fact that the cholesterol is going to be in the bile that is going to cause --

DR. FROMM: That is a very sharp and good point you are making. However, in many patients, the increased secretion of cholesterol is not present all the time, and the conditions to develop the disease -- to develop gallstones -- are not present all the time. So, therefore, a patient, after a -- and you know, there are long follow-up

and many -- both in the Actigall-treated patients and gallstone, the gallstones were dissolved; or, after complete freedom -- gallstone freedom -- after lithotripsy.

We have follow-up there for many years which shows that at least 50 percent do not develop any recurrence of stones, which is metabolically not fully explained. I mean, that is your point, basically.

DR. SADLER: Dr. Fromm, that is not really consistent with what was presented here this morning.

DR. FROMM: Would you specifically tell me what is not consistent --

DR. SADLER: They said that it was stone- and sludge-free, ranging at different times in different patients from 12 percent to about 45 percent. And there wasn't any long-term follow-up. So that, you know, while I respect clinical anecdotes, they are not part of --

DR. FROMM: No, Sir, no, Sir, I am not referring to the study, I am referring to the literature, which is -- there are many studies of long-term follow-up.

DR. SADLER: I did review the literature earlier this week --

DR. FROMM: Yes, yes. Yes --

DR. SADLER: I am not convinced that I can agree with you.

DR. FROMM: Would you -- I mean, there are German

studies --

DR. SADLER: Yes.

DR. FROMM: There are European studies --

DR. SADLER: Japanese studies, German studies, Italian studies --

DR. FROMM: -- which show -- which show the --

DR. SADLER: -- Danish studies, and a few American studies.

DR. FROMM: Yes, and you are not convinced of what?

DR. SADLER: I am not convinced that the --

DR. FROMM: But, the data --

DR. SADLER: -- result -- that either the clearing of stones is as complete as you imply, or that the recurrence is as low as you imply, and while your experience may certainly be different and better than the others, that is not consistent with what I have read or what was presented here this morning.

DR. FROMM: Well, Sir, I have to disagree with you. The long-term follow-up data --

DR. SADLER: We will disagree agreeably.

DR. FROMM: -- okay. The long-term follow-up data I think are clearly spelled out in the literature. And they vary, but I think the average is about 50 percent.

DR. MELMAN: Okay. I think -- thank you very

much.

DR. FROMM: You are welcome.

DR. MELMAN: I think, I --

DR. GARVEY: May I just clean up one [comment away from microphone] -- it will not long.

It was the issue of sedation during the procedure, which we did not come to closure on. In the original protocol, there was stipulation for either inhaled anesthesia, or intravenous sedation, sort of demoral-valium at that time, not demoral-versid. But, anyhow, what happened with time, it became apparent that general anesthesia was unnecessary. The idea was to immobilize the patient. The stuff we use in endoscopy works just fine.

DR. MELMAN: Thank you. Okay, I think we are going to go now to the FDA presentation, and Gena Gonzalez is the FDA primary reviewer of the submission, and will present an overview of the Medstone PMA.

Agenda Item: FDA Presentation - Overview

MS. GONZALEZ: Thank you. My name is Gema Gonzalez and I will be taking you through the FDA presentations.

I am a biomedical engineer, and a reviewer with the Gastro-Renal Branch. I would like to start with a brief introduction and a discussion of the non-clinical issues, and then we will move onto the next two presenters who will

discuss the clinical and the statistical issues.

I would like to start, first of all, with an introduction of the review team that worked on this PMA. Besides myself as lead reviewer, we had two clinical reviewers, Dr. Brian Harvey, and Dr. Hugo Gallo-Torres from the Center for Drugs -- Dr. Gallo-Torres -- and Dr. Harvey, of course, from the Center for Devices.

We also had a statistician, Dr. Lin, do the statistical review.

Dr. Gerald Harris did the engineering and the device design review.

We had two reviewers from Office of Health and Industry Programs do the device labeling and human factors issues.

Two reviewers, as well, from our Office of Compliance, who looked at the GMP and other compliance issues.

Of course, you have seen this already today, but I would just like to reiterate the indications for use that were included in the PMA submission for which the sponsor is seeking approval of this PMA.

According to the sponsor, combination therapy with the Medstone STS Lithotripter and Actigall, at a daily dose of 8 to 10 mg/kg/day, consisting of at least one week of pre-lithotripsy, and up to 20 months of post-lithotripsy

treatment with the drug; and up to 2,024 kV shocks is indicated in male and female patients for fragmenting and clearing the functioning gallbladder of symptomatic, radiolucent, noncalcified stones between 4 and 20 mm maximum diameter.

Of course, you have heard a device description and you have heard presentation of all the device components and the mechanism of action, therefore, I am not going to repeat that section. I would just like to point out a couple of important points.

The Medstone STS Lithotripter is currently approved for renal lithotripsy; that was approved back in 1988 under PMA P870015.

The current device going before the Panel today is identical to this device in design; basically, the sponsor has indicated that they have not implemented any device-related changes, in order to accommodate the new intended use of biliary lithotripsy.

Therefore, since all the engineering and device-related issues have been evaluated in previous submissions, we do not have any outstanding issues at this time.

Now, regarding the current intended use of biliary lithotripsy, the sponsor has included bench testing and animal testing data in their submission. The bench testing, of course, was done in vitro to evaluate gallstones, and the

animal testing included 8 dogs and 24 pigs. Most of these animals did not have stones, therefore these were viewed as safety studies and just validation studies for the bench testing.

One important thing to point out is that all these data were included in previous submissions; the IDE G870165 under which the sponsor collected the clinical data you have seen today, and of course, the previous PMA submission that came into the Panel in 1989; you have heard about that one today, also. Therefore, all these issues have been reviewed in the past, and we do not have any outstanding non-clinical issues.

Similarly, the GMP issues have also been taken care of. The devices that have been approved in the market for the last ten years or so, have been subjected to regular GMP inspections, and therefore a special GMP inspection has been deemed unnecessary at this point, so we do not have any GMP issues.

Since there are no non-clinical issues that I would like to speak to you about, I would like to move on to our next presenter who will take care of the clinical issues.

This is the clinical data that was collected under this IDE that I mentioned and, as you have heard before, the data was collected between 1988 and 1990, and some of the

data were included in the previous PMA.

You have heard a lot about different PMAs and different submissions, I just want to point to the current submission that is before you, and just to stay focused on that.

After Dr. Harvey finishes his presentation, you will hear from Dr. Lin, who will discuss statistical issues, and these are, of course, the comparison of the clinical data with the combination therapy and the historical control, and he will speak to you about the issues in statistics. Dr. Harvey.

Agenda Item: Clinical Review

DR. HARVEY: Good morning. I am Brian Harvey, and I am the Medical Officer in the Gastroenterology and Renal Devices Branch here at FDA. I am a gastroenterologist and general internist by training, and also have a Ph.D. in Lipid Biochemistry. I have done basic research in gallstone pathogenesis, but that was nonhuman studies using only prairie dogs.

What I wanted to talk about today was -- originally, I was going to give a talk giving an introduction on Actigall, gallstones, and then get into the data, but since we actually had an excellent introduction and background by Dr. Frank, and we have a lot of information given by the company, what I have actually done

is reworked my talk to really hit upon the key areas that we feel need to be highlighted, from the FDA perspective, and also to try to address some of the questions that have been raised earlier in the Panel meeting on some of the areas involving the various studies, both the Medstone studies and the Actigall studies.

This was to be my outline for my talk, but I will be focusing in on some of the Actigall data that was in the NDA, the GS-002 study, and then the overall summary with an extra focus on adverse events.

As you know, there is a large body of literature on Actigall. Actigall was an NDA that was taken to the Center for Drugs at the FDA back in the 80s, and as a public document, I had access to the NDA Summary Basis of Approval, and in that, they discussed how the Basis of Approval was based upon the eight studies that were conducted by the sponsor and in that, based upon the eight sponsors' studies, they found that complete stone dissolution occurred in 30 to 60 percent within 24 months of therapy with the ursodiol, at the doses between 7 and 15 mg/kg/day.

They also described that if you were more stringent in your patient selection, therefore taking ideal body weight, either equal to or less than 120% of ideal body weight, floating stones, stones less than 1 cm, and no stone calcification at study entry, you actually might expect

stone dissolution as high as 50 percent. This was the thinking of the drug's review team when the Actigall NDA was approved back in 1987.

This is the patient tree that was provided by the sponsor, outlining the various studies that support this PMA, the GS-001, 002, and 004. As we heard, the 003 only enrolled two patients, since that was to study lithotripsy alone, without any Actigall therapy. Taking that data, the sponsor has proposed to use the historical control of the Actigall database.

Since the sponsor has already gone into detail on the GS-001, let me say that the inclusion criteria of this GS-001, which was a pilot study, was actually different from the later trials.

One of the inclusion criteria was stones either equal to or greater than 4 mm, but less than 30 mm, whereas future studies were less than 20 mm. And actually, what this study showed was that there was no efficacy of the lithotripsy device-drug combination in stones greater than 20 mm. So it was actually based upon that pilot data, where they had 0 percent effectiveness in stones from 20 to 30 mm, that they decided that the little trial, the GS-002, and the confirmatory trial, the GS-004, would then limit the stones to being 20 mm or less.

In the GS-001 they were pre-treated for two weeks

with the Actigall and received the 2000 shocks at the 24 kV, with Actigall post-treatment.

Based upon the results of that pilot study, they moved on to the GS-002, which did have the randomization of Actigall or placebo in the pre-treatment period, followed by all patients receiving lithotripsy, and then Actigall post-treatment.

As we had heard earlier during the sponsor's presentation, they did both the crude and Kaplan-Meier life table analysis estimates, and the data that was presented in the PMA was 6-month and 12-month data, and then either 18- or 20-month data was the Kaplan-Meier life time analysis.

Then we can see, as was described earlier, about the effectiveness at 6 months in the range of 17 to 20 percent, increasing to the low 20s at 12 months.

One of the things that they did mention is that when they went from the intention-to-treat analysis, to the evaluable subset analysis, that patients were "excluded retrospectively." So, patients had been enrolled in the study, underwent the lithotripsy, underwent treatment with Actigall post-lithotripsy, but then retrospectively excluded, based upon whether they violated certain selection criteria, and it was based on that retrospective exclusion that they went from the intention-to-treat analysis to the evaluable subset analysis.

In the GS-001 study, all patients had to have general anesthesia -- and this may address the question that was asked earlier -- so, therefore, 100 percent of the GS-001 patients received general anesthesia.

The sponsor applied to the FDA for a change in the IDE, requesting that for the GS-002 study, that the patients could either have general anesthesia, or epidural, or IV sedation -- and actually, I went back to the PMA during the questions, and have looked, and it seems that about 50 percent of patients did receive general anesthesia in the GS-002 study.

There was wide variability between centers. Centers in the New Jersey-New York area seemed to use more IV sedation, but there were some centers that exclusively used general anesthesia. So, in the Volume 12 of the PMA, they actually list each patient by the time of anesthesia they received, and it appears that there was a sizeable portion that did receive general anesthesia.

In this table, in that GS-002 study, we see that there is a difference in effectiveness with the Actigall-lithotripsy combination, either in pre-treatment with Actigall or pre-treatment with placebo, depending upon stone number. And we see that effect that has been mentioned earlier, that with a solitary stone, you get a much higher effectiveness rate; certainly, with the smaller stones,

which drops off with the larger stones, whether they are pre-treated with Actigall or placebo, multiple stones do much less well.

Now, it is interesting to note that in this study where the exclusion criteria did not allow patients who had stones between 20 and 30 mm, despite that criteria, there were 66 patients that actually had stones greater than 20 mm, although the inclusion criteria for the study said that those patients should have been excluded. So, then, retrospectively, they appear to have been excluded, and were not included in the evaluable subset analysis.

We can also see in the GS-002 study, which sort of paralleled the GS-001, that there were patients that had to undergo a second lithotripsy. Patients were offered a second lithotripsy if the first lithotripsy did not produce fragments 3 mm or less, and about 66, or about two-thirds of patients underwent one lithotripsy, but about a third underwent a second lithotripsy session. And it appears that whatever anesthesia was used in the first was used in the second, so there are patients who had general anesthesia for both lithotripsy sessions. There are some who had intravenous sedation the first time and they had that on their second session.

Therefore, based upon the results of that pivotal trial, there was a confirmatory trial, the GS-004. They

took 99 symptomatic gallstone patients and there were two mobile units, one in Alabama and one in California, moving to multiple sites within each of those states.

All patients received pre-treatment with one week of Actigall. They had the 2000 shocks at the 24 kV, and then all received Actigall post-treatment. And that study was completed in September of 1990.

What the sponsor stated in the PMA submission, that of those 99 patients, only 81 went on to receive Actigall pre-treatment and lithotripsy. It was unclear how those were excluded. And then 26 additional patients were excluded retrospectively, since they did not meet one or more of the inclusion criteria. So, given the fact that we had the additional 26 patients excluded retrospectively, that leaves only 55 patients who were available for the evaluable subset analysis.

You can see that there is about a 10 percent difference consistently between the intention-to-treat analysis, and the evaluable subset analysis, using either the crude or the Kaplan-Meier, at either 6 or 12 months.

Once again, we can see an effect of stone size and stone number. Once again, those with a solitary stone doing better, and smaller sizes also doing better, which sort of raises the question that was asked earlier about the difference between the Medstone population and the Actigall

population.

If the Medstone population had about 50 percent of patients with a solitary stone, whereas the Actigall historical database had about 30 percent, you could see how a difference such as solitary stone versus multiple stones could have a sizeable impact, and how that is adjusted for and whether it is adequately adjusted for could have a major impact on the results of the study.

This is the blow-up of the patient tree that was in the sponsor's submission. And as you can see, based upon the GS-001, 002, and 004, there is a total of 769 patients, but due to various reasons, 184 of those have been excluded, they were not evaluable; leaving 585 evaluable patients.

Those patients had been randomized in the GS-002 up to either the Actigall pre-treatment, 341, or the placebo pre-treatment of 244. And since the sponsor's indication for use statement has asked for a combination therapy of lithotripsy with Actigall, that includes at least one week of pre-treatment; it then leaves these 341 patients to be looked at, to be evaluated, since it is only these 341 patients that truly meet the inclusion criteria -- truly meet what is outlined in the proposed indications for use statement.

This is just the second part of that patient tree. Of those 341 patients that received Actigall pre-treatment,

lithotripsy and then Actigall post-treatment, 61 of those were drop-outs, or 17.9 percent, and therefore, that leaves only 280 patients that had not dropped out and met all those criteria, and in their analysis they said, 111 out of 314, or a rate of 32.6 percent; 22.9 percent at six months and 28.2 percent, but really that amount is -- if you are looking at the intention to treat versus the ES -- those numbers could vary. They do say that those that completed participation without stone clearance was about 50 percent.

What I wanted to highlight here -- this was in the sponsor's briefing book -- this is a summary slide of the three clinical trials, the GS-001, GS-002, and GS-004, and I tried to highlight an example.

If you look at the 12-month Kaplan-Meier estimate in the intention-to-treat analysis at 12 months; in the GS-001 it is 27.4 in the Actigall pre-treated 12 months; and the GS-002 was 24.3; and in the GS-004, the same thing, 30.8.

If we look at 27.4, 24.3, and 30.8, we go to the next table, those somehow become 30.1, as a combined Actigall-lithotripsy therapy in the Actigall pre-treated patients. And so it is unclear whether that is an average or a weighted average, but even so, it is difficult to see how the sum of the three trials comes together to produce a combination therapy overall rate of 30.1 percent at the 12

months.

Also, given the information that was in the Actigall NDA, and the Summary of NDA Approval by the Center for Drugs at the FDA, where they spoke of a 30 to 60 percent effectiveness rate in Actigall at 24 months, and potentially up to 50 percent at 12 months, based upon the sponsor's interpretation of the Actigall data, we are looking at Actigall monotherapy of 11.1 percent at 6 months, and 21.9 percent at 12 months.

Which brings us into the adverse events. It appears that the definition of adverse event -- there were several different definitions. Serious adverse events were fairly straightforward. As one would imagine, those are hospitalizations and emergency room visits with cholangitis, pancreatitis, etcetera. And those, out of all 723 patients, were 45.

Now, cholecystectomies were not necessarily counted as serious adverse events, and in the data that was presented by the sponsor in the PMA, a number of the patients who underwent cholecystectomy had similar symptoms of those that were classified as serious adverse events. But since they underwent cholecystectomy, they were not included in the serious adverse events. So, there were 90 patients that underwent cholecystectomy versus the 45 that had serious adverse events.

In addition, we see there were 19 patient withdrawals, and the sponsor has already discussed the three patients' deaths.

Now, in the submission -- and actually, in the GS-001, GS-002, and GS-004 -- it actually states -- and I am quoting from the PMA -- that there was no provision made for the routine collection of data on adverse events. And therefore to replace the analysis of adverse events, this report evaluates Co-Start(?) coded, treatment-emergent patient complaints. So, the things that I will be discussing next were not deemed as adverse events, but were treatment-emergent patient complaints. And in the submission, they were in a separate section; in the briefing book, they were listed under adverse experiences, and things like abdominal pain, gallbladder attack, back pain, etcetera.

If you go back to the various studies, though, and go to similar tables for the GS-001, GS-002, and GS-004, the numbers actually are greater than what are listed here in the summary table in the briefing book, depending on what symptom one is looking at.

Even in the GS-002 study -- I am quoting -- there were 416 treatment-emergent complaints recorded in the database for patients in the Actigall pre-treatment group, and 353 for the patients in the placebo treatment group.

And that was in Volume 7, therefore, that was a total of 769 events for just the GS-002 group alone, which is more than what was reported here.

A concern is raised that, given the reliance on the Co-Start(?) -- on the computer search -- for adverse events, there might be an under-reporting of adverse events.

Based upon this analysis, it leads to a number of clinical concerns; one is the high drop-out rate, and the not evaluable rate. And we start off with the 769 patients, of which then only 585 were considered evaluable for the various reasons; and then, given the fact that only 341 received the Actigall pre-treatment, with the 61 drop-outs. So, we really are looking at 280 patients who have met the criteria of the indications for use statement -- proposed indications for use statement -- for this device-drug combination.

In addition, when you look at the Kaplan-Meier stone- and sludge-free rates in the briefing book, we see that there is 18-month data, and in the actual PMA, the vast majority of data is the 6-month and the 12-month, whereas it appears that the Kaplan-Meier is a life table analysis extrapolation. And if you go through the pages and pages of the individual patients, it appears that it is a small percentage -- or, certainly, less than 50 percent -- of patients who have made it out to that 18 months.

It of course would be helpful in any analysis to know the actual number of patients who made it to 18 months, because with that actual number, it would help the Panel in deciding the validity of that 18-month data.

A second concern is, Actigall as a historical control. And my question is not so much whether Actigall can be an historical control, but which Actigall data is the historical control? Because if you look -- as I have said -- looked at the Actigall NDA, the basis of the Center for Drug's approval was then the discussion in their summary -- the NDA Summary Basis of Approval -- was this 30 to 60 percent stone- and sludge-free, which is consistent with the published literature on Actigall monotherapy that we all saw back in the 80s.

Compare that to the sponsor's historical control of the Actigall database where they discussed 11 percent stone- and sludge-free at 6 months, and 21 stone- and sludge-free at 12 months.

My final clinical concern is about the adverse events. It appears that what are traditionally called adverse events, you really need to sum up the serious adverse events, the cholecystectomies, the treatment-emergent patient complaints.

There are also reports of cardiac arrhythmia in some of the studies. In the GS-004, it appears three

patients had cardiac arrhythmias during lithotripsy. In the GS-002, there were ten patients that had cardiac arrhythmias. In the GS-002 studies, there were some reports of some liver contusions -- also, in GS-004.

Hematuria has been mentioned several times. There was asymptomatic hematuria in up to 50 percent of patients in both the GS-002 and GS-004 studies; smaller percentages in the GS-001. The significance of that is unclear, but that was also not included in any sort of event analysis, and also, the withdrawals and some of the others -- the unknowns withdrawn for unknown reasons. That data was not available.

Based upon these clinical concerns in this review, it has led to the Panel questions, which have been given to the Panel and will be read after the statistical presentation by Dr. Stan Lin. Thank you very much.

Agenda Item: Statistical Analysis

DR. LIN: Good afternoon. I am going to present to you the statistical review. Since Dr. Harvey did such a great job reviewing the Medstone studies with you, I will just concentrate on the historical control comparative analysis, because that is the principle and primary relevant analysis for this submission.

Here is an outline of my presentation. A brief look at the data set for the comparative analysis. To me,

the fundamental issue for this submission is the group comparability, and I will review that with you.

I will have a few comments on the Poisson regression model which was used by trying to make the adjustment of the group imbalance.

I will give you one or two additional comments, and then I will give you a summary.

Here is the data set assembled together for the historical control comparative analysis. There were 769 for the combination treatment group; and there were 868 for the Actigall monotherapy group.

For the combination group, they came from three U.S. studies, as we have seen; 001, 004, 002, and 002 was by far the largest one, over 600 patients.

The Actigall data came from four Italian sites, one U.K. site, and three U.S. sites.

The final data set that went into the comparative analysis which used the Poisson regression had 689 out of 769 for the combination group. That is a difference, or exclusion, of 80 percent, amounting to 9.6 percent exclusion rate.

For the monotherapy, 671 out of 868 were used, and that is a difference of 197, and that amounts to an exclusion rate of about 23 percent. So, it is clear that there were substantially more exclusions in the Actigall

patients.

Here are just some of the reasons about patient exclusions. Notice that the Poisson regression model requirement -- meaning that certain covariables have to be present with a patient, and that resulted in some patient exclusions.

The Poisson regression model was based on Actigall patients alone. Notice that down here, when you look at the Medstone-Actigall combination group, there were substantial numbers of patients excluded, also based on the same regression model requirement.

Picking out of the submission, it said that a rudimentary effort -- I was not quite sure what was meant by that -- I would assume that it included conventional statistical methods -- it was said to be a failure to do the comparison between the two treatment groups -- the combination and the monotherapy.

The submission also stated that indirect adjustment would not be appropriate, but then we have seen, as we saw this morning, that some of them were provided to us, and I thought to me it was a little confusing.

I would agree, though, that the indirect adjustment would not be appropriate for this data set, but I would also say that other statistical methods are equally inappropriate for this data set.

As I said in the outline page, the fundamental issue here is the group imbalance, and that is the thing that I want to talk about.

Let me just add another comment. I say that other methods are equally inappropriate. Given that you have some serious imbalances -- as I will review with you -- that is because statistics is basically a data summarization tool. It is not a bias correction or bias elimination tool.

Going on to the group imbalance. As we have seen this morning, there was a significant difference in the time periods for data collection. For Actigall, it was between 1976 and 1994. And it was not until about four years later that the correction for the combination therapy data began; 1988 and 1990.

On the group imbalance, the Medstone lithotripsy-Actigall combination group was consistently and significantly heavier; consistently, I mean that if you look at the male or the female separately, you will see that the Medstone subjects were heavier -- 87.4 versus 74.6 for the males; and 72.8 versus 63.2; and both of them were highly statistically significant.

The percent of patients with single gallstone was highly significantly different. In the combination group it was about 55 percent, and for the Actigall monotherapy group, it was about 31 percent.

The difference of 24 percent was highly statistically significant.

Now, if you think that a single stone is easier to dissolve than multiple stones, obviously, this difference here has implications. As other speakers alluded to, the distribution of stone sizes was significantly different between the two treatment groups, also.

I looked at the overall distribution here, overall distribution here, and that difference is very significantly different.

Now, although it was pointed out that the body weight might be an important factor in predicting a stone-free event, however, to me it is important, because the ones that we have reviewed so far were the ones measured -- meaning that these were the measured imbalances. Because the treatments were not randomized, significant differences in other characteristics are possible, but were simply not measured. I would say that potential bias due to these known and other unknown imbalances cannot be satisfactorily and statistically adjusted. It is not simply just a statistical issue.

Moving on to some comments on the Poisson regression model. The fundamental issue that I see here is the model transferability, including justification and validation of the model.

Again, the model was solely based on Actigall patients only. When we used the model -- at this point, you know, I would ask you, how many times you have heard this morning the speaker was using the word, assume that you can take the model; assume something. I heard it about four or five times. But, I would think that in a regulatory setting, we would need more than to assume, we need to have some validation.

Dr. Lachin used some examples this morning to illustrate several points, and I would like to interject some examples. Suppose that we do a comparison -- and I will take you away from the device thing or drug thing -- suppose we are comparing the economy of two countries; let's say, Japan and the United States.

We know that there are covariables that are similar and there are covariables that are different. Now, would you think that if you build a model based on the Japanese economy, using their covariates, and you have a perfect model predicting almost like, let's say, 95 percent -- Would you think that that would be -- that model can be just assumed and be transferred to the United States side and do a decent job for the U.S. economy?

I mean, the other example I was thinking of at lunch time was that the gender usually in clinical trials -- I do not know if you are aware in the hypertensive drug

trials, they used to predominantly enroll male patients. So, therefore, all the response models on that was based on male patients.

What happened then, when people realized that the treatment needed to be given to some female subject, we realized that the model might not apply; there was a problem. And therefore, in the last few years, there was a big issue about the gender issue.

My point is simply that, you know, in statistics one of the basic principles is simply that, before you use some model, you need to justify it; you need to validate it. And perhaps, you know, I have not seen a clear picture of that.

There is also the symmetry problem. By that I mean, we are using the data from the Actigall patients, building a model, trying to use that model to predict a response on the combination group patients. Okay, so it is like forcing -- using my model to predict someone else's.

Now, what happens if you reverse that? Do you have the robustness in the modeling strategy? And that was not clear.

The last thing that I would say is simply that, we can build a model predicting one group very nicely, but that does not necessarily mean that that model can be transferred.

Some other issues about the Poisson regression model. The number of stones was a highly significant predictor of time to stone-free event in the GS-002 study.

When the Poisson regression model was developed, this was redefined, as you have seen this morning, into either single stone or not, meaning that we have changed from an ordinal, counting variable, into a nominal variable for doing a model.

Also, the categorization of stone size for GS-002 to the largest Medstone program, was different from that used in the Poisson model.

Another issue is that gender was a significant predictor for time to stone-free event in the GS-002, but when we looked at the model that predicts the response in the Actigall group, it did not even enter. That suggests to me, perhaps these two treatment groups need to be modelled differently, or separately.

This other issue is about multiple center clinical studies, and certainly, we do have that; however because the treatment -- the combination treatment and the monotherapy -- were not randomized within centers, and therefore the treatment by center interaction effect cannot be evaluated, as is usually done in such trials. And so, I see this as one other deficiency when one performs a historical control comparison. There is information that one cannot get from

such an analysis.

Okay, just to summarize the main points, main concerns, from this submission. The fundamental issue to me is the group imbalance, and I do not see a satisfactory statistical solution to this problem.

For the Poisson model that was used as an attempt to make an adjustment, you know, the issue I see is the transferability and validation problem, it was a basic problem.

There are other issues that I have not put on here, but were alluded to by multiple speakers this morning -- both this morning and this afternoon and that is, the clinical trial endpoint issue.

We are putting together a group of historical data and making the comparison. Now, had we designed a trial to do a parallel comparison between these two treatments, what would be the most appropriate endpoint? Should it be the 6-month stone-free event; 12-month; 18-month; 24-month? Any one of those, or all of those? Or, perhaps, one should take a longitudinal approach, and follow up these patients.

I will end my presentation to give you a quote from a well-known statistician, I think the quote has direct relevance to the submission we have in front. This is a quote that I have used in some of the courses that I have taught at the Center.

Let me just first note that I put the quote in quotes, because these are direct words from the statistician, so they are not my words. It says that people think -- this is Richard Peto at Oxford University.

"People think that they have tons of data and so they must be able to analyze it to see what works. They say they will use statistics.

"I have spent more than 20 years" -- and that was speaking back in 1994 -- "working as a statistician, and I have got a silver medal from the Royal Society, and I can assure you that you cannot use statistics to adjust."

Thank you very much.

Agenda Item: Panel Questions

DR. MELMAN: Are there any questions of the FDA from the Panel?

DR. JETER: I had that one question.

DR. MELMAN: Yes.

DR. JETER: I have the one question for the FDA and that is that, on January 12, 1998 a letter affirming the no filing decision was issued, and then Dr. Garvey said that the filing letter was issued on March 5, and he implied surprise -- said he was pleased -- and I wondered if we on the Panel might understand --

DR. MELMAN: Why.

DR. JETER: -- why there was this surprising,

pleasing, filing letter? Change of heart, maybe.

MS. RICHTER: I am Kimber Richter, I am Deputy Director in the Office of Device Evaluation. And I was involved in the appeal process of the filing and the decision to file the PMA.

As you have heard today, a number of the issues related to the PMA are scientific in nature, and we thought -- especially at a time when FDA had a new law and were going through a number of procedural changes and so forth -- that we concluded the most efficient way to resolve these issues might be to file the PMA and go forward, bring it to panel, and get some guidance so that we could resolve these, hopefully, as quickly as possible, both for FDA and for the company. And it was that that prompted our decision to go ahead at this time and to file the PMA.

DR. MELMAN: Any other questions? Thank you very much. Dr. Anthony Kalloo is now going to present the synopsis of the clinical study.

DR. KALLOO: I just have a few slides that I would like to present. Dr. Barbara Frank did such an outstanding job summarizing the clinical data from the previous presentation and beforehand.

I must tell you that I am somewhat disappointed that, as a clinician who takes care of patients, that pain was not an endpoint in this evaluation. That is the reason

why we are sending our patients for therapy; we want them to be free of pain. Whereas I know that the goal was to be free of stones, we are not treating the stones, we are treating the patient, and so for me, I was somewhat disappointed by that.

I was also disappointed that, in the ten years since the last submission, that there has been no dramatic, significant changes in the submission, from what I could tell.

We talked about a mechanism of pain and clearance of stones and Dr. Salen alluded to the fact that maybe sludge and microcrystals may be the cause of pain, but ESWL, as far as I can see, does not address microsludge and microcrystals.

I am going to skip over some of these slides and just talk about -- because most of this has been addressed in the previous presentations.

In 1998, the options other than ESWL are listed on this slide. The only option that really prevents recurrence of stones is cholecystectomy. Every other therapy, dissolution therapy, percutaneous therapy, endoscopic therapy, allows the gallbladder to remind in situ, and allows for recurrence of stones. And then one may debate about symptoms and complications, but in fact, it is the only therapy that prevents stone recurrence.

I am going to skip over this -- I am also going to skip this, because it has been presented. The oral dissolution therapy, as we mentioned, there is about a 10 percent recurrence rate in five years. Although side effects may not be a major problem, it is there with diarrhea and abnormal liver enzymes.

I thought that if you are looking at any therapy for gallstones, you have to look at probably what is the standard of care. And cholecystectomy, especially in the last few years as we have improved in our technique of laparoscopic cholecystectomy, has really been shown to have a very low mortality, and in some studies, a zero mortality, and a very low morbidity.

These are some recently compiled results of some very large studies that have looked at the outcome of laparoscopic cholecystectomy, and you can see, in many of them, there is a 0 percent mortality, and a very low rate of major complications, and bile duct injury. And we are looking at studies here that have at least 150, and in two of them, over 1000 patients.

I am not going to discuss the ESWL, except to say that, we know that ESWL does well with kidney stones, but in treating gallstones, there are different issues involved, and the issues are, for one, that kidney stones are calcified and you can use fluoroscopy; it is easier,

simpler.

Gallstones are generally not calcified and you need a bit more technical expertise; you need ultrasound.

Furthermore, with kidney stones, if you fragment the stones, there is a relatively clear path for the fragmented stones. But gallstones, even if you fragment them, there is a potential for obstruction of the cystic duct, which could result in cholecystitis -- acute cholecystitis -- obstruction of the sphincter of Oddi, which could result also in pancreatitis or acute cholangitis.

Furthermore, our urologists have an advantage; the ureter has peristalsis inherent. The common bile duct, there is no peristalsis and hence the ability to clear small fragments is much less.

As you know, this is a study that was initially published -- the first 175 patients -- published in the New England Journal of Medicine in 1988, and essentially, in this study, they found stone clearance rates of 90 percent in 12 to 18 months, when they used a combination of ursodeoxycholic acid. This was the initial study, it was a European study, a German study.

The study that followed this was a study in the United States performed at ten centers, and in this study, the stones varied from 5 to 30 mm, and there were 600 patients at 10 centers.

The inclusion criteria were biliary pain, functioning gallbladder, and stones -- in this study, the stones were less than 30 mm, and less than 4 -- 3 or less. And they found -- just to highlight the results -- that if you had radiolucent stones less than 20 mm, if you had ursodeoxycholic acid, 35 percent were free, as opposed to 18 percent who received placebo. And this was published in 1990 in the New England Journal of Medicine; 18 percent on placebo.

Then the question comes about, well, how many Americans will be eligible for ESWL? This was a study performed by Henry Pitt and Tom Magnuson. They looked at 100 consecutive patients who had cholecystectomy, and they evaluated these patients to see, well, how many of them would be eligible for ESWL?

They used the same criteria that you would exclude if you were going to perform ESWL on your patients. And in that 100 patients they looked at, they excluded patients with greater than 3 stones; with cystic duct obstruction -- I am sorry, this should be stones greater than 3 cm; calcification. The patients had CBD stones or gallstone pancreatitis.

What they found was only a small proportion, only 19 percent of these patients would have fulfilled all the criteria for ESWL. So, you have to think that you are -- in

all this data we have been looking at, this data is looking at this 19 percent who would be evaluable for ESWL.

This is the last slide I am going to show, and it is adapted from the NIH Consensus Conference, which was in the early 1990s, so some of this data is somewhat old, but may be applicable. And what they looked at was the outcome of treatment modalities of gallbladder stones comparing open cholecystectomy, lap choli, lithotripsy, all bile acid therapy, and cholecystolithotomy, a percutaneous approach to removing stones.

They looked at applicability, efficacy of initial stone clearance, adverse outcomes, and patient preference. As you can see, the applicability for open and lap choli; obviously, open was the greatest, with lap choli somewhat less. And lithotripsy, they estimated at 7 to 16 percent. All bile acid therapy, a little less. And cholecystolithotomy, even less.

Obviously, the efficacy of stone clearance with cholecystectomy at this time was 100 percent, and they actually used the data from that very first study that was published in the New England Journal, hence this high efficacy rate. But, the mortality and morbidity are some of the things that you want to look at.

Again, if you look at cholecystectomy, the mortality and morbidity is less than 1 percent. If you look

at discomfort, comparing laparoscopic cholecystectomy and lithotripsy, they were comparable. Leaves of absence of work was again comparable.

Again, this study is -- this was adapted from the NIH Consensus Conference in the early 1980s, so the data is old, but it gives you an idea of the relative comparisons of the various forms of therapy, and where lithotripsy would stand, or ESW would stand in relation to the other forms of therapy. And that is all I have to say. Thank you.

DR. MELMAN: Thank you, Dr. Kalloo. Now, Dr. Joseph Steinbach will discuss the statistical methodology, and present a review of the clinical data.

DR. STEINBACH: What I have to say about the statistics, there was a comment by Dr. Lachin -- We must, then, consider whether uncorrected biases could explain the differences observed.

Now, Dr. Lachin has shown us how to correct for -- and I will probably forget a few items -- physical characteristics like body mass; number of stones; size of the stones.

What he has not shown us is how to correct for things that we do not know about. I am humble enough to know that I do not know everything about gallstones and I do not think anybody else here does, either.

We have been told that there are about a million

patients a year who have gallstones. The large studies have included less than 1000 patients, so obviously, there is some kind of selection going on.

Is it all random? I doubt it. The difference in time of study may be important. The human anatomy has not changed in the last 100,000 years, so presumably, that is the same. But in 1984, when the Actigall studies were being done, there was no effective treatment.

Actigall was not known to work for gallstone dissolution, therefore, the patients that might be referred to an experimental study could be different than those in 1988, where one of the treatment arms was going to be Actigall, which is known to be effective. So, would this influence physician referrals and recommendations? The real answer is, I do not know; maybe you do.

Dr. Lin has said the same thing a different way; that if we just -- we do not know things, and so therefore, we cannot be sure that any particular group is comparable. Having said that, is this data set totally worthless? And I do not think so.

If you go to page 68 in your briefing book, you will see the Group 1 protocol from the protocol 2. And what it shows is that, if you do not pre-treat with Actigall, it is pretty much -- that lithotripsy is not very effective, it does pretty much what Actigall would be assumed to do, and

this is subject, of course, to the difference in populations.

Now, the paper in my copy is thin enough so that right underneath it, is the Group 2 data, and this is pre-treatment with Actigall for a week, before doing lithotripsy.

Now, there have been several suggestions, I am not qualified to comment on them; what about pre-treating for Actigall might not clear out stones? One would be that the gallbladder is filled with something that is less likely to re-form stones -- I do not know. But, what you can see is that, the two groups are different.

Now, one of the statistically acknowledged controls is applying a treatment in such a dose that it is not effective; for example, in the Actigall study, if they gave .5 mg instead of 8; yes, they gave some Actigall, but this could probably serve as a control group. And so that, if we assumed that lithotripsy with no Actigall is an ineffective treatment, maybe the sponsors would care to consider whether they can demonstrate the difference between Group 1 and Group 2 in protocol 002 in the handout -- after I find the reference to it -- protocol 002, Volume 1.7 of 23, page 70 says that, they found a .03 difference in these two groups. So, that is of interest there.

Also, their analysis was confounded by the fact

that, if you do a repeat lithotripsy, that means that the patient had the Actigall pre-treatment by at least a month. So, it is no longer a placebo group.

Now, this leads to a problem of, how do you -- could there be a separate -- where you just consider the effects of one lithotripsy and lose the data for the two lithotripsies? I have not considered all the implications of that statement.

Anyway, to a statistician, the limited size of the Actigall group and the limited size of the combination therapy group leaves the possibility that the two groups are not the same. It is slightly reinforced by the Actigall experience that, for some reason, being in Great Britain reduces your chance of clearing gallstones -- with apologies to my sainted grandmother, I do not think the Brits are different.

A study can pick up differences that we just do not know about, and that is why -- we have gone through this many times, that is why randomized control data is necessary, even though Dr. Lachin has shown us elegant ways to correct for many variables, like body mass, etcetera and stone size.

DR. MELMAN: Do we have any questions about the last few comments? Could I interpret that Dr. Steinbach and Dr. Lin vehemently disagree with the other statistician's

presentation, so that the reworking of the data was not useful, is that --

DR. STEINBACH: It is -- what he has done is correct for things he knows about. If he had a large epidemiologic group -- for example, like a cancer study where you are in the millions -- then you probably have a pretty good cross-section of that population.

If you are based on a study of 1000 out of a fraction of a million, you are -- I am just nervous how good your sample is.

DR. MELMAN: I would like to give the Medstone people an opportunity to respond before we go on.

DR. GARVEY: Interesting and resolutely negative review from the FDA. With respect to -- I want to let John Lachin deal with the statistical issues.

With respect to what Dr. Harvey was discussing, ordinarily, these differences in numbers found by the FDA and the sponsor are reconciled in pre-panel or pre-advisory committee meetings, and I am sure if we sat down together, we could find out where the disparities were, and precisely and just why. There were several problems there that I could have corrected instantly; for instance, keeping track of the numbers of patients remaining in the Kaplan-Meier estimates of gallstone dissolution.

I purposely put the numbers of patients in the

groups at the bottoms of the illustrations, as you will remember, so that one is easy, and just why that escaped his notice, I do not know. However, for the rest of it, most of the differences were minor, and I can assure you, there was no attempt at deceit.

That having been said, I do not feel it is useful to rebut most of what he said here, although the issue of a cholecystectomy in any patient who had an adverse event that precipitated cholecystectomy was included -- that event -- was included in the serious adverse event group. So that these were overlapping groups.

We considered those gallstone pancreatitis, cystic duct obstructions, so forth and so on, we considered these, if they resulted in -- they were all serious adverse events, if they resulted in cholecystectomy. They were also included in the cholecystectomy group.

I think we ought to allow John Lachin an opportunity to deal with what turns out to be, and which we had all decided was going to be, anyway, the central issue, the historical control.

DR. LACHIN: Well, I think what we see here is basically a difference in philosophy. I approached this from the perspective of my mentor, Jerry Cornfield, who was asked to write an article in the American Statistician to answer the question, is there a difference in the evidence

obtained from an observational study versus a randomized clinical trial? And Jerry's response that was published -- and I can give you the citation if you would like -- he said, basically, data is data, and pigs are pigs. Evidence is evidence. There is no difference in the quality of the evidence; there may be a difference in the nature of the evidence.

That is what I was trying to get at in my opening slide that said that the issue here is whether or not we can reasonably reach a conclusion as to the differential effectiveness of one therapy versus another, based on evidence that is not obtained from a randomized clinical trial.

Now, I tried to lay out for you exactly what the issues are. Now, Dr. Lin has said that, statistically, you cannot adjust for differences in the distributions of covariates, and if that is the case, then we should dismiss all of the many articles based on an epidemiologic assessment of differences between smokers and nonsmokers; people who exercise versus those who do not; and many other observational or exposures that are now widely assessed, and whose relative effects are widely believed, based on epidemiologic investigations.

The whole point of that approach, as I said, was to recognize that differences do exist, and then to try and

account for them as best you can. I, for one, am not prepared to dismiss the entire field of epidemiology based on a quote from Richard Peto, who can be highly opinionated, and frankly, I am not aware of the context in which that quote came from. I am sure it is something Richard would say, but Richard is also a highly acclaimed epidemiologist, and has certainly employed statistical adjustments in many of his epidemiologic investigations.

The real issue here is one of philosophy. Are we prepared, are we prepared to set aside, if you will, the holy grail of randomization and accept evidence that is based upon an epidemiologic approach that has now been established and widely accepted in medicine, widely accepted in statistics, as a way of addressing the relative risks associated with either environmental or occupational or chance exposures in a population? As I said, I am not prepared to simply dismiss that.

I should say, I am an ardent clinical trialist. I have published probably over a dozen papers in the Journal of Controlled Clinical Trials on methodological aspects of clinical trials.

I believe that if you want to answer a question as best you can, by all means, you should conduct a clinical trial. But I am not convinced that a randomized clinical trial is the only tool that can be used to answer certain

questions.

As you are aware, the FDA Modernization Act has now opened the door, so to speak, by saying that the FDA should be prepared to accept evidence that is least burdensome to the sponsor. And in that spirit, I feel that these data are indeed compelling.

The issue to me is not whether or not -- whether or not we can say with certainty that a relative effectiveness of 60 percent exists. I do not know what the true rate is. Even if we had a randomized clinical trial, we would not know what the true rate is. But, I am pretty certain that it is no less than that. I am pretty certain it is not on the order of 15 percent or 20 percent.

To me, it would be very difficult to introduce a sampling bias, or to conceive of the sampling bias, that could introduce a difference at this rate, that is observed consistently in analysis over analysis, in using different approaches.

Now, some of the other questions that were raised, such as the question of, can you transfer the Actigall model to the Medstone model? To me, that is an untestable hypothesis, because the question is, does the Actigall model really predict what would have happened had these Medstone patients been treated with Actigall?

I cannot answer that. How can we say that? I

have to take it on faith that the characteristics that influenced -- or were associated with -- gallstone disappearance in the Actigall cohort likely do apply to the patients that were recruited to the Medstone cohort.

Now, it is possible that you are right; we are dealing with, you know, maybe you know, 1/1000th of a sample from the entire population, and it may be that there are some huge sampling biases that have to do with referral patterns that could be related to this. I do not know. I find it hard to conceive, though, that that could operate here.

Now, lots of minor, minuscule things that really were raised -- and as Tom indicated, I think we would be able to resolve quickly if we could sit down with the Agency and say, well, gee, the reason why the Actigall data -- I am sorry -- the reason why the Actigall SBA said effectiveness rates of 30 to 60 percent -- I did those analyses; I helped write that paragraph. And the reason for that is that, when you look at patients within subgroups defined by stone size, and number of stones, it ranges from 30 percent to 60 percent. It is not an overall rate of 60 percent that we are talking about.

Dr. Lin criticized the Actigall analysis for having excluded 20 percent of the patients. As I showed you in my slide, it was 671 patients out of the 715 patients

that did not have common duct stones, and that were the appropriate comparison group. That is 94 percent of the appropriate comparison group in the Actigall database.

Lots of other little things like that that we could talk about, but overall, I think what you need to decide is whether or not you are prepared to accept the philosophy of an epidemiologic investigation of the relative effectiveness of this therapy, the combination therapy, versus the monotherapy.

DR. MELMAN: Yes.

DR. SADLER: I guess what I have to say is not so much a question for the sponsor, but just a statement of where I stand with this, because having chaired the Panel when it was turned down before, I want you to know that I did not come in presuming that it was to be turned down again. I came in to see what could be developed.

I do not have -- not being a statistician, I do not have any great difficulties accepting the fact that you have demonstrated that lithotripsy enhances the effectiveness of Actigall. I did not have any trouble with that in the first place, but Actigall is not a widely-used medication because of its limited effect and its also significant side effects.

The second part of my question, though, is, having demonstrated this, does it matter? Because I do believe

that a laparoscopic cholecystectomy is the gold standard. I do believe that it is applicable to almost the entire population, and it does remove the seat of gallstone formation, because it does not give the abnormal bile a chance to pool, and none of that is changed if we do lithotripsy and remove one set of stones; there may be another along behind it.

Having said that, if this were to be approved for use in some as yet undefined, limited population, how would we possibly keep it from being promoted as appropriate therapy for everybody, since we all know that the most persuasive people in America work for the advertising agencies, and that everybody who sells a product wants to sell as much of it as they can. That is perfectly natural.

I would like to know if you can suggest to me how one would define the applications, the limitations, of the use of such a thing, since this has to be -- if it is appropriate at all -- a niche product. And I really do not find anything explicit that I could say that would appropriately constrain it.

DR. FROMM: I think you are bringing up a very important point which concerns all of us, but it applies to any therapy. Laparoscopic cholecystectomy to this day is abused; is used in patients who should be operated on. It is many times very difficult to decide when a patient has

pain, whether it is really biliary pain. I do not want to go into any details.

I would like to also make one comment --

DR. MELMAN: Could you -- I would like you to answer the question which is, who it is going to be advocated for here.

DR. FROMM: Okay, okay, patients -- I think the indications should be very clearly spelled out, and you know, there are very clear indications for laparoscopic cholecystectomy, and I think there are ways to monitor -- for example, what could be done is a follow-up study, very carefully documented, that the company is asked to document every patient.

You can say, 100 patients, 1000 patients, whatever you want to do, to really determine and to monitor the use of this technology. But I just want to say that with any therapy, there can be abuses, and there are abuses. We see it everyday on TV when --

DR. SADLER: Dr. Fromm, you have not told me how to constrain the use of this therapy, to those who really need it, in lieu of any other.

DR. FROMM: Okay. Now, let me again restate what I said before. I would like to see a restriction to solitary stones, not larger than 2 cm -- and I would say, that the stones which are most applicable, from my point of

view, are those which are larger than 1 cm. So, basically, between 1 and 2 cm, but you know, that obviously is debatable. And these patients should be clearly informed about the treatment options available.

They should be told that surgery, laparoscopic surgery, is gold standard; that that should be the first choice, but they also should be informed about the risk of laparoscopic cholecystectomy -- Dr. Kalloo told us, there is virtually zero risk in terms of complications for lithotripsy, but there are complications from laparoscopic cholecystectomy.

I think there are ways one can very restrictively apply and introduce this technology, and monitor this carefully. I think that is very important, a post-approval follow-up study. And that is a wonderful opportunity to learn about what this technology really can accomplish, because obviously, this was not -- is not the best we can see with this technology.

DR. MELMAN: Dr. Yin.

DR. YIN: Thank you, Doctor. I would like to share with you one more time, we are here, not to try to approve a technology; we are here to look at this particular PMA, this particular device. You can tell from the NIH study, there are other products maybe somewhere, maybe -- whatever. But we are not here to review the whole

technology. We are here only to review the data in front of us, for this particular PMA. Thank you.

DR. MELMAN: Yes, go ahead. Dr. Frank.

DR. FRANK: Go ahead, you go first.

DR. EPSTEIN: I think that, just to summarize or capsulize what we have heard to date -- a lot of issues regarding the historical control, but in the PMA, there was first, the option to go and do those additional studies where there was the use of ursodiol as the sole control, versus using the historical control.

Failing that, it seems to me that, what would have given this panel more comfort level would have been a review, or at least a retrospective follow-up, of those patients that were treated, as an additional set of data points.

Thirdly, to rely on the historical literature is difficult, because there is a wide variability in it, particularly if you look at the German and European literature, where they have higher dissolution rates, and they often use repeated therapies, up to 11 sessions, of shock wave therapy in some of their studies. So, I think that is difficult when we have heard that brought up here.

I think that the PMA, if it had included either the ursodiol control, or if it had some retrospective data on those patients that had already been treated, it might

have brought us more comfort.

DR. MELMAN: What I would like to do is just use this portion to ask any questions, because we are going to go the non-public forum after this. So, just ask questions of people who have presented, and then we will kind of go to a summary statement.

DR. EPSTEIN: And I guess my question was, is there any thought with the manufacturer of doing historical follow-up, or a follow-up, or anything like that?

DR. FRANK: Is the data retrievable?

DR. GARVEY: The data, to a certain extent, are probably retrievable, but I think there is something of a disinclination to do so. This could be done. This could be done, there is no question about it.

I wanted to ask a couple -- the issue of the indications has come up a number of times. You know, what is the right patient group? In some of our early conversations with Steve Fred, I proposed to submit the application, specifically, for patients with gallstones between 10 and 20 mm in maximal diameter and for single gallstones.

Steve told me, no. We want to see the full range of activity of this intervention and hence, he said we could narrow -- suppose if we ever got to the point of approval, we could narrow it at that point. But the directive was,

show it for the full range of stones, both size and multiplicity. And that is why the PMA looked the way it does.

One other thing. Dr. Sadler, you referred to the toxicity of ursodiol, just what are you referring to?

DR. SADLER: No, I did not say, toxicity. I said, it has side effects.

DR. GARVEY: What are those?

DR. SADLER: Many people taking it have diarrhea, some people have abnormal liver function tests, and I --

DR. GARVEY: I think that the incidence of diarrhea on urso is extremely low; and in fact, the incidence of liver test abnormalities, which we in the trade refer to as transaminitis, is extremely low. It is a remarkably benign intervention.

DR. SADLER: But it is famous for having poor compliance with people taking it, I am told. I do not use it, so there is no first-hand experience in it.

DR. GARVEY: I do use it. I am not aware that it is famous for producing poor compliance. Maybe Dr. Kalloo, or Dr. Woods, might have a comment.

DR. KALLOO: Well, diarrhea and abnormal LFTs is a well-described side effect of ursodeoxycholic acid. It is not as high as chenodeoxycholic acid, granted, but it is a side effect.

DR. GARVEY: Very low incidence. Very low incidence.

PARTICIPANT: It is really uncommon.

DR. MELMAN: Dr. Yin.

DR. YIN: Now, I am just going to correct some statements. Dr. Garvey several times brought up Dr. Fred and in fact, this is another center, so this is -- you have submitted through the Device Center, rather than drugs. So, therefore -- not that we have dismissed the agreement or whatever, because if you do bring this back to drugs, maybe they will look at it. But for the Device Center, we just cannot do that.

DR. MELMAN: Thank you very much. Dr. Harvey is now going to present the Panel with questions the FDA would like the Panel to specifically consider and discuss. At this time I would like to remind public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate except at the specific request of the Panel.

Agenda Item: Open Committee discussion

DR. HARVEY: These are the questions from the FDA to the FDA Advisory Panel.

Question 1. The use of historical controls may constitute a valid approach to clinical study design. However, differences between the study and control groups

can be problematic when using this approach. There are several differences in the clinical protocol and the patient populations studied between the Medstone STS lithotripter/Actigall combination therapy, and the Actigall historical databases, including:

The differences in physical characteristics of the study populations, including mean body weight, mean percent ideal body weight, percent of patients with single gallstones, and distribution of patients with respect to maximum gallstone size.

Also, differences in the clinical practice during the time periods of data collection -- 1988-1990 for the Medstone STS lithotripter/ActigalI combination therapy, 1976-1984 for Actigall database.

Also, differences in imaging techniques used to visualize gallstones; and that is, oral cholecystogram versus ultrasound.

Finally, differences in the dose and treatment regimens of Actigall.

Therefore, based on the PMA data, including the information contained in the Panel briefing package:

A. Do these differences affect the validity of the Actigall database as a historical control for the Medstone STS lithotripter/ActigalI combination therapy studies?

B. Does the sponsor's proposed statistical method adequately address these differences, making a meaningful comparison between the Medstone STS lithotripter/Actigall combination therapy and Actigall monotherapy groups possible?

C. Are there concerns that the statistical method utilized has not been validated?

DR. MELMAN: Okay, what I will do now is give every Panel member a chance to comment after these questions.

The first question is -- which was just read to you -- really, it involves the use of historical controls that may constitute a valid approach to clinical study design. Whether the differences between the study and control groups can be problematic, using this approach.

There are several differences in the clinical protocol in the patient population studied between Medstone STS lithotripter/Actigall combination therapy, and Actigall historical databases, including differences in physical characteristics; differences in clinical practice during the time of the data collection; differences in imaging techniques; differences in the dosage and treatment regimens of the Actigall. Based on the PMA data, including the information contained in this Panel briefing package, these are the differences.

I would like to give everyone a chance to make their comments now, and we will start with Dr. Sadler.

DR. SADLER: My reservations are not so much about the historical control as about the product itself, so I will not belabor it. I do believe it would be more desirable to have a concurrent control group, but this is not my consummate concern.

DR. MELMAN: Dr. Donatucci?

DR. DONATUCCI: Well, I think -- I mean, we talked about the philosophical difference before, and I think -- I have a little bit of a philosophical difference in the sense that, this was a study designed in the 1980s; the bar has been raised in the 1990s. I do not think, if this study had been recently designed and performed, this would be satisfactory.

I do not think using the current requirements, that this study would not be -- this historical control would not be appropriate. But this is not a study that was recently designed. We are looking at a study that was done ten years ago.

It cannot be redone, realistically, given the market conditions. And we have a separate question to answer which is, is there still utility for a subset of patients? So, while I am not completely philosophically comfortable with it, I think I can accept it, in this

instance.

DR. MELMAN: Dr. Vertuno?

DR. VERTUNO: I certainly cannot resolve the differences between the dueling statisticians. I am not terribly troubled by the data as it has been presented. I am sorely disappointed that we do not know the natural history of the efficacy of treatment of those patients who were treated ten years ago. And it is just not acceptable to me that -- well, there is no interest in follow -- I mean, no resources to do the follow-up.

A patient list must be available. Questionnaires could be sent out. I think that is crucial data which needs to be obtained.

DR. MELMAN: Dr. Frank.

DR. FRANK: I do not have a great deal of problem with the statistical evaluation. I also do not feel competent to evaluate it, but I would tend to agree with Dr. Donatucci's comments.

DR. MELMAN: Dr. Epstein?

DR. EPSTEIN: Yes, I would echo the same position, as well.

DR. MELMAN: No comment? Dr. Steinbach?

DR. STEINBACH: The parts A, B and C? I am not bothered by the fact that they are making adjustments for known differences in gallstone size, etcetera. Adjusting

data, I might disagree with Dr. Lin here, is standard; however, I think in view of the small size of the groups involved, that that in and of itself is not adequate, because we have a fairly small difference between the Actigall alone and lithotripter/Actigall, so we have to know what Actigall alone will do with moderate precision, not, you know -- If we were 20 percent off, then we would not see those differences.

My concern is that the statistical method utilized has not been validated, I am not -- I do not object to the proposal because of Part C, I guess is the way to say it.

DR. MELMAN: Dr. Kalloo?

DR. KALLOO: I am not a statistician and it appears that we have to deal with the data we have, and so, whereas I am not 100 percent happy with the methods of analysis, I am willing to accept, with one provision that, as Dr. Vertuno mentioned, that there should be follow-up data on those initial patients that were treated. We should be able to get some follow-up on that initial group that was treated from the first submission.

DR. WOODS: I would agree with everything that has been said. While I am not a statistician, either, I believe that the information as presented by Dr. Lachin is acceptable to me. And I agree on the long term follow-up information.

I think that we show sort term efficacy with lithotripsy, but we have no information on long term outcomes, and the information we do have, historically looking at patients who have had medical dissolution of gallstones, suggests that there is a very high recurrence rate, and when you have a gold standard as medically acceptable as laparoscopic cholecystectomy, I feel we have to weigh this technology very, very carefully before we allow its widespread use.

DR. MELMAN: I would like to make a comment, also, and that is that I tend to agree with two of the comments and that is that, you are asking us to make a decision about your product with incomplete information.

In a way, if you were coming to us as a patient asking us to make a decision about you with incomplete information, we would be -- it is like asking us to operate on you with both hands tied behind our backs. And I am not sure that that is fair. And I think that is a big issue for us.

Now, Dr. Kalloo is going to kind of summarize the first question, the Panel's response to the first question.

DR. KALLOO: The consensus on the Panel's response is that, whereas the statistical methods are not ideal, and in the best of worlds could stand significant improvement, that it is acceptable to the Panel, with the provision that

we receive follow-up data on the patients that were initially treated.

DR. MELMAN: Okay. We will go to the second question.

DR. HARVEY: Question 2. The Medstone STS lithotripter-Actigall combination therapy clinical data consists of three separate trials: GS-001, GS-O01, and GS-004.

A. In your opinion, how similar or different are there trials?

B. Based upon the PMA data, including the information contained in the Panel briefing package, is it valid to pool the data from these three individual studies?

C. Are there concerns regarding the pooling of the data from the different investigational centers participating in the GS-OO2 study?

DR. MELMAN: We will start counter-clockwise. Dr. Woods?

DR. WOODS: I really have no problem combining the data as presented, particularly when we take out and look separately at the patients pre-treated with Actigall, so I think the data is acceptable as presented.

DR. KALLOO: I also concur with her statement.

DR. MELMAN: Dr. Steinbach?

DR. STEINBACH: I have no problem with the pooling

or of any of the groups.

DR. JETER: No problem.

DR. MELMAN: No problem. Dr. Epstein?

DR. EPSTEIN: I concur with that.

DR. MELMAN: Dr. Frank?

DR. FRANK: As well.

DR. MELMAN: You agree.

DR. VERTUNO: Support.

DR. DONATUCCI: No problem.

DR. MELMAN: No problem with that, Dr. Donatucci, Dr. Sadler?

DR. SADLER: -- constitutes 75 percent of the whole package, anyway.

DR. MELMAN: Could you lean closer -- there is a request that -- you are so mellow, that --

DR. SADLER: One of the studies constitutes more than 75 percent of the total population, it seems to make very little difference that they pool.

DR. MELMAN: Dr. Kalloo could you give an easy summary of that response?

DR. KALLOO: Yes, the summary is that the Panel accepts the combination of the different separate trials; it is acceptable.

DR. MELMAN: The third question?

DR. HARVEY: Question 3. Based upon the PMA data,

does the proposed indications for use statement adequately define the appropriate target population for the use of the Medstone STS lithotripter/ActigalI combination therapy?

DR. MELMAN: Dr. Sadler?

DR. SADLER: No. I think we can discuss it and expound upon it later, but I think it is clearly too broad, and my request for suggestions for explicitly narrowing it have not been responded to in an explicit way.

DR. MELMAN: Okay.

DR. DONATUCCI: I would agree that, as written, it is too broad. I do not know whether we are going to have a discussion about that point now or afterwards. I mean, in a sense, there seems to be some of the things that would make it too broad are covered in the subsequent questions, it seems.

DR. MELMAN: Well, let's do it now, so -- before we forget about what you are going to say. What would you like? I thought they actually did respond to the question.

DR. DONATUCCI: Well, right, but as written here --

DR. MELMAN: Yes. Okay.

DR. DONATUCCI: -- the question.

DR. MELMAN: Okay, so what would you like it to be? Yes.

DR. DONATUCCI: Clearly, I think that, in the

presentation, the sponsors did say -- I mean, they were not equivocal about it -- that this is not first line therapy for all patients, clearly. It is not even first-line therapy for the majority of patients. So, I would like a statement of some clarification because that is not expressed in this statement.

DR. MELMAN: Well, we could make a recommendation as to what we would like the population to --

DR. DONATUCCI(?): Is that correct, Dr. Yin?

DR. YIN: Yes.

DR. MELMAN: So, what I would like you to do now, and maybe we will have a little quick conference, we will come back and state what you would like the target population to be.

DR. DONATUCCI: Well, I think what we discussed earlier is there are certain subgroups of patients who are nonsurgical candidates that, for whatever reason, refuse to go through surgery.

That would be the target population in my mind; what I do not think we want to say is that, this is a therapy that can be equated to what is the gold standard, because I do not think that serves the general patient population well, if that is misunderstood.

DR. MELMAN: What about the restriction on the size of the stone or number of stones?

DR. DONATUCCI: Well, I think single stone has clearly been the -- it should say, single stone, and not greater than 20 mm in size.

DR. MELMAN: Okay.

DR. VERTUNO: The sponsor has clearly already modified this particular recommendation, and I think that needs to be heeded.

For want of a better term, this really becomes an issue of informed consent for me. We have to identify, particularly, that very small patient population where this may be an optimal approach, rather than offer this as an alternative for everybody else.

The patient needs to be advised that this is not definitive therapy, it is palliative therapy; it has a 40 or 50 percent chance of short term success, with a 50 percent chance of failure over the next five years. So, we are looking at long term results of 20, 25 percent. And this is not a question of somebody saying, no, I really do not want to be operated on.

There are some comments farther down in the document that say we have never made patient information part of the labeling, but I think we ought to really consider that, if we consider approving this.

DR. MELMAN: Dr. Frank?

DR. FRANK: I would strongly agree that approval

of the lithotripter should require that there be a patient information brochure that outlines the options that are available to the patient, as well as the risks and efficacies of the options. And I think that a solitary stone less than 20 mm is essential.

I do not how to spell it out, but I do not think this is a procedure for a young and healthy individual, even if they do refuse surgery, because the rate of recurrence is so high.

On the other hand, I do think that there are elderly patients; I think there are patients who have had multiple intra-abdominal procedures, and therefore are at high risk for bile duct injury with a lap choli, who definitely would be appropriate candidates for this procedure. And I think a patient information brochure might cover those things.

DR. MELMAN: Okay.

DR. EPSTEIN: I share Dr. Frank's concerns, because I believe that many patients are looking for a quick fix for their problem, and they are always asking, can they have a laser or some way to break up their stones. They have heard about this, and they think it is still available, and I agree that it probably should not be first-line therapy and should be restricted to those people that cannot, for medical reasons, undergo a laparoscopic

cholecystectomy, at least initially.

DR. MELMAN: Dr. Bennett, would you --

DR. BENNETT: Yes, I have a technical issue with this. I am experienced with renal lithotripsy and the variability of stones and the number of shock waves. It could be that in 1988 to 1990, when these patients were treated, that 2400 shocks might have taken care of some stones, although we know that some renal stones go at 1000 shocks, and some you have to take to 3000. And I would be very hesitant to put a number of shocks on a labeling, because now you are talking about medical treatment issues, and --

I mean, dosing of drugs is a lot different than the number of shocks you give to a particular stone, and so that is the comment that I have concerning this particular labeling issue.

DR. MELMAN: Dr. Steinbach?

DR. STEINBACH: I agree that the indication for use should somehow refer to the desire -- and I will leave it that -- to avoid surgery.

DR. MELMAN: So, that is a broader indication, because that gives the patient the right to decide what they want, not necessarily how old they are or what their --

DR. STEINBACH: Yes.

DR. MELMAN: Okay. Dr. Kalloo?

DR. KALLOO: Well, I agree with Dr. Sadler that the sponsor did not make clear the indication for use, but I certainly agree, and there is a subgroup who may have a single stone, less than 20 mm, that would be an appropriate indication for this.

DR. WOODS: Well, I agree with, particularly I think what Dr. Frank said, and that is that this procedure should not be offered to patients who are surgical candidates. And I have grave concerns that if this is approved -- as Dr. Sadler pointed out earlier -- with advertising and marketing and patient-driven decisions being made these days a lot of times by physicians, that patients who really should have laparoscopic surgery for their gallstones are going to come and have lithotripsy, not always for the right indications.

I would say that we should be very strong in our statements that this is a nonoperative technique that should be offered only to patients who are not fit for surgery. And I agree with the other indications that have been stated.

DR. MELMAN: I have a question for you, though, and I am surgeon, and I do not understand how you could tell someone they must have surgery and not a nonoperable procedure. I do not see -- I cannot imagine telling a person that.

DR. WOODS: Well, right now, you know, their choice is to have nothing, or Actigall, or to have surgery. And in a young, fit, healthy person -- and there are a lot of them out there who come into your office saying, well, I have these symptomatic stones and I heard about this laser thing and what can you do, I am afraid of surgery? And the bottom line is, they really do not understand what the surgery is about.

It really is an inform issue, it is not so much I think the patients wanting to avoid surgery. I think they are just fearful of the unknown, and I think properly explained, the vast majority of patients would opt for the long term, permanent solution, which is cholecystectomy. It is not leaving a diseased gallbladder in.

DR. MELMAN: See, the problem for me with this is that we really do not have any long term data here, and it is almost impossible -- it would be almost impossible for you to make a recommendation to the patient because you do not know what happens at five years in the people who have had this; you just do not know the information.

DR. DONATUCCI: But, didn't we say earlier there was a 50 percent failure rate in medical therapy, regardless of whether it is hastened by biliary lithotripsy or not?

DR. MELMAN: I do not think we know what happened with these people.

DR. WOODS: We can only draw on the Actigall data, the dissolution data.

DR. DONATUCCI: Fine, but I mean, the only difference I think is that this --

DR. MELMAN: We do not know. We do not know if the treatment makes it better, it might even make it worse. It may make it a more active occurrence, so you do not know.

DR. KALLOO: The only thing you know is that once the gallbladder is in, stones will recur.

DR. DONATUCCI: Right. If surgery removes it, it is not coming back. I accept that, there is no question about it.

DR. MELMAN: But that is a much harder question to --

DR. KALLOO: But you are saying -- what you are saying is right. It could potentially accelerate -- [simultaneous discussion]

DR. MELMAN: Yes, we have no information.

DR. KALLOO: We have no idea. There is no data.

DR. WOODS: You know, we already know -- it has been said a year of Actigall may cost $2,400. I do not know how much a treatment is going to cost, I would guess in the range of $1,500 to $2,000 for a physician charge, not including facilities fees. Then you start looking at how much does it cost to do a lap choli and, you know, if you

have a re-treatment, a third of the patients had a re-treatment, I --

DR. MELMAN: But I think cost is not in our purview here. The question that has been put to us is whether we should approve this application, and the cost is not the issue. The cost will be decided by other people. It is not that it is not relevant, but it is not within our purview.

Dr. Sadler, you wanted to say something? Craig?

DR. SADLER: Well, all I was going to say is that it sounds as if we certainly think that if this were to be done, it must be done with a patient brochure that gives explicit information, where we have it; that gives warning about the difference between palliative therapy and extubative therapy. And so, we would --

It would have to be a fairly carefully designed and thoroughly informative brochure to go with it. And, because we do not have the information, it would also be necessary that there be a follow-up to find out some of the things that have been raised.

DR. MELMAN: Dr. Kalloo? I am asking you to summarize this. You are summarizing each question.

DR. KALLOO: Okay. It appears that a consensus is that, there is a subset of patients in whom the indication of a single stone less than 2 cm in diameter, but with the

provision that there should be labeling and patient instruction. And the labeling should describe ESWL as:

1. Inferior in efficacy to cholecystectomy;

2. That it is not recommended for young and healthy patients;

3. That -- well, there was one issue that was brought about the number of shocks, but I do not think we have enough data to change that, so I have to leave that alone.

DR. FRANK: Maybe the FDA can say. Does that all go into the labeling, or does it go into a separate patient information brochure?

DR. YIN: You need to put it in both, for the physician labeling, and the patient labeling. You cannot just put it in the patient, without telling the physician what is in the patient labeling. And Dr. Bennett's statement is very good. Can anyone recommend how to do it in other ways?

DR. BENNETT: You just cannot tell a doctor how many shocks to give, and I do not know -- I am sure that your patients had a variety of shocks. I have treated a bazillion stones in the lithotripter, so I mean, I know --

DR. KALLOO: But that is a different -- that is a different stone -- [simultaneous discussion]

DR. BENNETT: -- that -- it is a different stone;

it is a different make-up, but I can --

DR. KALLOO: -- different differentiation.

DR. BENNETT: -- I will bet some stones break up with 1000 shocks and some -- 100 shocks -- and some you would -- it has to do with the bond, the chemical bond, and the crystal -- you know, whether they are cholesterol stones or --

DR. KALLOO: Yes, but you are bringing up a different issue of adverse events and problems with --

DR. BENNETT: No, actually, not. You can give a kidney 3000 shocks and you will get no more hematuria than you would if you gave him 1000 shocks. There is no evidence that increasing the number of shocks does any more damage.

Nor does re-treatment. And that has been studied for the kidney; it has been studied for hypertension; and Lillian knows this. So, what I am saying is in labeling like this -- I mean, it is like telling a surgeon how many sutures to put in the skin when he closes a wound.

DR. KALLOO: Yes. The problem is, we do not have that data for the gallbladder. You could surmise --

DR. BENNETT: We did not have it -- Lillian, what about the kidney --

DR. KALLOO: -- you could surmise and assume --

DR. BENNETT: -- what about the lithotripter approval? Does it tell the surgeon how many shocks to give

the kidney? I do not think so.

MR. ST. PIERRE: Don St. Pierre, FDA. Actually, for the renal lithotripsy, that information is in the labeling, but it is not part of the indications statement. So, you can still have this information in the labeling for the physician, and also put it in the patient brochure for the patient if they want to know that information, but it does not necessarily have to be part of the indications statement.

DR. YIN: But the important thing is, we know what -- you know, what to put in. But Dr. Bennett's question is, do we know what to put in?

MR. ST. PIERRE: Well, I think that the number that should be put in there --

DR. YIN: Well, if we do.

MR. ST. PIERRE: -- should be what was studied.

DR. BENNETT: The sponsor has already said that they had a wide variety of shocks that they used, so maybe, to solve the problem, they could just put the range of what they used in these, you know, 600 or 700 patients. Which might solve the problem.

MR. ST. PIERRE: I guess that is for your discussion.

DR. MELMAN: I find lithotripsy very boring and I give that to other people to do, so --

DR. BENNETT: I do not do it any more, either.

DR. MELMAN: But I think you cannot say you -- you see, I think the problem is, if you put somewhere in the labeling that you have -- you can only give a maximum of 2000 shocks, and you give 2100 and there is a complication, that the lawyers are going to jump all over the -- that is the problem.

I think that what Dr. Bennett suggested was a very good idea, and that you could put a range, a suggested range, and that that is how it should be listed, without giving an absolute maximum. And the FDA can take, look at it -- suggest that to the FDA, that they take that under advisement.

The next question.

DR. HARVEY: Question 4. Does the PMA data support the current indications for use of treatment of radiolucent, non-calcified stones between 4 and 20 mm in maximum diameter?

Should other stone characteristics, such as the number of stones -- single versus multiple -- be considered?

DR. MELMAN: Well, Dr. Kalloo, why don't you just summarize that, because we have kind of beat that to a pulp. We have talked about that.

DR. KALLOO: What we said was that the PMA data supports the treatment of a single, radiolucent, non-

calcified stone less than 20 mm in diameter.

DR. MELMAN: That is our summary. Next.

DR. HARVEY: Question 5. Considering the indications for use as discussed earlier and the risks and benefits of shock-wave biliary lithotripsy as demonstrated in this PMA, do you believe that the Medstone STS lithotripter, in combination therapy with Actigall, is reasonably safe and effective for the treatment of symptomatic patients with gallstone disease?

DR. MELMAN: Dr. Sadler?

DR. SADLER: I believe that it is probably safe and it is somewhat effective. I wish that it were better, but there is not evidence that it is, and when we talk about symptomatic patients with gallbladder disease, we have to drop symptomatic, because we do not have any data.

DR. DONATUCCI: I agree with those comments.

DR. VERTUNO: Agreed.

DR. FRANK: I would agree, with the qualification that this be followed up with careful subsequent follow-up of the patients to see what really does happen as far as efficacy.

DR. EPSTEIN: Just quoting a little bit from an editorial in Gastroenterology, it says that the biliary lithotripsy is competitive with laparoscopic cholecystectomy in only 7 percent of patients with stones.

Even in this group, lithotripsy is unlikely to find a following, because of the need to regionalize services, to make it more cost-effective and clinically effective.

They also point out the need for repeated treatments; the average cost of the treatment of $2,000 per session for kidneys, and similar costs assumed for biliary. And up to four treatment sessions, in some cases.

The need for taking medicine for up to a year, which increases the cost. Repeated exposures to anesthesia or conscious sedation and repeated trips back to the hospital. Not to mention and overall 10 percent complication rate with abdominal pain, and particularly in the first two months of post-treatment, you tend to get recurring attacks of biliary colic and then the question is, is that pancreatitis? Do they have to be seen by the doctor? Do they have to come back? What are those painful attacks.

I think those questions are still hanging open at this time.

DR. MELMAN: So, what do you think? I mean, you kind of raised questions, what is your opinion?

DR. EPSTEIN: That all the answers are not in.

DR. MELMAN: Dr. Bennett?

DR. BENNETT: No.

DR. MELMAN: No comment?

DR. STEINBACH: I do not think that, as written so far, they have shown that it is safe in the sense, reduces number of hospital days, versus not doing it. And effective in gallstone disease.

DR. MELMAN: I did not see any information about hospital days.

DR. WOODS: No. There are no --

DR. MELMAN: There are no hospital -- it is an outpatient procedure.

DR. STEINBACH: Well, the hospital days would be saved lap choli days. They gave some evidence that, group two, that it went down from seven lap cholis to two, depending on whether you used the effective treatment or not. So that you could balance saving the patient that unpleasantness would tend to compensate for the problems with the procedure.

People forget that safety means, it is the difference of whether -- before -- to the extent it saves you other problems, it is allowed to have side effects; it has some. There are not major.

DR. MELMAN: Dr. Kalloo?

DR. KALLOO: I think, based on the data that it is reasonably safe. We have no data about symptom relief, so based on the data, I cannot say that it is effective.

DR. MELMAN: Dr. Woods?

DR. WOODS: Go ahead.

DR. KALLOO: Specifically, because the question asks, treatment of symptomatic patients.

DR. WOODS: I believe it is reasonably safe as presented and it is effective in the short term, at least we know, in removing gallstones from the gallbladder. I cannot comment, as Dr. Kalloo said, on the symptoms or the long term efficacy, but as presented and as discussed, I think I agree with that statement.

DR. MELMAN: Would you like to summarize?

DR. BENNETT: Arnold, can we ask the FDA what they meant by symptomatic?

DR. MELMAN: Sure. Would you like to ask?

DR. BENNETT: I did.

DR. YIN: Fine.

DR. BENNETT: I mean, in this question.

DR. HARVEY: Well, this question just relates back to the indication for use statement, so we were basing it on the fact that both the Actigall NDA -- so, the drug component as well as the combination lithotripsy-Actigall combination, indication of use, says it is to be used in symptomatic patients, as opposed to asymptomatic. So, all the standard definitions of symptomatic apply --

DR. MELMAN: Which are?

DR. HARVEY: Well, I guess --

DR. FRANK: Biliary colic.

DR. HARVEY: Biliary colic, pain --

DR. BENNETT: But that was never one of the primary or secondary endpoints in the study.

DR. HARVEY: That is true. It was an entry criteria.

DR. BENNETT: -- entry criteria. But it was not followed in the --

DR. HARVEY: Well, except it was -- of course, it was done retrospectively through the Co-Start(?) analysis, where they looked at pain, the abdominal pain, gallbladder attack. And of course, that is where the issue of under-representation of adverse events came up.

DR. YIN: But you were correct.

DR. MELMAN: I am not sure I understood that. What are we calling a symptomatic person, now? Someone who is entered in because they had right upper quadrant pain and they belched?

DR. BENNETT: Well, you know, the way I am reading it, for the purposes of the study, symptomatic patient -- because it is all that is really measured -- is whether the stone was eliminated. Because we do not have any data on pain, post-treatment. But, the entry criteria to get in the study, from what I gather, is colic, as one of the entry

criteria. But, colic episodes were not measured --

DR. MELMAN: As an endpoint.

DR. BENNETT: As an endpoint.

DR. KALLOO: Stones, by definition, are not symptoms. Colic would have to be the definition of symptoms. Stones are a clinical finding.

DR. MELMAN: So, your point is that -- what you have said already is that, basically there is no measurement of the relief of symptoms after this treatment.

DR. KALLOO: No. That is correct.

DR. MELMAN: Okay. So, why don't you summarize now?

DR. KALLOO: Based on the data that the Medstone STS lithotripter is reasonably safe, no efficacy has been demonstrated for symptomatic relief. There is data to show efficacy in elimination of a single gallstone of less than 20 mm.

DR. MELMAN: Okay. Question 6.

DR. HARVEY: Question 6. And it is referring to the medical device-drug combination labeling.

Is the proposed contraindications section appropriate? Are there any additional contraindications for the use of this device?

For those who do not have that handy, this is the contraindications section in the labeling. It is:

Coagulation abnormalities as indicated by abnormal PT/PTT bleeding times, including patients currently receiving anticoagulants, including aspirin;

Inability to tolerate general, intravenous or spinal anesthesia or analgesia;

Pregnancy;

Inability to image or position the stones; and

Evidence of bile obstruction, cholangitis, pancreatitis, cholecystitis, or significant liver disease, such as hepatitis.

DR. MELMAN: Dr. Woods, would you like to comment?

DR. WOODS: Okay. Number two, inability to tolerate general IV or spinal anesthesia or analgesia. I do not know that we have to include general anesthesia there, since we are hopeful that this procedure would replace lap choli and general anesthesia in people who do not qualify for surgery, so, we may want to eliminate that.

Also, I think we should include some of the criteria that we have already discussed that allowed patients to enter this study; for instance, the cystic duct needs to be patent; you know, the size of the stone, the number of stones, that we have already discussed.

Also, I am not clear, since the shocks are administered with the QRS complex, if the patient has an arrhythmia, is that a relative contraindication? Is that an

absolute or a relative?

DR. GARVEY(?): [Comment away from microphone] -- Absolute.

DR. WOODS: So, any cardiac arrhythmia, a baseline arrhythmia. Intermittent PVCs, does that count?

DR. GARVEY(?): [Comment away from microphone] -- It could.

DR. WOODS: And what if they have a pacemaker? A pacemaker is okay?

DR. GARVEY: No, it is not -- [simultaneous discussion]

DR. MELMAN: -- you would have pacemakers and arrhythmias.

DR. WOODS: So, all the people that we want to do this on, cannot have it done.

DR. SADLER: I guess the other contraindication is the absence of biliary colic -- [simultaneous discussion]

DR. BENNETT: Well, an occasional PVC is not a -- an occasional PVC is not a contra --

DR. MELMAN: I think we are getting giddy. Dr. Kalloo, do you have any comments?

DR. KALLOO: No, I absolutely agree with Dr. Woods. We must include the criteria that -- we must have as contraindications the criteria that excluded patients from the study. And I think cystic duct patency is very

important, and all the other factors. I, right now, cannot think of any other factors -- the cardiac arrhythmias and pacemakers should be added to that list.

I think if the patient cannot tolerate general anesthesia, in addition to the others, they should be excluded as well, to be honest with you. So, I disagree with that. That is it.

DR. MELMAN: If they cannot tolerate general anesthesia? Why would you have that -- If they do not tolerate the procedure, you just stop.

DR. FRANK: I think the patients we need to do it on are the ones that we are concerned about submitting to general anesthesia, so I -- I would not want to make that a contraindication.

DR. STEINBACH: Item 5, there are reports in the literature that extracorporeal shock wave is very effective for common bile duct stones -- different machine -- but --

DR. MELMAN: But they are not putting in for that here.

DR. STEINBACH: Yes, I guess it is the problem of putting in for it and precluding --

DR. SALEN: It is the same machine but a different position. Instead of the patient being prone, they sit up; instead of using ultrasound to focus, it is done like the kidney, with the bile duct visualized with radiopaque

material on the stone. But it can be used effectively.

DR. MELMAN: That is not --

DR. YIN: Just to remind everyone. You are only reviewing this PMA.

DR. MELMAN: Right. It is not for this indication. It is a good idea, but it is not for this indication. Dr. Bennett? No. Dr. Epstein?

DR. EPSTEIN: I just think --

DR. MELMAN: Just lean forward, so that --

DR. EPSTEIN: Oh, I am sorry. Yes, the general anesthesia, I -- I mean, I think that that would be a good group to treat, and since we have heard that they subsequently switched from using -- at least at some sites -- from using the general to the intravenous conscious sedation, then that should not be a contraindication to any labeling.

DR. MELMAN: Dr. Frank?

DR. FRANK: I am not sure why the liver disease is a contraindication. I do not think that should be a contraindication.

DR. MELMAN: Why did the FDA include that?

DR. HARVEY: This was taken from the company's proposed labeling, so I asked them.

DR. YIN: Dr. Garvey, please?

DR. GARVEY: The reason that I did that is, I was

not thinking so much about hepatitis, but you know, obstructive liver disease, and other sorts of liver disease, where you might interfere with the secretion of the bile acid into the gallbladder, and obviate the effectiveness of the urso.

DR. KALLOO: Cholestatic liver disease.

DR. GARVEY: Cholestatic liver disease.

DR. MELMAN: So we could add that word to it.

DR. GARVEY: Yes, that would do it. Cholestatic liver disease is an obvious contraindication.

DR. SADLER: Well, you know, until we know better, it might be just as well to be reluctant to put shock waves into an actively inflamed liver.

DR. MELMAN: Dr. Vertuno?

DR. VERTUNO: No comment.

DR. MELMAN: No comment?

DR. STEINBACH: I am out of order, but I think -- I do not see in the precautions that the patient having a functioning gallbladder is -- maybe this is not the spot to write it --

DR. KALLOO: No.

DR. FRANK: They mentioned patent cystic duct -- [simultaneous discussion]

DR. KALLOO: Patent cystic duct, probably should imply, and a functioning gallbladder, yes.

DR. MELMAN: Okay. Good idea.

DR. DONATUCCI: And I am not sure whether this should be listed under contraindications or precautions, but for the same stone, multiple lithotripsies may not be -- I mean, is there a limit to the number of treatments for the same stone, or when do you consider it a failure? Is it contraindicated after three shock waves? Should you go back and try to shock it again?

Where does that have to be -- is that something that needs to be considered?

DR. MELMAN: That is not a -- I do not think that is something that should be put in the contraindications.

DR. DONATUCCI: Does that fall into the same category as the number of shocks?

DR. MELMAN: Yes. Dr. Sadler?

DR. SADLER: I concur with the expanded list.

DR. WOODS: One other thing, should we put inability or refusal to take oral dissolution therapy, following the procedure?

DR. STEINBACH: Do we have to, because that is part of the therapy -- I am getting -- professional advise says yes, it would have to be there.

DR. MELMAN: Really, the people will have to have been on the drug a week before they get the shock wave treatment. I do not think we should list that.

DR. KALLOO: Well, it is important, because if we are fragmenting stones, and we do not have the oral dissolution therapy, you will run into the problem of fragments going into the cystic duct and causing acute cholecystitis, or obstruction of the sphincter of Oddi, so I think that is an important aspect, based on the data we saw, actually, presented here.

DR. MELMAN: I think that, for the people to have the treatment, though, have already been on the medication for a week or they cannot be treated that way, so. It seems like that is overkill to me.

DR. KALLOO: It is not an overkill, because if you fragment the stones with oral dissolution therapy available, you run the risk of passing fragments into the cystic duct that can obstruct the cystic duct and cause acute cholecystitis.

DR. MELMAN: Right. But they cannot be treated unless they go on oral therapy first.

DR. STEINBACH: Dr. Kalloo, we agree with you, it is just that the treatment proposed is that they take the pill. And it seems redundant to put it into the contraindications that they refused to take the therapy.

DR. WOODS: My only concern, though, is that we have patients who need Actigall for other reasons, who frequently do not take it because they cannot afford it, or

cannot get it, or in some instances, in patients who might have this procedure, perhaps we are doing it to them because they cannot swallow, or they would not be able to take a pill, for whatever debilitative reason they have, that we chose to do lithotripsy over surgery.

I think maybe it needs to be explicit.

DR. STEINBACH: But isn't the PMA for the combination?

DR. YIN: That is an indication --

DR. WOODS: I mean, we are assuming that they are going to stay on it for probably six months after. I could easily see patients being on it for a few weeks and falling through the cracks and not staying on it until their stones have been documented to --

DR. STEINBACH: Okay.

DR. YIN: But you are aware that contraindication has a very special meaning; meaning, it cannot be done, not because it is not nice. Okay, contraindication --

DR. KALLOO: Well, we are saying that there is a problem if the patient is unable to take an oral dissolution agent.

DR. BENNETT(?): Inability to take oral dissolution agent.

DR. MELMAN: Those patients could not have the study to start with.

DR. BENNETT: Right, that is true.

DR. YIN: Yes, that is right.

DR. MELMAN: So they will not get the treatment. So we are fair, I am going to take a little informal vote on this so that you can make your conclusions. How many people are in favor of listing in the contraindications that they must have the ability to take the oral medication -- of the voting members of the panel?

DR. FRANK: I vote we leave it up to the FDA.

DR. MELMAN: No, we are just making a recommendation, they can do what they want, anyway.

DR. FRANK: But I think they have policies.

DR. MELMAN: No, but -- no, but -- we have to make a recommendation in the list of contraindications now. So, we have to decide among us whether we are going to include that. So, does that mean that -- the people who raised their hands, that you want that to be included as a contraindication? Is that what you meant?

Let's do that again. How many people want to be listed as a contraindication that people must be able to take the oral medication both before and after? Two. Okay, so the nays have it, then. Okay. So, you are going to summarize, Dr. Kalloo?

DR. KALLOO: Right. The listed contraindications, the modifications are that we will remove from

contraindication, number 2, general anesthesia; that we will change to cholestatic liver disease; that we will add to the list of contraindications all the criteria that were used to eliminate patients to begin with. That is, calcified stones, stones greater than 3; stones greater than 20 mm.

We will also include cardiac arrhythmias and pacemakers. And we will also include that patients -- it is a contraindication that there is a cystic duct obstruction or non-functioning gallbladder.

DR. MELMAN: Okay, next question?

DR. HARVEY: Question 7. Should the labeling include a warning or precaution statement which alerts users that the long term (beyond 18 months) effectiveness, including the dissolution of primary stones and the risk of recurrence of stones, of the proposed combination therapy has not been demonstrated.

DR. MELMAN: Well, we have already said that -- well, I have a different take on that and that is that, again, we cannot comment on this, because we do not know about it, and one of the things that we could propose to the FDA is we be given that information before we -- before this approval, that we ask for the information. And then in some way, the FDA asks for that. Because you cannot put down --

You cannot inform the patients what you do not know, so I will ask you to --

DR. FRANK: Doesn't this say that, that we do not know? It says -- it says that the long term effectiveness has not been demonstrated.

DR. MELMAN: That would go into the label, that is correct, it would say that.

DR. KALLOO: But you are saying we should add that as a condition, is that --

DR. MELMAN: I think that we should know that information before we make some decision about it, personally.

DR. STEINBACH: I think formally -- should it be in the label, to warn the patients, is the formal question. And I think, yes, it should be in the label.

DR. MELMAN: Okay. Everyone -- Dr. Epstein? Yes?

DR. EPSTEIN: Yes.

DR. MELMAN: Dr. Bennett?

DR. BENNETT: No vote.

DR. MELMAN: No, we are not voting, we are asking your opinion.

DR. BENNETT: I think it should be in the labeling. I do not agree with you, but -- because I think we should have a --

DR. MELMAN: That is the first time.

DR. BENNETT: I think we should -- you know, I think a post-market study is what is clearly indicated,

which will answer your question. This will be very hard to do; ten years?

DR. MELMAN: Okay.

DR. KALLOO: Summarize? The answer is yes.

DR. MELMAN: Does the -- okay, you gave your seven -- that is the seventh one, right?

DR. HARVEY: Question 8. Does the panel have any additional recommendations or suggestions regarding the medical device labeling?

DR. BENNETT: Move on to number 9, that -- [simultaneous discussion]

DR. HARVEY: Number 9.

DR. FRANK: Onward.

DR. MELMAN: Okay, I -- the answer is no.

DR. HARVEY: Next question. Question 9. Previously approved lithotripters for use with renal stones have not included patient labeling.

Should patient labeling in the form of a brochure to inform patients of procedures, risks, and expected outcomes, be used for the proposed device?

DR. MELMAN: Everyone is shaking their heads, yes. Is there anyone who disagrees with that? I think the summary is that the answer is yes.

DR. YIN: May I ask one question? Should we provide the patient brochure before they get a treatment,

right? Rather than after.

DR. MELMAN: Yes.

DR. YIN: Thank you. Well, usually, it is included in the --

DR. MELMAN: Ten.

DR. HARVEY: Question 10. Do you think that a post-market study is necessary for the proposed device? If so;

A. Should the patients from the pivotal PMA study be surveyed to determine gallstone recurrence rates, and cholecystectomy rates after initial Medstone STS lithotripter-ActigalI combination therapy?

B. What other endpoints should be followed?

C. What is the appropriate length for such a study?

DR. MELMAN: Why don't we have comments about that?

DR. SADLER: As much as we would like to see it, I do not think that the sponsor and the investigators have any stomach for getting us much information out of patients from a ten year old study.

I would like them to try, but I have very little hope that we would get anything particularly useful from it. I do think under B, the other endpoints that should be followed are relief of symptoms and side effects.

Under C, I think that they should follow the patients that go into the use of this product; initially, they should follow at least 1000 patients for at least three years.

DR. MELMAN: Three years.

DR. DONATUCCI: This is always an interesting time for me, because we recommend a lot of post-market studies and I have never heard the results of a single one. But, yes, I mean, theoretically, yes. Obviously, I think there should be a post-market study of the patients who were done. That is all I have to say.

DR. MELMAN: Well, for how long?

DR. DONATUCCI: Well -- I do not know how to come up with a number to answer that question. It is already ten years, so that is like a round number. It is done. I mean, how much longer, from this point, or -- because we are really talking about --

DR. MELMAN: No. I am talking about new patients now, this is not old patients.

DR. DONATUCCI: Yes, but that does not say that. That says --

DR. MELMAN: Post-market.

DR. DONATUCCI: Well, but if so, A, should the patient -- sorry, are we talking both the original study and additional patients?

DR. KALLOO: Additional new patients.

DR. MELMAN: Well, it says, from the pivotal PMA, that is the old patients. You are right. That is for the old --

DR. DONATUCCI: Right --

DR. MELMAN: You are right.

DR. DONATUCCI: So we are, then, talking about a different population.

DR. MELMAN: Yes.

DR. DONATUCCI: I do not think a new population has to be studied for ten years. Three years, for want of a round number, seems reasonable.

DR. MELMAN: Okay.

DR. VERTUNO: I would make it at least five years, actually.

DR. MELMAN: Dr. Frank?

DR. FRANK: I would like to encourage Medstone to please, please try to get as much data as you can from the previous patients. I think that is very important, number one.

Number two, I do think we need a post-market study. I think it is important not just for the results of lithotripsy, but if we are going to stimulate the investigations of medications to prevent recurrences, and I think we need the data on recurrences, if we are going to

study ways to prevent them.

I think it has to be at least five years, because there is some suggestion that maybe there is another blip after four years.

DR. EPSTEIN: We already heard from the manufacturer, they were not going to support any post-marketing studies, so is this a moot point? I mean, are we --

DR. BENNETT(?): No, that was the -- [simultaneous discussion] -- that was the original study.

DR. EPSTEIN: In that case, I think the answer to A should be yes. I do not think that -- I think if they can just survey the PMA patients, I do not think that yet another post-marketing study would be indicated, in addition to that. If they can get adequate data from those original patients.

There is a lot of literature out there on the recurrence rates with lithotripsy, indicating that it is about 50 percent at five -- between 30 and 50 percent at five years. So, those studies have been done with hundreds of patients.

DR. MELMAN: Dr. Bennett, no comment?

DR. STEINBACH: Dr. Sadler suggested 1000 patients. I would just suggest that the patients in Part A be included in those, which might provide incentive for the

company to get the longer data. And so, yes, I would like to see a post-market approval; five years seems appropriate. And other endpoints would be pain, essentially, for relief of symptoms.

DR. MELMAN: Dr. Kalloo?

DR. KALLOO: Yes, I do think that a post-marketing study is necessary. I think the endpoints should be relief of pain. Also, quality of life evaluations should be performed. And I think the appropriate length for this study should be at least five -- at minimum -- five to seven years.

DR. WOODS: I agree with that, and I think, if you think about patients possibly being on Actigall for up to 20 months, that is almost two years, so what we really want to see is what their stone-recurrence rate is, off of oral dissolution therapy, which means you may need to take it out to seven years; you know, ideally ten years, that may not be feasible, but I would say, five to seven years would be good.

DR. MELMAN: I am not sure -- I agree with everything -- but I am not sure that the statement that the company does not have the stomach to go back and get the ten years' data is appropriate.

DR. SADLER: In the past ten years, they have not done it. I believe in history.

DR. MELMAN: If we want the information. And the FDA is going to have to decide if they want that, but so -- do you want to give your summary of what we are recommending?

DR. KALLOO: The summary is:

A. Yes, it should be yes. There should be a post-marketing study.

B. The other endpoints should be pain and quality of life assessment; and

C. The appropriate length for such a study should be seven years.

DR. YIN: I do have a question, just from what I just heard. Now, if we do not have this post-market study, do you still feel that this product is reasonable to be on the market? You cannot say, well, leave it to FDA. We would to know exactly how you propose -- not to think later, well, maybe that is what they meant.

DR. KALLOO: Your question is that if -- without or with the post-market study?

DR. YIN: Suppose that we are unable to get the post-market study, do you still feel that it is okay, or -- I mean, we need to know what you really want.

DR. MELMAN: Okay, I think that is crux -- I would like to raise an issue, because there is some difference of opinion on this, and that is that, it is my belief that we

should ask for the information and if the company sees it as a rainbow at the end of the study, they will have the stomach to do it, and I think the data should be available to have 633 patients, some of whom have disappeared or died, but the information should be out there.

The question you are asking is, should we ask for that information first? And although I cannot vote unless there is a tie, my opinion is that we should ask for that information, because otherwise we cannot base a recommendation on the actual efficacy of the treatment.

DR. SADLER: I do not have any objection to asking, but in my skepticism that we will receive an effective answer, I have suggested that they do a study of incident patients, and if they had an adequate study of the previous patients, then I think that it would be permissible for the FDA to discontinue a study of incident patients, and allow that to be done by individual investigators. But, unless adequate data is forthcoming from the original study that would make them confident that no broad study was necessary of incident patients, they should have it from there.

DR. MELMAN: I am not sure what you mean by incident patients?

DR. SADLER: Patients getting it done, forthcoming. In other words, a prospective study of

patients treated with the combination therapy.

DR. MELMAN: But if you -- that is based upon approval from the FDA, and what I am saying is that, shouldn't we have the information, because you do not have enough information yet to go ahead.

DR. SADLER: Well, if the company comes back in three months and says, we just cannot find these patients, are we going to tell them no, you cannot be approved because you cannot find the patients? I think that is what they are going to do, and I hope it is not, but I think it probably is.

That being the case, I think you give them an either/or, so that they get the carrot of being of approved, but they get the stick of having to do a new study if they do not round up this data.

DR. MELMAN: So, that is a lot of positive incentive to get the patients. Dr. Donatucci, you --

DR. DONATUCCI: I am for positive incentive. I mean, I would not add to that.

DR. MELMAN: No, we are going to have to vote on this, because we have to make a recommendation, and that -- so, I am going to raise --

DR. DONATUCCI: Okay, well, I think then the general feeling is that the data as it stands have not truly proven symptomatic efficacy, and we want to see that, and

that could be provided through poling the patients who have already been done, or in prospective fashion from this point on.

I think that a conditional approval might be granted; such a mechanism exists, and with final approval forthcoming with presentation of that data.

DR. YIN: All that means, that you are not really approving the product. You are going to -- this study has to be done before you really approve it.

DR. DONATUCCI: That is right.

DR. YIN: I am hearing different things.

DR. MELMAN: So we are asking -- are you going to make a motion -- we are going to vote on this now, and I am asking to make a motion as to whether or not we want that information before the FDA approves it? That is, that they have to go back and do a little work on what has already been done. It is not an expensive study to do, and find out what the efficacy is.

DR. DONATUCCI: So moved.

DR. VERTUNO: Yes, I second that. I think that is more important information than analysis of the statistical probabilities of the study, so I think we really need that data.

DR. FRANK: I strongly disagree. I think that we should approve the device and insist on post-market studies.

DR. MELMAN: Dr. Epstein?

DR. EPSTEIN: Oh, I think it is well-known that the stones will recur, so I think the Panel can consider that information that is out there in the body of literature, and make a decision based on that particular information. So, in a sense, I agree with Dr. Frank.

DR. STEINBACH: The Panel wants to approve the machine, but I think they also want to have a post-market study done, so I want to approve the machine with the provision that a post-market study be started.

DR. MELMAN: Okay, we will take a vote as to --

DR. STEINBACH: Which is no, I guess, to the motion as carried.

DR. MELMAN: Right. Okay. Dr. Kalloo?

DR. KALLOO: I would rather have the data beforehand than after it is approved, so I feel strongly that I would like to see data ahead of time prior to approval.

DR. MELMAN: Dr. Frank -- Dr. Woods.

DR. WOODS: Let me ask this. If we ask for post-market information and it is forthcoming, and we do not like it, and we have approved the machine, what recourse do we have?

DR. YIN: You may ask FDA to withdraw the approval.

DR. WOODS: Will there be an automatic reconvening of this Panel to assess the post-market information?

DR. YIN: I think we would -- in that case, we would definitely bring it back to you.

DR. MELMAN: Okay. So there is a motion that has been raised -- what?

DR. YIN: But the part is that we need to let you know, to withdraw a PMA with no dead bodies around is not easy. But they did have three, so.

DR. MELMAN: Alright. So, there is a motion on the floor and the motion is that, we would request that we have data obtained from the initial study that was done ten years ago, before making a recommendation for approval of this PMA to the FDA. So, how many people are in favor of that?

DR. KALLOO: I am sorry, are there two choices, or --

DR. MELMAN: You can say yes or no.

DR. FRANK: First we have to vote on that choice.

DR. MELMAN: Yes. So, how many people are in favor?

DR. SADLER: I do not think anyone objects to it, it just that -- [simultaneous discussion]

DR. MELMAN: No, no. We have to -- no, people -- Dr. Frank -- Dr. Frank and Dr. Kalloo objected so -- and you

agreed, so I am asking you to vote at this point.

DR. SADLER: Is the person that made the motion going to vote in the affirmative or not?

DR. DONATUCCI: No, I made the motion, but I think I am convinced that the two colleagues who said that we can accept the literature that they will occur at a certain rate. I made the motion, but I am not voting for it.

DR. MELMAN: So, no one -- no positive votes.

[By show of hands, the motion did not carry.]

Okay, so then, the motion does not carry. So, we will not make the recommendation.

DR. KALLOO: What is it -- could you repeat the --

DR. MELMAN: We are voting among ourselves now, because we have to suggest to the FDA that we want information based upon the first study, the study about ten years ago, follow-up data, before we make a recommendation to them.

DR. DONATUCCI: As I saw it, it was that the data had to be forthcoming before the PMA would be approved.

DR. MELMAN: Yes.

DR. DONATUCCI: In a nutshell.

DR. MELMAN: Yes. So, I am asking for a vote on that. How many people say -- one person?

[There was one vote in the affirmative; the motion did not carry.]

So, it does not carry. So, we are not going to recommend that.

DR. YIN: Okay.

DR. HARVEY: Question 11. Based on the safety and effectiveness data, is a physician training program necessary to instruct in the use of the Medstone STS lithotripter?

DR. MELMAN: I would recommend that the -- in the same way that there are criteria set forth for doing renal lithotripsy, that use the same type of criteria for -- I will summarize that -- for the biliary lithotripsy.

[Simultaneous discussion away from microphone]

Okay, so, before entertaining a motion recommending an action on this PMA, Mary is going to remind the my panel of our responsibilities in reviewing today's pre-market approval application, and of the voting options open to us.

MS. CORNELIUS: Before you vote on a recommendation, please remember that each PMA needs to stand on its own merits. Your recommendation must be supported by data in the application, or by publicly available information.

You may not consider information from other PMAs in reaching your decision on this PMA. Your recommendation may be one of the following:

You may recommend approval of the PMA.

You may recommend that the PMA be found approveable, subject to specific conditions, such as the resolution of clearly defined deficiencies cited by you or the TDA staff. Examples could include resolution of questions concerning some of the data, or changes in the draft labeling.

You may conclude that a post-approval requirement should be imposed as a condition of approval. These conditions may include a continuing evaluation of the device and a submission of periodic reports.

If you believe such recommendations are necessary, then your recommendations should address the following points:

The reason or purpose for the post-approval requirement;

The number of patients to be evaluated; and

The reports required to be submitted.

You may recommend that the PMA is not approveable. Of the five reasons that the Act specifies in section 515 B2 (a)through (e), three are applicable:

The data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the labeling. To clarify the definition of safe, there is some reasonable assurance that

the device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks.

The data do not provide reasonable assurance that the thee device is effective under the conditions of use prescribed, recommended or suggested in the labeling. A definition of effectiveness is that there is a reasonable assurance that the device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use, and warnings against unsafe use, will provide clinically significant results.

The PMA may be denied approval if, based on a fair evaluation of all the material facts, the proposed labeling is false or misleading.

If you make a non-approveable recommendation for any of these stated reasons, we request that you identify the measures that you believe are necessary, or steps that should be undertaken, to place the application in an approveable form. This may include further research.

DR. MELMAN: Is there anyone from the public who would like to make a comment at this time? Seeing no one from the public, is there anyone from the sponsor who would like to make a comment at this time?

DR. GARVEY: I want to thank you for the time and attention that you have devoted to consideration of this PMA.

DR. YIN: Please come to the microphone.

DR. GARVEY: I want to thank the committee, and even FDA, for the time and attention that has been devoted to this PMA.

DR. MELMAN: We will now consider the Panel's report and recommendations concerning approval for the Medstone International's STS Lithotripter, application P970042, intended to fragment biliary stones together with the reasons or recommendations as required by section 515 part C(2) of the Act.

The underlying data supporting a recommendation consists of information and data set forth in the application itself, the written summaries prepared by the FDA staff, the presentations made to the Panel, and the discussions held during the Panel meeting, which are set forth in the transcript.

As stated before, the recommendations of the panel may be approval, approval with conditions that are to be met

by the applicant, or denial of approval. And I would like to ask now for a motion on this question.

DR. STEINBACH: I move that the device be approved, with conditions of patient labeling that have been discussed in the, I guess, 11 questions, so far.

DR. MELMAN: Okay, so Dr. Kalloo has been assiduously writing down the conditions, and he is now going to list -- do we have a second for the motion?

[The motion was duly seconded by Dr. Sadler.]

DR. MELMAN: Okay, the motion is seconded. And I would like Dr. Kalloo to list the conditions, and then we will take a vote on those conditions. Or, if there are any objections to the conditions, we will take them.

DR. KALLOO: The conditions that were summarized were the following:

First, that the Panel believes that, although the statistical methods were suboptimal, that we would accept the data if follow-up data is provided.

On the second one, it was acceptable to pool data from the different clinical trials, the three different clinical trials.

For number four, that the indications should be for a single stone, less than 20 mm in diameter.

Number five, we said that we believe that the indications were that it was reasonably safe; there was no

efficacy demonstrated for symptomatic patients, but there was short term efficacy for stone clearance.

For number six, we included cholestatic liver disease. We included all the exclusion criteria from the initial study. We included cardiac arrhythmias, calcification of the stones.

We also included, as a contraindication, a cystic duct that was not patent or a non-functioning gallbladder.

For number seven, we said that, yes, the labeling should include -- that there should be labeling including a warning or precautionary statement about the long term effectiveness.

Number ten, we said, yes, that a post-marketing study was necessary and that the endpoints of pain and quality of life should be measured, and that the appropriate length for such a study was seven years.

For number eleven, we said, yes, that a physician training program is necessary to instruct in the use of the Medstone STS lithotripter.

DR. MELMAN: Is there any discussion about those recommendations?

DR. EPSTEIN: Two items, number one, I think it was the second question. We need to include, that it is a functioning gallbladder with a 20 mm stone in it -- with a patent cystic duct.

DR. MELMAN: Yes, right.

DR. EPSTEIN: And secondly, I thought the majority of the panel said five years was --

DR. MELMAN: Well, that -- Dr. Woods thought that it should be five years after the cessation of the Actigall, so that made the seven years.

DR. EPSTEIN: Oh, seven years. Okay.

DR. MELMAN: But you did not list in that as an endpoint, recurrence of stone; it just said symptoms and quality of life, but stone recurrences should be included.

DR. WOODS: And cholecystectomy.

DR. MELMAN: And cholecystectomy. Any other --

DR. WOODS: Are we making it clear that we want post-market data to accumulate and be brought back to the Panel, and that we would like follow-up on the patients that are available in the original application?

DR. YIN: Is that what you meant by number one; you said, follow-up data needed. Is that what you meant? The first statement from Dr. Kalloo.

DR. KALLOO: Yes.

DR. MELMAN: Well, I have a question about that -- when does that -- so, what do you do with that? So we said, yes, you should get that --

DR. YIN: No, the follow-up data, do you mean that, after -- after it has been marketed, then you want the

data? We can ask for yearly submission and we can send it to you.

DR. MELMAN: Yes. That would be --

DR. FRANK: Yes. We would like information on follow-up of patients from the original PMA, as well as post-market evaluation of subsequently entered patients.

DR. YIN: That is through the annual report.

DR. FRANK: Yes.

DR. YIN: But, this is what you meant by follow-up data, right? We need to get it very clear, because that is the first statement that Dr. Kalloo, you addressed. Is that post-market, right?

DR. KALLOO: Well, we have -- but I -- we have not established the fact whether we will require this data prior to approval or not?

DR. FRANK: Yes, we did.

DR. DONATUCCI: Well, it is conditional approval.

DR. KALLOO: Conditional approval.

DR. DONATUCCI: Right. Approval with condition; I mean, that is the motion on the table is approval with condition.

DR. WOODS: I would also like in our monitoring to monitor compliance with the indications to see that the numbers of patients who are actually undergoing lithotripsy meet the indications that we believe are correct; that we do

not --

DR. YIN: I do not think it is fair for us to do that, because that is invading, you know, a physician's ability to use an approved product for non-approved use. That is -- I do not think we should do that. Because the physicians are allowed to use other approved products for non-approved use, at your own discretion. So, therefore, there is no way we can monitor that and then tell you why he is not abiding to whatever. But, that is correct --

[Comment away from microphone] --

DR. MELMAN: No, you cannot. Thanks, anyhow.

DR. YIN: But by the same token, that if they chose to -- if the physicians choose to not use it with Actigall, that is again, it is --

DR. MELMAN: Okay. Alright, so -- I would like to subject this motion for a vote, with all the conditions that we have just modified, and -- I would like to know how many people are in favor of the motion?

Dr. Sadler, Dr. Donatucci, Dr. Vertuno, Dr. Epstein, Dr. Kalloo, and Dr. Woods -- how many people are against? Dr. Steinbach.

[The motion was carried by a hand vote of six to one.]

Now I would like to poll the panel as to why they are first in favor of this, and then -- just the negative?

I am being prompted to say, just to find out why you are against the motion.

DR. STEINBACH: I am against the motion because there has not been an appropriately controlled study to demonstrate its effectiveness.

I would accept demonstration that the placebo pre-treatment in fact constitutes a control, and if they can verify a .03 probability, I would accept this, and I would also accept a new study with a randomized placebo control. Or, best yet, I would accept a study with Actigall alone as a control group.

DR. MELMAN: Okay, so I would like to thank everyone for their attention and their hard work, and the FDA for their hard work, and call an end to the meeting.

DR. YIN: No, we thank the panel very, very much, and we also commend the company for doing a good job. Thank you.

[Whereupon, at 4:15 p.m., the hearing was concluded.]