U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANESTHETIC & LIFE SUPPORT

ADVISORY COMMITTEE

87TH MEETING

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Tuesday, January 12, 1999

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The Advisory Committee met in the Center for Drug Evaluation and Research Advisory Committee Conference Room at 5630 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Terese Horlocker, M.D., Chairperson, presiding.

PRESENT:

TERESE HORLOCKER, M.D. Chairperson

MICHAEL ASHBURN, M.D.

AMANDA S. CARLISLE, Ph.D., M.D.

MARIA CONNOLLY, D.N. Sc.

WINSTON C.V. PARRIS, M.D., FACPM

JOSEPH REVES, M.D.

PRESENT (Continued):

CHARLES ROHDE, Ph.D.

JOHN SAVARESE, M.D.

RICHARD SMILEY, Ph.D., M.D.

TOBIN, JOSEPH, M.D.

MEHERNOOR WATCHA, M.D.

KATHLEEN REEDY, Executive Secretary

CONSULTANT PRESENT (non-voting):

JOHN DiMARCO, M.D.

INVITED GUESTS PRESENT:

ANWAR GOHEER, M.D.

CYNTHIA MCCORMICK, M.D.

THOMAS PERMUTT, Ph.D.

BOB RAPPAPORT, M.D.

MONICA ROBERTS, M.D.

C O N T E N T S

C O N T E N T S (Cont'd)

P-R-O-C-E-E-D-I-N-G-S (9:00 a.m.)

Call to Order and Opening Remarks

DR. HORLOCKER: Good morning. I'm Terese Horlocker. I would like to call this meeting to order.

Today we will be speaking about Chirocaine, a levobupivacaine derivative, a long-acting, local anesthetic.

I think the search for a long-acting, potent, reliable, local anesthetic started back in the 1970s after the initial reports of cardiac toxicity and difficult resuscitations after bupivacaine toxicity in parturients that had received greater than .5%.

Preliminary data suggested that levobupivacaine was of similar efficacy, but had less toxicity, and when the Company approached the FDA initially, they requested that the black box be removed from the labeling of Chirocaine when the drug was eventually approved.

An Advisory Committee meeting was held in March of 1997 to discuss, among other things, labeling

issues, and specifically at that time, the Sponsor requested that the Advisory Committee tell them what information would be needed to remove this black box label, and also what additional data would be needed for them to be able to make the claim that Chirocaine was less toxic than racemic bupivacaine.

I think most of the groundwork discussion was performed during that meeting. The recommendations included that there should be additional clinical and laboratory studies done; specifically, finding at least a 25% reduction in cardiac toxicity in one study, and also the Committee members at that time requested that additional obstetrical and pediatric patients be studied.

So, at this point in time, we are ready to go over the results of those studies, and evaluate Chirocaine for approval and discuss the additional labeling issues.

At this time, I would like to have the Committee members introduce themselves, perhaps just a quick, your name, where you are from.

Introduction of Committee

I'm Terese Horlocker. I'm from the Mayo Clinic. I am an Associate Professor there. Dr. Reves?

DR. REVES: Jerry Reves from Durham, North Carolina.

DR. SMILEY: Rick Smiley from the University of New York.

DR. CARLISLE: Sue Carlisle, University of California, San Francisco.

DR. ASHBURN: Michael Ashburn, University of Utah, Department of Anesthesiology.

DR. WATCHA: Mehernoor Watcha, Children's Hospital, Philadelphia, University of Penn.

DR. TOBIN: Joe Tobin, Department of Anesthesia and Pediatrics, Wake Forest University School of Medicine, Winston-Salem.

DR. DiMARCO: John DiMarco, Cardiac Electrophysiologist from the University of Virginia.

MS. REEDY: Kathleen Reedy, Executive Secretary, Food and Drug Administration.

DR. ROHDE: Chuck Rohde, I'm Professor of Biostatistics at Johns Hopkins.

MS. CONNOLLY: Maria Connolly, Associate Professor of Medical-Surgical Nursing, Loyola University, Chicago.

DR. SAVARESE: John Savarese, Cornell University, New York Presbyterian Hospital.

DR. GOHEER: Anwar Goheer, Pharmacologist at the FDA.

DR. ROBERTS: Monica Roberts, Pediatric Anesthesiologist, FDA.

DR. RAPPAPORT: Bob Rappaport, Deputy Division Director.

DR. MCCORMICK: Cynthia McCormick, Director, Division of Anesthetics, Critical Care and Addiction Products, FDA.

DR. HORLOCKER: Ms. Reedy, would you like to read the Conflict of Interest Statements?

Conflict of Interest Statement

MS. REEDY: Conflict of Interest Statement for the Anesthetic and Life Support Drug Advisory Committee, January 12, 1999.

The following announcement addresses the issues of conflict of interest with regard to this

meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted Agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

In the event that the discussions involve any other product or firms not already on the Agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and discussion, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon.

DR. HORLOCKER: Dr. McCormick, would you like to make your opening comments, please?

I would also like to state at this time that our discussions can occur at the end of

presentations; however, if someone needs to make a clarification, we could interrupt the speaker at that point in time, only.

Opening Remarks

DR. MCCORMICK: Thank you. Dr. Horlocker, Committee members, sponsors of levobupivacaine, consultants, members of the ublic, and FDA staff. Good morning, and welcome to the January 12th, 1999 meeting of the Anesthetic and Life Support Advisory Committee.

Dr. Horlocker, we have asked you and our Advisory Committee to meet with us today to provide advice to the FDA on a subject of very narrow focus, as we prepare to take action on this product over the next month.

We are not specifically seeking your advice about the risk-to-benefit ratio of this product, as we have reviewed the Sponsor's materials and data on the clinical development in the NDA, and we are satisfied that these criteria have been met. Instead, we would like to limit your focus and discussion on the cardiovascular safety of this

product.

We have provided for you reading background materials that include the transcripts from three advisory committee meetings, all of which have relevance to today's meeting. We had hoped to see an agent emerge with the efficacy of bupivacaine without the cardiovascular side effects.

We have considered how we might gain assurance, since we can never be absolutely certain, that a product indeed might have a more favorable safety profile.

As you will hear from the Sponsor today, there is a strong theoretical basis for postulating a differential toxicity between racemic bupivacaine and the enantiomer on cardiovascular toxicity.

The early preclinical work is quite compelling. How this unquestionable, theoretical advantage translates into a clinically meaningful advantage has been a matter for our review team to grapple with.

In some preclinical studies, for example, the catheterized ewes studies which Dr. Mather no

doubt will discuss today, IV levobupivacaine was capable of causing the very same cardiovascular effects attributed to bupivacaine, but at a higher dose.

How does this dose separation for toxicity extrapolate in a practical way to the human or clinical situation, or does it? And at what doses does one expect to see significant human cardiovascular toxicity? At what concentrations, and in what setting? And will they be achieved in the normal course of anesthesia or pain management?

You will hear that, in an FDA database of nearly 1500 subjects and patients, there was not an identifiable difference between the safety profile of levobupivacaine and bupivacaine, not even in the studies designed to focus on subtle EKG changes, so the differences remain largely theoretical.

In 1997, this Committee deliberated on the development of this product prospectively. The Sponsor has completed some of these studies which you have recommended, and they will discuss these results today. The remainder of the studies are either

awaiting completion, or have not yet begun.

The question you will be asked to help us with, given the background materials and the preclinical and clinical data submitted is, to paraphrase the question actually submitted, does the existing data support a lesser warning than exists for bupivacaine? And if so, what evidence is most compelling for you?

If not, should further study be undertaken? And will the satisfactory completion of the preclinical studies yet to be performed contribute to changes in the warnings that currently exist in the bupivacaine label for this product?

Remember that a product's labeling is the FDA's tool for informing the public through the prescribing physician and directly, about the product's potential risks.

Every fact that is or is not disclosed in the labeling makes a statement. What goes into the labeling should be an accurate, truthful synopsis of what we know or don't know, based on the data presented to us in the NDA.

While you may no doubt be aware of the effects of your decisions on the marketplace and clinical practice, keep in mind that CDER's mission is to make safe and effective drugs available to the American people, so let science inform your deliberations and let the public safety guide your judgments and recommendations.

Thank you.

Open Public Hearing

DR. HORLOCKER: Thank you. At this point in time, is there anyone that would like to speak as part of the Open Public Hearing? Very well. We can proceed then with the Sponsor Presentation, if you are prepared.

Sponsor Presentation: Introduction, Rationale, Agenda

DR. GENNERY: Dr. McCormick, members of the FDA Division, Dr. Horlocker, and members of the Advisory Committee, my name is Dr. Brian Gennery. I am the Medical Director of Chiroscience, and also the Project Leader for the product that we are discussing today, Chirocaine, or levobupivacaine.

First of all, I would like to say how much we at Chiroscience appreciate the opportunity of being invited to this meeting and share with you our ideas and data on levobupivacaine that has been developed over the last two to two and a half years.

I also want to make it clear that all of the speakers here who are here on behalf of Chiroscience, are consultants or investigators to whom we have paid fees, expenses, and where appropriate, funding for their department in order to carry out the research programs.

If I may spend just a moment about telling you who we are, because various names appear in the documentation. Chiroscience Group plc is an emerging bio-pharmaceutical company based in Cambridge in the United Kingdom, and Seattle in the United States.

Darwin Discovery is the Research and Development subsidiary within Chiroscience, but for today, we will refer to the name, Chiroscience, throughout.

I would like to spend a moment or two describing to you the rationale for developing

levobupivacaine.

You are very familiar with bupivacaine as a potent, long-acting, local anesthetic with more than 20 years experience in clinical practice, having excellent sensory block and a good motor-sensory separation ratio; however, its use has been clouded by the occasional episodes of central nervous system and cardiovascular toxicity, which has occurred very largely in overdose, which is usually presumed to be an unintentional intravascular injection.

And this has led to the boxed warning here in the United States such that 0.75% concentration of bupivacaine is not permitted for use in the obstetric patient. And similar warnings exist throughout most countries throughout the world.

There was some evidence in the literature that the dex enantiomer of bupivacaine has a higher potential for causing both the CNS and the CVS toxicity than the levo enantiomer, and therefore it seemed to make some sense to try and develop the levo enantiomer.

More encouraging than simply this fact,

was also that there was some evidence that the levo enantiomer had the same efficacy as the racemate when used in the clinic.

Thus, our objectives, which were partly formed after our discussion with this Committee nearly two years ago for which we were very grateful to have that guidance, was this.

To demonstrate in animals and humans that there is a diminished risk of CNS and cardiovascular toxicities if levobupivacaine is administered by an unintentional intravascular injection, when compared to bupivacaine at the proposed therapeutic doses. Obviously, with humans, we couldn't go above a certain dose, for ethical reasons.

And we agreed at that meeting that something like a 25% difference, at least a 25% difference, would be required to satisfy the Committee that an objective had been achieved. And whilst that was relatively easy to plan into protocols in animal studies, it of course was much more difficult within the human studies, although we believe we have tried to keep within the spirit of that discussion.

We also wished to demonstrate that levobupivacaine had an equal anesthetic effect when used at the same concentrations and volumes as bupivacaine.

And in our clinical trial reports, we tried to avoid the use of the word, potency, per such, but, equal anesthetic effect. We have described potency in the preclinical section of the NDA with a variety of animal experiments.

We also wish to provide a comprehensive data package to the practicing clinician illustrating the use of levobupivacaine in a variety of surgical, pediatric, and pain management studies.

We clearly recognized the challenging of the labeling discussion that would occur, and indeed was pointed out at the meeting two years ago.

We believe that the data will show that the potential for cardiovascular and central nervous system toxicity of levobupivacaine has been adequately evaluated at the proposed therapeutic doses.

And the differences between levobupivacaine and bupivacaine will show that the

boxed warning would not be appropriate for levobupivacaine.

Our presentation this morning will focus on a broad range of preclinical studies which consistently show at least a 25% difference in cardiovascular toxicity between the racemate and levobupivacaine; human studies showing differences in both central nervous system and cardiovascular system toxicities between the two products; and a review of the clinical trial database to include the limited experience we have of inadvertent accidental intravascular administration, and we have now completed a meta-analysis of EKG data which was submitted as individual studies within the NDA.

Our Agenda is here. Dr. Robert Gristwood, who is a consultant in biology to Chiroscience, will present to you preclinical data in both in vitro and in vivo studies.

Professor Laurie Mather from Sidney, Australia will describe his sheep model, and also comment on the work that Dr. Alan Santos has done, who unfortunately couldn't be with us today.

We will then move on to a discussion of clinical data; human volunteer studies looking at cardiovascular parameters will be introduced by Dr. Walter Nimmo.

And then the clinical trial experience in terms of efficacy will be described by Dr. Kopacz and an overall view of safety by Dr. James Crews.

And finally, I will try and bring it all together at the end of our presentation. I would now like to hand over to Dr. Gristwood.

In Vitro and In Vitro Studies

DR. GRISTWOOD: Good morning, ladies and gentlemen. My name is Robert Gristwood. I am a pharmacologist-biochemist, currently acting as a biology consultant to Chiroscience on the levobupivacaine development program. I have been associated with that program for the past five years.

In my presentation today, I am going to review preclinical evidence that levobupivacaine is less cardiotoxic than racemic bupivacaine.

Okay, cardiotoxicity has been a concern for bupivacaine in the clinic, and the seriousness of

this has been indicated by the very large number of preclinical studies that have been carried out to look into the etiology of the cardiotoxicity.

And these have shown that bupivacaine can have both direct and indirect effects on the heart, the indirect effects largely arising through interactions with the central nervous system, but there are a large number of direct effects.

And these include blockade of cardiac ion channels including sodium, potassium, and calcium channels, which result in mechanical changes, reduction in contractility; electrical changes, changes in action potential configuration; conduction delay, abnormal EKGs and arrhythmias; and also, decreases in heart rate.

As you know, bupivacaine is a racemic mixture of levobupivacaine and dexbupivacaine, and there is good evidence that bupivacaine cardiotoxicity is enantiomer-selective.

And data from preclinical studies I believe clearly show that levobupivacaine is less cardiotoxic than both the racemate and dexbupivacaine.

An important question is, how much less cardiotoxic should levobupivacaine be than the racemate, in order to confer a clinical advantage?

And this question was discussed at the ALSDAC meeting in March 1997, and the outcome from that meeting was that the Committee would like to see more than one preclinical model predicting a substantial, defined as 25% or greater, difference between the bupivacaine enantiomers, and between levobupivacaine and racemic bupivacaine.

Data from the preclinical studies has been summarized in a table, which is included in the Briefing Document and the NDA, and what I am going to do now is take you through the table, looking at effects on cardiac ion channels, and looking at toxicity on isolated whole hearts, and then moving on to look at cardiotoxicity in intact animals.

Okay, so this shows the cardiac ion channel data. The layout of the table is as in the documentation; it shows the parameter, the species from which the data were obtained, and the relative cardiotoxicity of dexbupivacaine to levobupivacaine,

and racemic bupivacaine to levobupivacaine.

And the relative cardiotoxicity is defined by the percentage by which dex and racemic bupivacaine exceeded the cardiotoxicity of levobupivacaine, where 0, a 0% would indicate that there is no difference between the two.

A positive value tells us that levobupivacaine is less cardiotoxic, the bigger the value, the greater the advantage for levobupivacaine.

Okay, so here we have data for cardiac sodium channels and cardiac potassium channels. Sodium channel data was obtained using guinea pig myocardium, which is considered to be a good model of human myocardium.

Three studies were obtained with this; two compared dexbupivacaine with levobupivacaine, and one compared racemic bupivacaine with levobupivacaine.

Looking at this column, first of all, the first study, which was a functional study, showed that dexbupivacaine was 140% more toxic than levobupivacaine on the sodium channels.

In this study, it was also shown that not

only was dexbupivacaine more potent in its ability to block sodium current, it also bound faster and unblocked more slowly than levobupivacaine, which are important kinetic considerations, indicating further advantages for levobupivacaine.

In this study, which looks at sodium channels, it was found that dexbupivacaine was 66% more toxic than levobupivacaine.

In the study comparing racemate with levobupivacaine, it was found that the racemate was 54% more toxic than levobupivacaine.

These are data from the Chiroscience study, and I will show some values in a moment from this study.

For the cardiac potassium channel study, a study was carried out using human HKV 1.5 delayed rectifier potassium channels, and it was found that dexbupivacaine was 560% more toxic than levobupivacaine on the channel.

I would just like to point out that there are possible interactions between the channel blockade, and it is known that under certain

circumstances that potassium channel blockade can actually intensify and prolong sodium channel blockade, so this value for dexbupivacaine could actually feed back and be relevant for the sodium channel blockade.

This shows the Chiroscience data. This is looking at guinea pig papillary muscles, and action potential parameters measured using standard microelectrode techniques.

It shows the effects of bupivacaine and levobupivacaine on Vmax. Vmax is the maximum rate of upstroke of the action potential, and reflects the sodium current.

Shown here are the effects of the drugs at 3 micromolar and 30 micromolar. And the yellow numbers indicate where significant changes compared with pre-drug values occurred.

So, bupivacaine at 3 micromolar, which is a significant 14% decrease in Vmax, indicating sodium channel block.

At 30 micromolar, it produced a much larger decrease, a 55% decrease in Vmax.

Levobupivacaine at 3 micromolar did not produce a significant effect; at 30 micromolar, produced a much smaller effect than was produced by bupivacaine.

And as you can see, the between-drug comparisons indicate a statistical significance, and these data clearly show that levobupivacaine is less active on cardiac sodium channels.

Now, moving on to look at isolated hearts, whole hearts. And this summarizes data from two studies, one obtained using guinea pig hearts, the other using rabbits. And I would like to point out that these species are appropriate species to use for whole heart profusion models.

I am looking first at the guinea pig. Prolongation of AV conduction. It is found that dexbupivacaine was 54% more toxic than levobupivacaine, and racemate was 30% more toxic than levobupivacaine.

QRS duration in the rabbit heart. The QRS duration of the ECG is affected by sodium block, which would tend to prolong the duration. In this, it was

found that the racemate was 229% more toxic than levobupivacaine.

I will show you more data from this study. This is the Mazoit Study, using isolated rabbit hearts, and this looks at the effects of levobupivacaine, bupivacaine, and dexbupivacaine on these parameters: the QRS increase, the incidence of atrial ventricular block, and ventricular fibrillation.

On the QRS increase, levobupivacaine produced an increase of 59 ms; bupivacaine, an increase of 194 ms; dexbupivacaine, an increase of 236 ms. And as you can see, big differences here between these and levobupivacaine.

On atrial ventricular block, the incidence with levobupivacaine was 66%, and for bupivacaine and dexbupivacaine, the incidence was higher, at 100% in each case.

For fibrillation, no fibrillation occurred in the levobupivacaine-treated hearts; it occurred in 66% of the bupivacaine-treated hearts; and 83% of the dexbupivacaine-treated hearts.

The important conclusions from this study was that levobupivacaine in comparison with these, produced less prolongation of QRS duration, a lower incidence of atrial ventricular block, and it did not produce ventricular tachycardia, or ventricular fibrillation.

Now moving to look at cardiotoxicity in whole animals. And this shows arrhythmia data for the rat and the sheep. And immediately, you can see that there were advantages for levobupivacaine in both studies.

I am going to show data from the rat study, and Professor Mather will talk about the sheep data in the next presentation.

This is in anesthetized rats. This is the Denson study, looking at the administration of 2 mg/kg intravenously of levobupivacaine and dexbupivacaine.

Looking at these parameters, for bradycardia, with levobupivacaine, mild bradycardia occurred in four out of twelve animals; with dexbupivacaine, severe bradycardia occurred in all of the animals.

For Wenckebach rhythms, this is second degree heart block, this occurred in two out of twelve of the levobupivacaine rats, and all of the dexbupivacaine-treated rats.

And looking at deaths. This occurred in two of twelve of the levobupivacaine-treated animals; and all of the dexbupivacaine animals.

DR. WATCHA: Was that statistically significant?

DR. GRISTWOOD: Yes, that was. Okay, now moving on to look at the effects in the anesthetized pig model, and I will make the point here that the pig, like the dog and the sheep, is a widely accepted large animal model to look at local anesthetic-induced cardiovascular toxicity.

Here we are looking in anesthetized pigs at QRS prolongation, and ventricular fibrillation in lethal dose.

For QRS prolongation, again a clear advantage for levobupivacaine; it was between 25 and 47% less cardiotoxic.

And on ventricular fibrillation,

levobupivacaine was 58% less cardiotoxic.

I am now going to quickly run through the data to substantiate these values. This is the Morrison and Reitz study in anesthetized pigs.

The study was carried out in anesthetized pigs, using blinded parallel treatment groups. The drugs were given by coronary artery infusion to avoid effects on the central nervous system complicating interpretation.

The drugs were given in 3 mls over 10 seconds. In each animal, a dose response was carried out, starting at 0.375 mg, and then increasing the dosage shown, up to the point by which the animals died through ventricular fibrillation.

The key measurements were a 12-lead EKG from which PQ, QRS, and QTc intervals were measured.

This shows the effects on QRS duration. Here we have the increase in QRS duration in milliseconds, and this is the dose of drug administered. Now, this is shown on a little scale.

This is the dose response curve here for bupivacaine, and this is the dose response curve for

levobupivacaine. And you can see the levobupivacaine is to the right of that for bupivacaine, showing that it is less effective in increasing QRS duration.

Making comparisons between the drugs at two levels. At the 40 ms increase there was a 25% difference between the two drugs. And at the 90 ms increase, there was a 47% difference between the two drugs.

The numbers here indicate the points at which animals died. Back here, there were seven animals in each group. And this shows that for bupivacaine at this point, two animals died.

There is an indication that animals died with bupivacaine at lower increases in QRS duration than with levobupivacaine. The suggestion is that the pigs could tolerate larger increases in QRS duration with levobupivacaine than with bupivacaine.

This shows the lethality data in greater detail. Here we have the drug injected, the dose injected, and the mean lethal dose with the range.

I will take you through one of the bupivacaine animals. This was first of all given

0.375 mg, then 0.75, up to 5 mg, the figure here shown in the white box, which is the point at which the animal died.

Looking at bupivacaine, the animals died at 4 mg, 5 mg, and 6 mg, and for levobupivacaine, they died at 7, 8, and 9 mg.

There is no overlap here between the doses that cause death in bupivacaine, and those that cause death with levobupivacaine. We had to give more levobupivacaine to produce a death in this model.

Looking at the mean lethal doses, for bupivacaine, this was 5 mg; for levobupivacaine, it was 7.9 mg, which is a highly statistically significant difference between these two values, indicating a difference of 58%.

Okay, so I have taken you through the Summary Table, and looking at the numbers that are shown here, which relate to relative cardiotoxicity, I believe that this is a powerful, compelling argument that levobupivacaine is less cardiotoxic than racemic bupivacaine, and if you look at the magnitude of the numbers, I believe the body of the data show that we

are hitting the 25% difference between the two drugs, and in many instances, vastly exceeding that value.

To summarize, we believe we have a large body of in vitro and in vivo data from a wide range of animal species, which show levobupivacaine to be less cardiotoxic than racemic bupivacaine on cardiac ion channels, EKG variables, arrhythmogenic potential, and lethality.

And I would now like to hand over to Professor Mather to talk about the Awake Sheep Model.

Sheep Studies

DR. MATHER: Dr. McCormick, Dr. Horlocker, members of the Committee, ladies and gentlemen, my name is Laurence Mather and I am the Professor of Anesthesia and Analgesia Research at the University of Sidney.

I am an independent researcher who has been working on bupivacaine for at least 30 years, and published my first paper on bupivacaine 30 years ago, and I'm still trying.

I am interested in -- I'm a pharmacokineticist and much of my approach is that of

a pharmacokineticist interested in anatomical and physiological reality in my pharmacokinetics.

In the series of studies I performed over the last five years that were sponsored in my laboratory by Chiroscience and immensely interesting projects, I set out to study the central nervous system toxicity effects of bupivacaine compared to levobupivacaine, notably its convulsant potential.

I set out to study the effects on the cardiovascular system, particularly the mechanical and electrical aspects, and also hemodynamic effects, and last but not least, pharmacokinetics.

I wanted to know about the dose and blood concentration relationships; I wanted to know about the blood concentration and tissue concentration relationships.

I also wanted to put this together and know about the blood concentration and effect relationships.

Methods were used comprising two protocols in my laboratory, and one protocol from the laboratory of Dr. Alan Santos from New York. I will describe

them this way.

In my laboratory, I set out to study two separate dose ranges of bupivacaine in comparison to levobupivacaine administered in a crossover manner in sheep.

A sub-convulsant protocol was chosen in which the dose was administered up to 37.5 mg maximum over one minute.

I also compared this to a potentially convulsant, potentially lethal protocol in which doses up to 200 mg were administered over three minutes.

The importance of dividing these into sub-convulsant and potentially convulsant protocols is because the act of achieving convulsions causes profound cardiovascular system disturbances, and makes interpretation of the data very muddy, indeed.

Because in the first series of up to 200 mg of levobupivacaine, we never had a death due to levobupivacaine, I designed what I call the extended dose series in which I used incremental doses of levobupivacaine, starting at the maximum of the previous study; that is, 200 mg, and then incrementing

by 50 mg at a time, until death ensued. I wanted to find out why animals died of levobupivacaine intoxication.

In Alan Santos' study, he addressed the question of pregnancy and the old stories that have been circulating now for many years that pregnant animals are more sensitive to local anesthetic intoxication than nonpregnant animals.

In his model, he used a repeated intravenous bolus technique, in blinded study with parallel groups of animals, in which the doses were repeated until a lethal outcome ensued, in much the way that this protocol would be the analogy of top-up doses to epidural administration.

Basically, the model looks something like this. The chronically cannulated sheep preparation in my laboratories and Alan's laboratories; mine are more sophisticated in terms of the numbers of cannulae and placement of the cannulae than his, but the broad principles are the same.

Adult sheep, females, gender, around 50 kg; sometimes in Alan's studies they are up to 60 and

sometimes in mine they are as low as 40, but broadly, 50 kg animal, in which cannulae are placed into the aorta, pulmonary artery, coronary sinus, sagittal sinus, and the jugular vein.

These cannulae are used for obtaining regional blood samples that can be used in mass balance pharmacokinetics calculations.

Monitoring cardiac function most sensitively is by placing a pressure-sensitive transducer into the left ventricle, for monitoring the dP/dt.

We also place microsonometer probes into the left ventricular free wall, for measuring the shortening of the myocardium during contraction, and also for obtaining an intra-cardiac electrocardiogram signal.

We measured hemodynamic effects, cardiac output, left coronary artery, brain blood flow, by sagittal sinus measures, and umbilical artery.

In order to achieve this, we use various combinations of transit time probes and doppler probes.

We also measure central nervous system excitation by videotaping the whole procedure, and then using a quantitative graded scale; whereas, most researchers would normally use the presence or absence of convulsions as a quantile measure, we have decided to use a graded response measure, and I will explain this more a little bit later on.

In some studies, we also measured metabolic characteristics such as oxygen extraction by the heart, and various pharmacokinetics parameters in association with those.

Well, to start with, let's look at some results, and the most prominent result from local anesthetic intoxication is that of depression of left ventricular myocardial pressure, dP/dt.

It is a common effect of all local anesthetics, and on this slide, I have two pieces of information. I have the time course of the series of doses, and on this side, I have the main decrease of the change in dP/dt.

You will see, bupivacaine is the blue, levobupivacaine is the green, and here are the main

values for doses of 12.5, 25, and 37.5 mg.

The drug was administered over one minute, the maximum change occurs at around three minutes, and recovery occurs quite quickly for both drugs.

Comparing both drugs, you can see there is no difference in the way they depress the myocardium, and this is a common feature for all local anesthetic agents. Indeed, they seem to cause depression in myocardial contractility in roughly the proportion to their local anesthetic potency.

Some data showing the next most prominent effect is the convulsant effect of local anesthetics. On this slide, there are two pieces of information. Again, on the left side, you have data from individual animals; on the right side, you have the group mean, and 95% confidence intervals. Bupivacaine, blue; levobupivacaine, green.

These are individual animals and the doses at which convulsions ensued. So, this is the frank convulsions quantile response relationship.

And there is a separation of the values between bupivacaine and levobupivacaine, such that

when analyzed statistically, there is about a 20% -- or rather, a 20 mg advantage in terms of the dose at the onset of convulsions. Levobupivacaine has about a 30% greater convulsant dose to convulsions than does bupivacaine. And so, this is the first clear indication that there is a difference between the drugs.

This is now the Central Effects Index. This is really the graded sum of convulsant effects, using a scale which I can explain in more detail, should any Committee member require it.

But it looks at the things starting to occur such as twitching -- and this is a lower level score than is arching of the neck, etcetera, until finally, frank convulsions are scored at 100%.

Now, these are mean scores for groups of animals as a function of different doses. Again, the green, levobupivacaine and the blue, bupivacaine.

At the lowest dose here, levobupivacaine has a much less convulsant potential, much lower score, because essentially it is not convulsant at this dose, whereas bupivacaine is frequently

convulsant at this dose.

You see that these are peak effects, and so by the time that the animals are convulsing with larger doses, there is essentially no real difference in the peak effects, but on the right side you see quite marked differences.

These low ones here, the 75 mg, represent the convulsant potential, and indeed, the initiation of convulsions, but by the time you get out here, the values for bupivacaine are much larger, because these represent a much longer duration of convulsions.

And so, not only is levobupivacaine less likely to cause convulsions; if they do ensue, they are usually of a shorter duration than from bupivacaine.

Electrocardiographic effects of course are our greatest concern, and these are two representative cases. This is a case where 200 mg of either bupivacaine or levobupivacaine was infused over three minutes.

Here is the baseline electrocardiogram in each case, and there is a strip of which there is the

start of some fairly serious action starting to occur. Let's look at these intentionally.

You will see that the electrocardiogram strips may not quite look like what you are normally used to reading as electrocardiogram control strips, because they are intra-cardiac ECGs obtained from the microsonometer crystals.

But you see, this is a control level, here. A 3-minute infusion, or 180 seconds, you can see by about 3.5 minutes, there is already the start of quite serious arrhythmias with bupivacaine, of the form of ventricular tachycardia, leading about 30 seconds later to ventricular fibrillation, and very shortly after, to death.

On the other hand, the same dose of levobupivacaine on a previous occasion in the same animal in fact, produced some widening in QRS, not surprisingly here, but this is about five minutes; at about six minutes, you can see there is bigeminy, but the animal lived to tell the story, that the dose was nonfatal.

Now, putting some combined groups of data

together. You have seen single animal cases, now look at some combined data. On the left side, you see the initiation of arrhythmias, and on the right side, you see the sustenance of arrhythmias, as a function of dose. Again, the green is levobupivacaine, the blue is bupivacaine.

Within the observation period, at 75 mg doses, neither drug caused significant arrhythmias, but by the time we increased that to 100 mg, four out of six animals demonstrated significant arrhythmias with bupivacaine, none out of six with levobupivacaine.

And you can see the dose response curve preceding. The different number of animals are occasioned by deaths occurring in the series, because they were a crossover series, but it is quite clear that the dose response curve for bupivacaine initiates the greater propensity for bupivacaine to induce arrhythmias.

And on the right side, you see the duration of the arrhythmias. You see also that those arrhythmias are more sustained than they are with

levobupivacaine.

And so, the arrhythmogenic potential for levobupivacaine is this, and the duration of arrhythmias when they occur is this, and the nature of the arrhythmias when they are produced are less malignant than with bupivacaine.

Looking together at the fatalities that result from these. Again, two pieces of information; individual animals with 95% confidence intervals.

There are two pieces of information for each animal. There is a lower symbol which is joined to a higher symbol.

The lower symbol is the dose which was survived, and the higher symbol is the upper dose, which was incremented, and which proved fatal in that animal. They are 50 mg apart.

It is clear there is separation between the fatal doses of bupivacaine and levobupivacaine, such that when the group means are observed over on the side, there is about a twofold advantage in favor of levobupivacaine over the racemic bupivacaine.

So. indeed, the fatalities due to

ventricular arrhythmias, leading to fibrillation, the propensity for that occurs to a much greater extent with bupivacaine than levobupivacaine.

Let's look at some of these so-called extended dose data now. I am going to show you two slides. The first is cardiac output from 250 mg of levobupivacaine, administered over three minutes, and these are individual animal sets of data.

You can see, this is 100% of the pre-drug control value, and you can see there is a great deal of variability in response to cardiac output.

Sometimes cardiac output is increased markedly. This is a consequence of course of the animal's all convulsing, and indeed, they get autonomic excitation producing a marked increase in cardiac output in these animals.

In some animals, cardiac output decreases. But the important point from this slide is, that by the end of the experimental period, they have all returned to near their baseline values.

Now, there are no data that are comparable for bupivacaine, because bupivacaine at the same dose

is almost invariably fatal.

Some more data from the same set of animals, the same animals, the same color codes. This is the widening of the QRS complex of the electrocardiogram. And you can see, again, there is a marked widening occuring of the QRS complex.

But you can also see that these return to essentially baseline values in these animals that survive. And one more time, I repeat, there are no comparable data for bupivacaine, because bupivacaine is usually fatal at this dose.

Putting together some pharmacokinetics and some effect data now. On the left side, I have an example from one animal; on the right side, I have group mean data in this cohort of animals.

This shows all of the blood concentrations taken from the aortic blood concentrations taken from a range of doses, from 75 up to 200 mg, all plotted as a function of time, a three-minute infusion followed by a fall-away in blood concentration.

On these graphs, I have superimposed a green dot for the onset of frank convulsions for

animals receiving levobupivacaine, and a blue dot for those receiving bupivacaine. And again, it is clear that the animals receiving bupivacaine demonstrate their convulsions at lower blood concentrations than those receiving levobupivacaine.

There is one green dot out here you may notice; it is from one of the lower doses in fact, in which the onset of convulsions occurred after the peak concentration in arterial blood. And it is one of my philosophies that things like measuring concentration maxima as a way of demonstrating pharmacokinetics interactions is rather a weak technique.

And now I have also plotted triangles which demonstrate the end of the convulsive period. When we look at the combined data over on this side, we can see that the time taken to the onset of convulsions, amongst all doses for levobupivacaine, is significantly greater than that for levobupivacaine.

When it comes to the time of offset of convulsions, in this cohort, there is no significant difference.

Some more pharmacokinetics. This is a

conventional pharmacokinetics analysis that was done for two main reasons. First of all, it was done to demonstrate the differences between the two enantiomers of bupivacaine.

And this has long been known -- I amongst others have published this kind of material in the literature over the last ten years -- that if we look at the conventional pharmacokinetics with reference to a two-compartment open model, measured from intravenous administration with arterial blood sampling, and applying all of the usual criteria for kinetic modeling, we see this.

The top two are distribution volumes, initial and total distribution. Down here, is internal body clearance and slow half life.

It is clear by comparing the red with the green, there is no differences in distribution between the R enantiomer and the S enantiomer of the racemate.

It has long been known that the R enantiomer of racemate has a higher total body clearance and a shorter half life than the S enantiomer.

But the important point is that, what I was addressing with these studies, is the other green bar, which is for levobupivacaine administered alone. And there is no significant difference for any parameter in the pharmacokinetics of levobupivacaine administered alone, or as a component of the racemate. That is an important feature.

The other important feature that you can't see from this graph is that the data are the combined data set from the trivial 6.25 mg doses, right up to the nearly toxic 200 mg doses. And indeed, there is no significant deviation from these as a function of dose. In other words, there is totally linear pharmacokinetics over this whole range.

Some data from Alan Santos to address this question of pregnancy versus nonpregnancy. Alan Santos performed these studies in pregnant animals and nonpregnant animals. And here in this particular graph I have got the accumulated dose to two different endpoints.

First of all, the dose to convulsion, and indeed, looking at these data, the first point is,

there are no significant differences between pregnant and nonpregnant animals; however, there are significant differences in the dose of levobupivacaine, which is higher than that of bupivacaine, to the onset of convulsions in both pregnant and nonpregnant animals.

When it comes to the dose to circulatory collapse, and the CC:convulsive ratio, no significant differences were found.

At the same time, he needed serum concentrations of the drugs, and because serum concentration profiles were non-normally distributed, he reported these as the median and the upper quartiles for each toxic event.

In this particular case, the serum concentrations for producing convulsions were not significantly different, but the serum concentrations for producing circulatory collapse were.

Indeed, the concentration of levobupivacaine was significantly greater than that of bupivacaine. In other words, there is greater tolerance of levobupivacaine than there is

bupivacaine.

Alan is also interested in placental transmission of drugs The placental transmission, looking at maternal and fetal plasma concentrations at delivery, gives an indication of the relative I guess multifactorial effects that go to regulate this.

Many factors, such as plasma binding and blood flow and things like this, go into this equation, but simply using the data as culled sets of data, there is generally observed a large maternal to fetal ratio for bupivacaine. And that ratio for bupivacaine and levobupivacaine is the same.

And looking at that ratio down here, the maternal to fetal ratio for levobupivacaine and bupivacaine is not significantly different.

In terms of the placental transmission, it can quite clearly be stated that there is placental transmission of levobupivacaine, as there is of bupivacaine, but there is no greater or lesser placental transmission of levobupivacaine, when used alone.

Summarizing. I have looked at the central

nervous system toxicity of these agents, Alan did, too, in his studies, and we both came up with the same conclusion. That levobupivacaine has around a 20 to 30% advantage in dose-producing convulsions. So, levobupivacaine is less toxic in CNS than is racemic bupivacaine.

Cardiac toxicity, the same thing pertains. Levobupivacaine has around a 20 to 30% advantage in dose in the onset of arrhythmogenesis. Certainly, arrhythmias will occur with levobupivacaine, but when they occur, they are of a briefer duration than they are with bupivacaine, and the types of arrhythmias are less malignant than they are with bupivacaine.

Fatal doses. Performing the estimated mean and 95% confidence internal, we say that that for bupivacaine has a mean value of around 161 mg, levobupivacaine, 307 mg in the sheep studies.

Pregnancy; once and for all, I believe Alan has provided convincing data that there is no effect of pregnancy on either cardiovascular system or central nervous system toxicity of local anesthetic agents, both bupivacaine and levobupivacaine.

Pharmacokinetics, summarizing it. The pharmacokinetics are linear over a very large dose range, and they are not different for levobupivacaine when administered alone, or as a component of the racemic bupivacaine.

Thank you. Now, Professor Nimmo is going to speak about clinical human pharmacology.

Human Volunteers

DR. NIMMO: Dr. McCormick, Dr. Horlocker, ladies and gentlemen, good morning. I hope that my Scottish accent will not be too difficult for you to follow.

My name is Walter Nimmo. I'm the Chief Executive of Inveresk Research, a contract research organization working with Chiroscience.

I would like to present a link between the preclinical data you have just seen, and the clinical trial data you are about to see, by describing the comparison of effects of levobupivacaine and bupivacaine on the heart in two healthy volunteer studies.

The studies will be known to you by the

numbers 004801, as a comparison of the cardiovascular effects of levobupivacaine and bupivacaine following intravenous administration; and 012105, as a comparison of the effects of levobupivacaine and bupivacaine on QT dispersion, EKG, and the signal averaged EKG.

Study 004801 was the first administration to man of levobupivacaine intravenously. In 14 healthy male volunteers, a lidocaine pretest was conducted; lidocaine was infused until the volunteers all experienced CNS side effects, such as tingling of the tongue, circular molar analgesia, or lightheadedness.

Approximately one week later, they entered a double-blind, randomized, crossover study and all volunteers received levobupivacaine and bupivacaine one week apart.

The drug was given by IV infusion at a rate of 10 mg/minute until there was evidence of CNS symptoms, similar to what they had experienced with the lidocaine.

In this study, a variety of tolerability

observations were made; pulse rate, blood pressure, EKG, and continuous monitoring of the EKG, and in addition as a monitor for safety, we measured cardiac index and other variables using the BoMed thoracic impedance apparatus.

This machine presents on screen the average of the previous 16 beats, and the equipment is registered as a regulatory Class II by the FDA.

We monitored cardiac index, stroke index, ejection fraction, and acceleration index. Your reviewer, Dr. DiMarco, says that these observations are not blood-independent and that is true, but the acceleration index attempts to do this by measuring the initial acceleration of blood in the left ventricle in the first 10 to 20 milliseconds after the aortic valve opens.

These are the dosing details from this study, and the doses of drugs administered did not differ significantly. For levobupivacaine, the mean dose was 56 mg and for bupivacaine, the mean dose was 47.9 mg.

The dose range you see was 17.5 to 150 mg

for levobupivacaine, and only in this group did any volunteer achieve the maximum dose allowed, which was 150 mg, without CNS effects.

The bupivacaine range was 22.5 to 110 mg. The mean maximum concentration was achieved at the end of the infusion and did not differ significantly between the two groups, it was 2.62 micrograms/ml for levobupivacaine, and 2.25 micrograms/ml for bupivacaine.

This slide, ladies and gentlemen, shows the statistically significant cardiac contractility results. You see data for stroke index in ml/m^2. Acceleration index per second/per second, and the ejection fraction as a percentage.

And you see the mean change at the end of the infusion for bupivacaine and for levobupivacaine, and the p-value.

Notice that in the bupivacaine group, there was an average change of almost 11 mm/m^2, between the beginning and the end of infusion, and only 3.3 mls/m^2 in the levobupivacaine group, and this was a highly significant difference, and greater than

25% was requested.

For the acceleration index, the change from pre-dose to the end of infusion was .18 per second per second, and in the levobupivacaine group, it was .06 per second per second. This also achieved significant difference.

In the ejection fraction, there was a significant fall from pre-dose in both groups, but the difference between the groups was not significantly different.

These data are shown graphically on this slide, as a percentage fall. In the bupivacaine group for stroke index there was an average, almost a 20% fall in stroke index, compared with a 7% fall for levobupivacaine.

For the acceleration index, you see the data, almost 40% fall from beginning to end of infusion, compared with just under a 5% fall for acceleration index.

In the 12-lead EKGs, this slide shows the only significant differences achieved. For the PR interval, there was a significant increase from pre-

dose in the bupivacaine group, from 165 msec on average, there was an increase of 11 msec, which just, just achieved significant difference.

And in the levobupivacaine group, there was no significant increase from pre-dose, 165 on average before infusion, and increased by an average of 5 msec. This was not significantly different, but there was no significant differences between the groups.

In the QTc interval, measured in these Hewlett-Packard EKGs, once again there was a significant increase in the bupivacaine group. It just achieved significant difference with an average increase of 22 msec from a baseline of 384.

And in the levobupivacaine group, there was no significant increase, it just failed to achieve significant difference, 21 on average, increasing on a baseline of 388.

And once again, there was no significant difference between the two groups.

So, the conclusion from this first administration to man study was that levobupivacaine

has less effect on cardiac contractility measures than bupivacaine, and there was no between treatment differences seen in the EKG intervals.

We went on to study another human volunteer study in an attempt to review more in-depth the EKGs. On this occasion, 22 healthy volunteers were entered into the study, and completed the study.

Once again, all 22 received a lidocaine pretest to identify CNS symptoms in all the volunteers.

On this occasion, all 22 volunteers received bupivacaine at an infusion rate of 10 mg per minute, until they achieved the same side effects. And the dose range was 30 to 120 mg.

The 22 volunteers were then randomized to a double-blind, parallel group to receive levobupivacaine or bupivacaine, 11 in each group, and this randomization was stratified according to dose.

Observations that were made, apart from safety observations, included the 12-lead EKG, QT dispersion, and signal averaged EKG, using a Marquette.

The data from this study are shown on this slide. On the top of half of the slide you see the doses that were given. Once again, there was no significant difference in the mean dose administered between levobupivacaine and bupivacaine.

The dose range was 40 to 110 mg for levobupivacaine, and 30 to 120 mg for bupivacaine.

The mean Cmax was very similar to the previous study, 2.75 micrograms/ml for levobupivacaine, and 2.44 micrograms/ml Cmax in the bupivacaine group.

The only significant difference found in this study was in the QTc interval in volunteers who had received more than 75 mg of drug.

In the bupivacaine group, there was a significant increase in QTc, which was of 24 ms on average, compared with 3 ms in the levobupivacaine group. This was a significant observation.

In conclusion, from this study, at doses greater than 75 mg intravenously in healthy volunteers, bupivacaine produced a significantly greater QTc increase than levobupivacaine.

No other significant differences in effects on the EKG were detected.

And the conclusion from both studies, levobupivacaine has less effect on cardiac contractility measures than bupivacaine. Levobupivacaine in doses greater than 75 mg has less effect on QTc than bupivacaine.

We believe that this concurs with the preclinical evidence you have already seen, which shows that, compared with bupivacaine, levobupivacaine is associated with a lower binding affinity to human cardiac potassium channels, and significantly greater doses are required to prolong QTc in the pig.

Thank you very much. I would like to hand over to Dan Kopacz, who will present some clinical efficacy data.

Clinical Trial Experience

DR. KOPACZ: Good morning, ladies and gentlemen. My name is Dan Kopacz. I'm a staff anesthesiologist at the Mason Clinic in Seattle.

I have been asked to address the efficacy of levobupivacaine in the trials that have been

performed, comparing it to bupivacaine, as used in the operating suite or in the obstetrics suite for Cesarean Section.

I will cover four studies; they are all epidural studies. They are all double-blind, randomized, parallel group studies, with bupivacaine as the comparison drug.

The first two studies are in Cesarean Section, the methods of which are combined actually on this slide, because they are quite similar.

The differences are, one study is 25 mls of study drug, or racemic bupivacaine, the other study used a total of 30 mls.

Both studies used 0.5% study drug.

The standard for obstetrics, a lumbar epidural was placed in the left uterine displacement position. Drug was injected through a catheter after a test dose, which included epinephrine in one study; that was a lidocaine test dose. In the other study, it was a study drug containing test dose.

What I hope to show on going through these four studies are that, from a clinical perspective,

these drugs are very similar and actually indistinguishable, but there are some minor differences, and where these appear, I will point them out, but I think you will see that the differences relative to the similarities are relatively small.

This is the first obstetrics study. Again, comparing 0.5% levobupivacaine on the left, 0.5% racemic on the right, which will be the standard convention.

Just to go through the schema of this slide, because you will see it again in the other studies as well, the onset data for both drugs will be on the outside slide; the regression data will be on the inside of the slide; and the endpoints will be on this dermatome man, if you will.

So what you see here is an onset to T5, which was the predetermined primary efficacy point in this study, of about ten minutes for levobupivacaine, and six minutes for racemic bupivacaine.

This was statistically different, and I will explain more about that in a second, and you see no difference in any of the regression data, with the

exception that levobupivacaine takes a little longer to regress and you will see that again, as a trend, that in only one instance is that statistically significant.

These are two patients that were excluded from that trial because they didn't reach the T5 block height. One patient reached T6, which actually occurred at 15 minutes.

The default mechanism for someone who didn't reach a T5 block height, was to use the time of start of surgical incision, or the start of the C Section as the onset time. This patient's C Section got started at 40 minutes.

The second patient had a block of T12 at ten minutes; that was clearly going to be inadequate. They rolled this lady back up and did a spinal anesthetic, and the surgical procedure started 29 minutes after end of drug injection.

So, these two patients had onset times of 40 and 29 minutes, which was included in that onset time from the previous slide, which somewhat skews the results. And if you remove these two patients, which

is not a statistically nice thing to do, the onset time drops to eight minutes, and the difference between those two drugs disappears.

I will also point out that that is the only place in any of the studies I will go over, and any of the studies actually that were done clinically, where there was a difference in onset time.

Various muscle relaxation measures were also made in these studies. For the Cesarean Section studies, a simple scale, four-point scale, actually, there is a grading of poor, fair, good, and best for the abdominal muscles, where it was rated by both the obstetrician, as is shown in this slide, and the anesthesiologist.

I think you can see quite clearly that these drugs work the same, with the vast majority of patients having neither good nor best conditions for the C Section.

This data is identical for the anesthesiologist, or quite similar, I should say, to the anesthesiologist, not only in this study, but in the next study, which is the other Cesarean Section

study.

Patients also rated their pain during their C Section at five different time points. What you see on the left is a truncated VAS pain scale, where 0 is no pain whatsoever; 10 is the highest pain, which is off on the ceiling.

They rated pain at skin incision; abdominal opening, the musculature; uterine incision; uterine manipulation, after the baby was delivered; and in the recovery room.

Now, the protocol stated that all of these time points should be added together and a comparison be made on the sum of all of these time points. And there was no statistical difference when you did that, not only in this study, but in the next study as well.

But there is some suggestion there may be a difference at the time of uterine manipulation with significantly more pain with the bupivacaine group. However, when you look at the same data from the second study, this peak is in existence, so it's just isolated to this study.

This is that second Cesarean Section study

data, again, comparing 0.5 to 0.5, onset similar to the last study. It takes a little bit longer because this study had the lesser of the two drug amounts, 25 ccs relative to 30 in the first one.

But again, ten minutes versus nine minutes. Again, not different in this study. And regressions to T10 at about five hours, and about eight hours for complete regression of blockade. Once again, a little bit longer it appears with levobupivacaine, but no statistical significance.

Motor blockade of the lower extremities was measured by a standard Bromage scale in both of these studies as well. Not really clinically relevant, because they are having abdominal procedures, but just to go through the scale briefly.

Zero is no lower extremity muscle blockade whatsoever. The other extreme is a completely flaccid lower extremity at grade three.

In this second study, there was statistical significance in that fewer of the patients -- I should say, more of the patients in the levobupivacaine groups tended to have less motor

blockade using this Bromage scale, relative to bupivacaine.

This same measurement was also made in the first study, and this propensity of levobupivacaine to produce less motor blockade wasn't apparent in the first study. So you have, again, one study saying one thing and one saying slightly different.

The protocol also stated that patients that had no lower motor blockade whatsoever should be excluded from measurements of offset of motor blockade, so that these patients are excluded when you measure the time that motor blockade resolves.

There is statistical significance and it appears that levobupivacaine produces a longer duration of motor blockade; but again, that is only in the patients that got any degree of motor blockade whatsoever. That difference also wasn't apparent in the first C Section study.

To summarize the C Section studies, both drugs produce adequate anesthetic for the intended procedure. There tended to be shorter onset with levobupivacaine in one study, statistically; I'm not

sure it was clinical significant, but there tended to be a little less motor block in the other study. Again, I am not sure that is clinically significant, either.

The third epidural study is shown here. This now is a three-group study in surgical patients having lower limb vascular surgery. Again, the 0.5 to 0.5 comparison, now with the third group added in, being 0.75% levobupivacaine.

The other difference in this study, relative to the obstetrics study, is that now it is a smaller dose, 15 ml total, as opposed to 25 to 30 in the Cesarean Section study patients.

These are the results from this study. Onset time again shown on the outside. This is first appearance of anesthesia, which is not clinically relevant whatsoever.

Peak block height of T7 versus T8. Onset time of 15 to 20 minutes, no differences there. Again, regression at about four hours to T10, complete regression, six to seven hours. No differences in any of these parameters.

What is also shown on this slide is, not only the mean peak block height of T7 and T8, but also the range of peak block height. One patient in the 0.5% bupivacaine only got a peak block height of L2, with 15 ccs. The lowest peak block height was T12 with levobupivacaine, and one patient had a T6 for the racemic bupivacaine. Not statistically different, but gives you more of a clinical feel for how this drug is going to behave.

The data on the left side are identical to the last slide. The data on the right side is what's new; that's the 0.75%, the third group in this study now.

The only significant difference in this group, relative to either of the other two groups is the total duration of sensory blockade. There is no difference in onset, regression to T10, but as you would expect, as you give 50% more drug, same volume, higher concentration, you now have a total duration of about eight hours.

Using that same Bromage scale that I talked about in the second obstetrics study, motor

blockade was also assessed, with a Bromage scale in this study, grades zero, one, two, and three.

When you compare the three groups, it tended to be a significant difference, but it didn't reach statistical significance, and what you see from looking at that graph, grossly, is the 0.5% levobupivacaine tended to produce less motor blockade.

As you would expect, the 0.75% group tended to produce a little heavier motor blockade, and the racemic group was intermediate between the two.

Therefore, as you would likewise expect with using a higher dose, you get a little bit greater degree. It takes a little longer to get that greater degree of motor blockade with the 0.75%, and it likewise lasts a little bit longer, but likewise, compared to the top, there is no real statistical difference between these drugs.

The final study is my favorite, because I was the principal investigator. It compares 0.75% levobupivacaine, 0.75% bupivacaine in patients having lower abdominal surgery, 56 patients, equally distributed between the groups.

The protocol also had provision that during surgery, if the patient needed or if the investigator felt that the patient needed more blockade, they could get a top-up of 7ccs.

One patient in the levobupivacaine group, and two patients in the racemic bupivacaine group got top-ups. Those patients obviously are excluded from the data that I will show in the next slide, and in addition, one patient in the racemic bupivacaine group only got an L1 block with 20 ccs of 0.75% bupivacaine. That patient likewise is excluded.

And here are the data. There was a difference in primary endpoint in this study. The primary endpoint was actually onset of sensory anesthesia to T10, which was the lowest level which we felt we could initiate the surgical procedure. That is the intermediate number and onset, 14 minutes, onset to T10.

Peak onset to 25 to 30 minutes; a little bit higher than the previous slide, because we are giving a bigger dose-up, obviously, but T5, again similar ranges. This is that one patient that was

excluded.

Regression now is two segments, T10 and complete regression. Five hours, six hours, and nine to ten hours. And this is one point where there is actually statistically significant difference between the two drugs, with the longer duration, 45 minutes longer with 0.75 levobupivacaine.

But I would suggest to you, after eight or nine hours, a difference of 45 minutes really isn't clinically significant, in my opinion.

The other test that was done in this last study was another abdominal muscle test, that being the RAM test, which stands for rectus abdominous muscle.

Basically, what you had to do is make the patient do a sit-up with their arms behind their head. If they can do that, it's a grade zero -- I'm not sure everyone can do that, but --

A grade one, you have to fling your arms in front of you to do the sit-up, and as your muscles get more and more relaxed, you are less able to do a sit-up, so you get a grade two, grade three, grade

four, and grade five. Grade five, you basically can't even more your shoulders off of the table.

For abdominal surgery, you need a grade three to have enough relaxation of the muscles for the surgeon to operate.

And you can see here, by and large, 90% of the patients got grade three at 30 minutes. And the muscle relaxation was adequate without any other intravenous muscle relaxants to perform the operation. No difference, again, between the two drugs.

There are also a number of other clinical studies that compare bupivacaine and levobupivacaine. By and large, they all show no difference, statistically, or clinically. One of those was a supraclavicular block and brachial plexus. There were two ophthalmologic blocks comparing peri-bulbar anesthesia.

There are infiltration studies, two of them, for patients having hernia operation under straight infiltration analgesia. And also labor analgesia patients and other obstetric patients. All of this data is available, so if anyone has any

questions about it, feel free to ask about it.

By and large, again, they show that both drugs are effective, clinically, and that there are very little difference between them.

In conclusion, the points that I basically wanted to get across are, both drugs are very effective local anesthetics when given at equal concentrations, equal volumes, and therefore, equal doses, for the various regional block that we perform in surgery.

There are some minor differences, but by and large, those differences are not very obvious, relative to the similarities.

There may be some slight differences at onset as shown in the first study. There may be some differences in duration, as has been shown in most of these studies, but only statistically in the last, as well as some differences in motor blockade as shown in some of the four studies that I reviewed.

Now, I would like to pass the microphone to Dr. Jim Crews, who is going to review the safety data from the clinical program.

free EEG epochs were taken from each significant time point during the observation period, and submitted for power spectrum analysis.

I won't go into a lot of detail on this. It was, as you might imagine, a very complicated study and the amount of data that was produced from this study is impressive in terms of its volume, but basically, the conclusions that can be drawn here was that, bupivacaine showed a slowing of the EEG, which is consistent with the CNS depressant effect that you might expect with any CNS depressant type drug.

Levobupivacaine produced a similar CNS depressant effect, but the effect was less in terms of both the magnitude of the CNS depression, as well as the extent, or the areas of the brain involved in EEG changes, representative of CNS depression.

More adverse events were reported by the subjects during the bupivacaine infusion than by the same subjects during the infusion of levobupivacaine, including an increase in blood pressure during the bupivacaine infusion which was not seen during the levobupivacaine infusion.

This just shows the plasma concentrations obtained in the patients with normal renal function. On this axis you see the values expressed in mg/l or micrograms per ml, with most patients having peak plasma concentrations in the range of 1 to 2 micrograms/ml. A couple of patients up around 2, and one patient at 3.7.

Twenty-six of the twenty-eight patients had adequate surgical anesthesia within 30 minutes of performing the block, which was the cutoff time set in study.

The two patients who did not have adequate surgical anesthesia within the 30 minutes both had a complete block, postoperatively.

No hemodynamic or CNS changes suggestive of either cardiovascular or CNS toxicity were noted in any of the patients, including the patient who got the highest peak plasma concentrations.

The average maximum concentration obtained in the study was 1.58 micrograms/ml, and the time to that maximum level was 39.5 minutes.

So, what we can conclude from this, in the

cases of the single highest doses of the drug, in the range of 250 to 300 mg for brachial plexus block, that this dose is well-tolerated without any signs of cardiovascular or CNS toxicity.

Looking at the maximum dose of levobupivacaine administered cumulatively over a 24-hour period, we can look toward the four clinical trials where levobupivacaine was administered for continuous postoperative analgesia, following the use of levobupivacaine for surgical anesthesia for the surgical procedure.

There were 326 patients in these four clinical trials. No patients demonstrated any signs or symptoms of either cardiovascular or CNS toxicity related to the cumulative dosing during the 24 hour study period.

This just shows a breakdown of the types of doses that were received. Six of the patients out of the 326 received 24 hour cumulative doses exceeding 600 mg.

Another eight patients received doses in the 500 mg range; 45 patients received doses,

cumulative doses, in the 400 mg range, and then the remainder of the patients received doses in the 250 to 400 mg range, in the cumulative dose over 24 hours.

There were three cases of investigator-suspected intravascular injections, which occurred during the phase II and phase III studies. This involved a total of over 1350 patients; 879 of these patients received levobupivacaine, the remainder of the patients received racemic bupivacaine.

And out of the total of the 1355 patients, there were three suspected cases, when the blinding was broken, two of these patients had received racemic bupivacaine, and only one patient had received levobupivacaine.

Looking at the response that patients had in these cases of suspected intravascular injection, the first patient we will discuss was from one of the C Section trials where the patient received epidural bupivacaine, 0.5%, a dose of 120 mg.

The patient exhibited slurred speech, became unresponsive, bradycardic, hypotensive, and had transient uterine hypertonia.

studies, where the patient received a dose of 142.5 mg of levobupivacaine 0.75%.

This was administered via an epidural catheter, following a negative test dose for intravascular injection.

The patient became drowsy, had slurred speech, and a period of excitation where she had some screaming, which was self-limited, exhibited at no time any changes in cardiovascular status, and did receive two doses of IV thiopental which were said to be for convulsant prophylaxis.

This is the only pharmacokinetics profile that we have from the intravascular, suspected intravascular injections. Again, this occurred with bupivacaine, not levobupivacaine.

And you can see from the data, this was from the supraclavicular block study, the patient receiving intravascular injection had a observed peak plasma concentration of greater than 5 micrograms/ml, with the remainder of the patients having peak plasma concentrations in the 1 microgram/ml range.

So, from the information that we have

seen, both from the clinical data, as well as the preclinical data, there does seem to be an equivalent clinical effect for levobupivacaine as compared to bupivacaine, and a greater margin of CNS and cardiovascular safety in the event of an unintentional overdose or intravascular injection.

I meant to mention this in the beginning, but on the Agenda it says that I would be discussing cases of overdose. There were no cases of overdose of local anesthetic in the clinical development program, but the overdose term on the Agenda refers to these cases of unintentional intravascular injection.

Thank you.

DR. GENNERY: Thank you very much, Dr. Crews. Before I just finally wrap-up, I would like to draw the Committee's attention to the Briefing Document that we provided to you, where we noted that, having supplied Dr. Raymond Woosley of Georgetown University Hospital, all the original data on 012105, he had actually come to a different conclusion in terms of the outcome of the electrocardiographic analysis.

And fortunately, Dr. Woosley has been able to join us here today, and before I wrap up, I would just like to give him the opportunity of explaining where he sees these differences lay.

Electrocardiographic Analysis

DR. WOOSLEY: Thank you, Brian. I don't have any slides, but I think your document does have the graphs that I will refer to.

Chiroscience asked me to be a consultant on this project sometime ago, and to look at the electrocardiographic data that they had available, and the preclinical pharmacology on the isomers, probably because of my previous interest in differences in sodium channel blockade the myocardium, so it was something of interest to me, and it was an interesting challenge.

When I looked at the pre-clinical pharmacology data, Study 012105 had subset analysis that indicated that there might be a trend toward a difference in the QT data, so I suggested that there may be some confounding variables in this.

The two that I thought might be playing a

role were, one, a change in heart rate, which could certainly change the Bizette-corrected QT interval, and then the second was the fact that the data that they had obtained was using the Marquette System.

And we have published an abstract -- we don't have a final publication out, but -- of a comparison of the Marquette and the Hewlett-Packard automated systems to what we and many other people use, which is more manual, a bit pad method for comparing the QT interval -- for analyzing the QT intervals.

We analyzed the QT intervals and the QRS data in that study, and found that there were, as we had seen before, major discrepancies between our measurement and the machine measurement. And in the document, you will see the comparison of those.

There were some differences due to the change in heart rate that was seen in that study, but the major differences were caused by a general under-reading of the QT interval by the Marquette, compared to our data.

So, when we did the analysis, you will see

that we felt that there was no difference in the QT in the two data sets.

My conclusion at the end of that, as you will see in my report, was that this study indicated the maximum ethical attempt to administer this drug to normal volunteers, to examine potential differences in the electrocardiogram, and I didn't see that there were any statistically significant changes in the QT interval.

And then, putting that in -- adding to that, the preclinical pharmacology data, I felt that they had demonstrated in the preclinical data that there was a significant pharmacologic difference in so many models, but that it would be unethical to take normal volunteer studies to anything, any further point.

And that, the maximum tolerated dose that they had been able to administer to normal volunteers was inadequate to produce any changes in the QT interval, and therefore, unlikely that they would be able to show any differences between the QT with the L isomer compared to the racemate.

So, if there are questions about the data that I have presented, I would be glad to answer those, but those were my general conclusions.

Concluding Remarks

DR. GENNERY: Thank you. Thanks, Ray. If I could just take the opportunity then of summing up. We believe that we have managed to show a clear difference between the cardiovascular toxicity seen with levobupivacaine and bupivacaine, in all the preclinical models that were tested, and that these all well exceed the 25% that we discussed two years ago.

That in clinical pharmacology studies we have seen differences, including those in the central nervous system, between levobupivacaine and bupivacaine.

And finally, the meta analysis of the studies that was presented by Dr. Crews showed that small differences can be seen, even when the drugs are being compare in normal use. And this is perhaps a somewhat unexpected finding.

We believe that these differences are

relevant, in that levobupivacaine has been shown to have the same efficacy as bupivacaine when used at the same concentrations and volumes, in a wide variety of applications, including epidural use in surgery, and Cesarean Section, and peripheral blocks.

What I have tried to do here is to tie everything together, and see how the story sort of comes together.

In specific observations, the implication of those observations and how that may translate into a clinical situation in the event of an unintentional overdose.

So, looking first at the cardiac sodium channel effects being less with levobupivacaine. That is the, that will translate into a lesser prolongation of QRS, and we have seen that in the pharmacology studies that we have presented to you, implying a lower risk of ventricular arrhythmias, particularly tachyarrhythmias in the event of an unintentional overdose.

Less effect on potassium channels, which translate into less prolongation of QT and QTc.

Again, we have seen that in some of the pharmacology models, lower risk of Toursade des pointes.

And then we are seeing less prolongation of PR interval, suggestive of less effect on calcium channels, with a lower risk of reentry arrhythmias or of complete heart block.

We believe that we have addressed the questions posed by the Agency to the Advisory Committee and we have shown that levobupivacaine is a quantitatively different drug to bupivacaine, particularly in respect to its cardiovascular and central nervous system side effects, and the PI should therefore not contain a boxed warning. And that the safe and effective use of levobupivacaine can be ensured by appropriate wording in the labeling.

Thank you.

Questions From the Committee

DR. HORLOCKER: Could we have the lights up, please? We will now entertain questions from the Committee. I would like to start out. I have two questions, one on clinical and one on the laboratory studies that have been done.

First of all, some of the striking characteristics of the bupivacaine-induced toxicity was that the CV toxicity occurred without prior CNS toxicity. And then secondly, the parturients were very difficult to resuscitate.

In any of your laboratory studies, did the animals in either the bupivacaine or the levobupivacaine groups demonstrate a CV toxicity, prior to the CNS toxicity, or did that always have the excitatory, seizure-type disorder first.

And then secondly, do we have any data on the resuscitation of these animals? Are they more easily resuscitated when they receive levobupivacaine?

And my second question concerning the clinical studies is that, certainly you have demonstrated that there is a decreased magnitude and shorter duration of the CV and CNS effects, but do they occur at similar levels, similar timing, or is it just that they occur at the same time, but they are of less magnitude?

DR. GENNERY: I wonder if I could ask Dr. Mather to address the first issue?

DR. MATHER: Dr. Horlocker, the course of the events is fairly predictable. There is always a CNS effect.

Now, we use a three-minute period of infusion intentionally to clarify this. We want to see things happening. And we can always see the prodrome of convulsions in our experimental animals and certainly subclinical toxicity of course is attendant, for example, changes in left ventricular dP/dt and left ventricular and diastolic pressure increases.

They are occurring all of the time without any overt CNS symptoms, but the serious CNS symptoms to which you refer, in our experience, are never without a preceding CNS syndrome.

DR. HORLOCKER: Are there any other resuscitation data available on these animals?

DR. GENNERY: Yes, sure. Thanks very much. One of the protocols that we agreed to do was one in dog resuscitation, and the experimental phase of that is finished.

Dr. Feldman, who is the investigator, has

come with us, and he has a little bit of preliminary data to show on that, if I could ask him to come to the microphone.

DR. FELDMAN: These experiments, I just wanted to stress that this data is extremely preliminary. We just finished these studies about two weeks ago.

We did a cursory examination to look at some very specific points, which we felt were the most critical points probably of the Study, just to be able to present some of this preliminary data to the Committee.

These experiments, just to give you a brief outline of what they were, we had an in a series of experiments prior to this, determined the convulsive dose in the dog by intravenous infusions, 2 mg/kg/minute of levobupivacaine, bupivacaine, and robivacaine.

We used those convulsive doses in this study. In this study, the convulsive dose was administered over 30 to 40 seconds, intravenously. Resuscitation was begun 30 seconds after the onset of

seizure activity.

And the resuscitation basically consisted of we would treat whatever toxicity happened to be most life-threatening at the time.

If seizures were the only form of toxicity which were occurring, then we treated them with barbiturates, intubation, and oxygen ventilation.

We treated arrhythmias, ventricular arrhythmias, with Bertyllium. Hypotension was either treated with amranone; we used atropine and phenylephrine if necessary. In the worst cases, we had reverted to chest compressions and DC cardioversion.

So, this slide represents the first portion of the study, which is the convulsive dose, given as I said over about 40 seconds, intravenously.

We haven't broken the code on these experiments yet, so we have assigned them just a drug code, D, E, and F, so that we were able to group them to see what was going on in the different groups.

Because the data has not been analyzed, we would prefer not to break the code until we have

completely analyzed it.

I should also point out that incidents of AV block and incidents of ventricular arrhythmias are rather broad in this definition, meaning that if we had two incidents of AV block in a particular animal, it is listed here. If we had one PVC, it's listed here.

If we had a burst of ventricular tachycardia that went on for 20 seconds, it's listed here. We haven't broken down into severity yet, so you have to keep that in mind when we're looking at this data.

Essentially the AV block data, there was no difference between any of the three treatment groups. We did do a chi-square and a Fischer Test on these just to see if there were differences between groups.

We found no differences in the occurrence of AV block, ventricular arrhythmias. We had no incidents of ventricular fibrillation in this particular portion of the study.

The onset of seizures was within seconds

of ending the injection. Either a few seconds before or a few seconds after. And no deaths in this portion of the study. Based on this data, we see virtually no difference between these three drugs.

This is the second portion of the study which was conducted 48 hours after the first portion of the study.

This involved injecting two types of convulsive dose, because of the volume, and we wanted to keep the rate relatively constant. These ere injected over approximately 60 seconds.

Again, we had some slight differences in the AV block but not significant.

Again, same thing with ventricular arrhythmias. Three out of six, five out of six, and one out of six. Statistically, there is no difference there.

The incidents of ventricular fibrillation, again, there is a slight distribution between the three groups, but statistically not significant.

Onset of seizures generally occurred when about half the dose was administered. Obviously, this

is two times the convulsive dose. We tried to keep the rate relatively constant.

So that, seizures were occurring at the time drug was being infused. So, it's a rather severe situation if you look at a clinical scenario.

As far as resuscitation. If you look in the last column we had two out of six animals in this particular group die. They both died of ventricular fibrillation. One out of six in this group died and we had no deaths in this group.

As far as treatment, we were generally successful in treating a majority of the toxicity, which was primarily CNS, with barbiturate and oxygen ventilation. We've been relatively successful in that.

There are two animals, one in this group and one in this group that had ventricular tachycardia, which we were able to successfully treat with Bertyllium and amranone.

And we had very little success treating any of the animals that developed VF; we had no success, in fact. And that included chest

compressions, DC cardioversion, and all the drugs that we have available.

DR. WATCHA: A question for you. Are you going to continue recruiting more dogs in this study?

DR. FELDMAN: The protocol is completed for this study and we have, at this time we have no intention of adding any additional.

DR. WATCHA: The reason I asked that is that you have got here a situation where you have got five out of six in one group, whatever that group is, having ventricular arrhythmias, as opposed to one out of six in the others.

If that continues on, I'm pretty sure it will reach a point of statistical significance, whatever those two groups are.

DR. FELDMAN: I think that that may be true; however, I think that the severity of these, what these numbers represent -- in fact, I can tell you that one of these animals represents a single premature ventricular contraction.

DR. WATCHA: That still leaves four others.

DR. FELDMAN: Excuse me? That still leaves four others, that's correct.

DR. WATCHA: And I mean if you're going to state on statistics, just -- I mean, if you are looking at percentages, you are referring to a fairly -- even if you take four out of six, that's a 66% situation there, compared to a 33% in the other group.

DR. FELDMAN: Correct.

DR. WATCHA: You may have something, if it's more animals.

DR. FELDMAN: That may be true. I think my recommendation would be to further analyze the severity and the type of these arrhythmias before we decide to do that. As I said, these are grouped, and we haven't looked at severity or duration or anything yet.

We occasionally even see PVCs in the pre-drug control on some of these animals, and AV block, also. So it really has to be further analyzed.

But statistically, I think you are probably correct.

DR. WATCHA: Which brings one other

question, Madame Chairman. Are we going to be voting on acceptance otherwise of this drug, based on what has been presented, or is this just an ongoing, one in a series with regard to this drug?

DR. HORLOCKER: Specifically, we are asked to address the two questions that we were sent regarding the labeling of this drug, and we will make our recommendations to the FDA members, based on the data we see today, and whether we require additional studies before the actual labeling can be finalized.

So, the answer is --

DR. WATCHA: Perhaps this is not the time to discuss it.

DR. HORLOCKER: Correct. We'll defer that until later.

DR. WATCHA: I'll pick up at that point, then.

DR. FELDMAN: Anyway, to conclude the, again, the incidence of deaths and ventricular fibrillation in these, were not statistically significant between the three groups.

DR. GENNERY: Can I ask Dr. Mather back to

the podium, because he pointed out in his studies some differences in the types of arrhythmias that developed and how they behaved.

DR. MATHER: Dr. Horlocker, Committee, once again, the issue of -- return to the point of convulsant and the arrhythmogenic doses, the fatalities.

I was looking here at my data from Study 1249107PH in which we have studied the so-called extended series. I note here from my notes here that at doses of 200, 250, 300, and 350, respectively, the main convulsive doses were 111, 123, 136, 137. Quite consistently low levels of the onset of convulsions.

And as we know, no animals died of 200 mg. Seven out of ten animals survived 250 mg. Three out of seven animals survived 300 mg, but none out of three survived 350 mg.

So, I believe there is quite a significant separation between the CNS for frank convulsions, and the cardiovascular. In fact, fatality is not going to occur.

Returning one more point to the issue in

Study 055, where the arrhythmias that were generated in the levobupivacaine group all returned spontaneously to normal rhythm, whereas the animals treated with bupivacaine, as we saw, several of them died with ventricular fibrillation at the same doses that they survived levobupivacaine.

So, does that clarify the point you were raising there? I think the literature became a little confused about these deaths. I doubt very much whether a serious analysis of the situation would really support that position.

DR. HORLOCKER: In the clinical studies, then with the human volunteers, did you see, did the symptomatology occur at the same dose of levobupivacaine and bupivacaine, but the effects were of lesser magnitude, of shorter duration, or did they occur at statistically different doses?

What I am asking, is there a margin of safety, if you do have an intravascular injection, could you give more levobupivacaine before you would see any symptoms, compared to bupivacaine? Do you have any data to evaluate that?

DR. GENNERY: Do you want to --

DR. NIMMO: Thank you. My name's Nimmo and I'm from Inveresk Research. I could respond to that with regard to the volunteers.

In the first study, one of the volunteers had no CNS side effects, despite receiving 150 mg of levobupivacaine.

It was designed, as you remember, to be given until they had CNS side effects, or a maximum dose of 150. Whereas all the volunteers in the bupivacaine group had CNS side effects.

In the second study, where it was a parallel group study, all 11 volunteers in the bupivacaine group had CNS side effects, but only 6 of the 11 in the levo group had CNS side effects before the maximum dose was achieved

So, it does seem you can give more intravenously before CNS side effects are seen with levobupivacaine.

DR. HORLOCKER: And that's a statistically different --

DR. NIMMO: Those were small numbers and

that was not tested.

DR. HORLOCKER: Are there any other questions from the Committee?

DR. DiMARCO: I have a couple of questions, if I might. Dr. Mather, could you explain the dosage on your sheep studies? Were those done, did each animal receive multiple doses, and were they done on separate days, or were they on the same day, with a wash-out period, or were they rapid sequence? I couldn't tell from your presentation.

DR. MATHER: Sorry if that was unclear. No animal had more than one dose on a day. There is always at least 24 hours between subsequent doses.

The principles of all of those studies I designed are single dose studies. Dr. Santos' study was a cumulating study, but my own studies were each a single dose, no attempt to resuscitate animals. It was to observe the time course.

So, all the low dose and the high dose studies were one dose per day, at a maximum per animal.

DR. DiMARCO: And one of your endpoints

was number of arrhythmias.

DR. NIMMO: Yes.

DR. DiMARCO: And I mean, one episode of VF to me is worse than 400 PVCs.

DR. NIMMO: I accept that, indeed. We were looking for a comparative scoring system, indeed, and we did characterize the numbers and the data were complex, and I have not presented them in a slide, but certainly, the range of rhythms, or arrhythmias, that were demonstrated by the two sets of animals, they were in each case.

There were, you know, ventricular tachycardia bigeminies and trigeminies and that kind of thing demonstrated; however, the multiform ventricular tachycardia was the most significant leading on towards VF, and that was the predominant in the lower doses of the bupivacaine series.

And also, in the so-called extended dose, the higher doses, where there was quite a large dose range given, between 250 and 300 mg, that was more likely to occur.Dr

DR. HORLOCKER: Dr. Savarese.

DR. SAVARESE: I think in all of the comparative studies that have been reported today, the comparisons are in terms of milligrams of levobupivacaine versus milligrams of racemic bupivacaine.

And I guess the data is fairly convincing that there is a difference in the cardiovascular and CNS relative safety when you compare the two drugs, milligram for milligram. And that means the key issue simply is, what is the potency difference between the two, if any?

Now, that is my question. In the presentations that were made of the human studies, the clinical studies, the two gentlemen who reported those studies were reporting them as though they considered the local anesthetic potencies of levo and racemic bupivacaine to be identical. So, that is my first question.

In humans, are we sure that the local anesthetic potency of each of those two drugs is identical? That 0.5 mg/kg of one -- I'm sorry, 0.5% of one equals 0.5% of the other, in terms of ability

to do a brachial plexus block or an epidural or a whatever. My first question.

DR. GENNERY: Can I ask Dr. Kopacz to respond to that, please?

DR. KOPACZ: I guess I will give you two answers to that question. One is, just a clinical impression, and that is, since the studies were all blinded, and I did one of the studies, clinically, they are indistinguishable. You didn't know what drug you were going to do.

Statistically, and I'm not a statistician but looking through the concerns of the statistician about the studies that were designed for equivalence, and three of the studies that I performed were designed to show equivalence, and there were some methodology errors in -- not errors, but methodology assumptions that were wrong in the first two, but the third one did show equivalence.

Actually, all three showed equivalence. In the first two, which were the C Section studies, the assumption that was used to demonstrate equivalence was a ten-minute difference, but the data

that was used to derive that was 18 minutes and onset.

So, it was felt that if the onset was less than eight minutes or more than 28 minutes, it would be different.

DR. SAVARESE: I, I mean, I'm not quibbling with your data --

DR. KOPACZ: Okay.

DR. SAVARESE: -- I mean, I think the human data that you presented is quite convincing, also, in terms of equivalent potency, and I'm just asking for some reassurance from yourself and Dr. Crews, that your feeling as clinicians is that you get the same effect from equal quantities, milligrams, total milligrams given to the patients, of the two drugs.

Because then that sets up the impression that the safety ratio does seem to be greater for levo than for racemic bupivacaine.

DR. KOPACZ: Well, I won't speak for Dr. Crews, but I guess the first statement that I made was my clinical impression, that in doing a double-blind study, you couldn't tell which drug was which.

DR. SAVARESE: Okay. Then, how about Dr. Crews?

DR. CREWS: The studies that I did using levobupivacaine were not blinded comparison studies, and I do have experience with the 0.75% for surgical anesthesia and epidural, 0.25% for continuous epidural infusion for post-op, and the use of 0.5% for axillary brachial plexus block.

And to me, I saw no evidence that there was any difference in terms of -- again, I hate to get into this semantics issue around potency, but when you are referring to potency, are the two drugs equipotent, I think what we need to define is, that we are talking about the same amount, same concentration of drug producing the same sensory block effect.

I think what is important to point out is that there are some very subtle differences between these drugs that you can tease out in terms of things like time to onset, kinetics differences, duration of motor block, and the relative sensory motor block, these types of things that really cloud the potency picture, but in terms of the clinical use of

levobupivacaine versus bupivacaine, my impression is that they would be used at the same doses and concentrations that we are clinically using now.

DR. SAVARESE: Okay, let me just follow-up. I mean I am not trying to split hairs here, I agree with both of your presentations, and I'm just looking for more reassurance, that's all. And what we are really interested in here is safety ratios, you know, that's the key issue.

So, I think that answers my questions on the human data. I have the same sort of questions about the animal data. All those comparisons were made, sort of milligram for milligram, and didn't address relative local anesthetic potencies in animal species.

It would be nice to see that sort of comparison made, together with the relative potency data as well. Just -- it's a very simple question, do we have demonstration in animals that the local anesthetic potency of levo versus racemic bupivacaine is the same?

DR. GENNERY: Yes, we do. We can show you

a few slides to --

DR. SAVARESE: Don't need to. That's all I need is that kind of reassurance.

DR. HORLOCKER: Go ahead.

DR. WATCHA: With regard to a particular -- speaking about problems with toxicity, there's a particular patient population where there is a problem, and two years ago when we sat over here, I had requested some information about that.

That is, the children below the age of six months, who have a greater tendency to develop problems, particularly with the infusions of bupivacaine. Will you be presenting such data? Do you have any studies on the way to collect such data?

DR. GENNERY: Yes, we have two completed pediatric studies, one of which was filed with the NDA, another one of which, safety data was presented.

Since the 120-day update period, we have moved a lot further forward with those studies, and we are able to show you, if you would wish to --

DR. WATCHA: Now, let me be very specific. We are not asking for a single dose comparison of

local blocks, or a single dose caudal block. I was asking you two years ago for data on continuous infusions, because the patients who would develop toxicity in the pediatric age group, are the younger ones who have got continuous infusions for a period of time.

And do you have data on such, or are you planning such studies?

DR. GENNERY: Such studies are underway, and we have accumulated a certain amount of data already. If you would like to see where we stand on that, Dr. Joel Guenther, who is one of our principal investigators, could show it to you, or we can show it later in the day.

DR. HORLOCKER: Should we show it now?

DR. WATCHA: Well, it's up to you, Madame Chair.

DR. HORLOCKER: Let's go ahead.

DR. GUENTHER: I'm Joel Guenther. I'm a pediatric anesthesiologist at the Children's Hospital Medical Center in Cincinnati, and I have served as a principal investigator and consultant to Chiroscience.

The results I am going to show you right now are part of an ongoing study that is taking place in a multi-center format.

Patients are receiving a loading dose of 0.175% of bupivacaine, and then are receiving one of four postoperative infusions, 0.125% levobupivacaine, 0.0625% levobupivacaine, 0.0625% levobupivacaine with Fentanyl, and Fentanyl alone, and the primary efficacy variable is the proportion of patients requiring rescue in the first ten hours.

But, what Meb I think is asking is about safety data in patients under six months, and Kate, if you will show that table.

This study is ongoing. It has not been unblinded. We don't know what drugs these patients got. These are the patients under two years who have received infusions of levobupivacaine, presumably three-quarters of them have, and we have this slide here and the other -- Kate, if you will flip -- and what we see is -- go back please -- no reported serious adverse events, and no reported adverse events considered to be possibly related to drug, except for

vomiting.

In terms of prolonged infusions in patients under six months, we don't have that. We do have some pharmacokinetics data and some summary data available on a single shot caudal injection of levobupivacaine, including some patients under six months, if you would like to see that.

DR. WATCHA: A follow-up question. I noticed that your youngest patient in that list was 11 months.

DR. GUENTHER: Yes.

DR. WATCHA: I see. Thank you.

DR. HORLOCKER: Thank you. Any other questions from the Committee?

DR. SMILEY: I fear I will belabor the point, but I wanted to approach Dr. Savarese's point in a slightly different way.

You have been careful to claim that you are presenting these drugs with equivalent clinical effect and potency, I understand that, but if one is going to make a case or not make a case for the safety issue, the clinical studies you have done have been

done at moderately generous doses, so that were there to be differences in the -- I mean, the epidural doses, the brachial plexus block, were generous.

One would expect, you know, clinical efficacy from those doses, even if the drugs were, say, 20, 30% difference in potency. And in fact, in the robivacaine story, a similar kind of story, increased safety, there's been claims of equivalent potency.

There is now legitimate controversy in the literature about the relative potency of the drugs, where people claim the difference is as much as 20, 30, 40%.

So, I guess -- and it maybe the same question and it may be the same answer, and if it is, I don't want to hear it, but is there -- what is the chance that these drugs in fact are different -- have a difference in potency of, say, 25, 30%?

I mean, we have to at least keep that in mind as we think about proper labeling and the proper description of the safety factors to the clinicians, so is there any evidence, or are there any plans for

doing studies with this drug, at the limits of its effect?

Whatever, whether it's pain management or obstetrics, or areas where you use the drug and get a better sense of when it does work or doesn't work. You are using it in all the studies we have seen, pretty much at doses that would be expected to work, even if differences in potency of 20, 30% were there.

DR. GENNERY: Well, I think we could probably tackle that from two or three points of view. And it may be helpful, and if it's not, please say so, to actually show you the preclinical data, which is quite rigorous in the way the experiments have been set up, and then invite our experts back to reinforce, and perhaps address, what is I think the issue that you are raising, whether or not there is a hidden 20% difference there, and which we don't believe there is, and I'm happy to go down whichever path you think is appropriate.

DR. SAVARESE: Yes, could I reinforce your question. That was going to be my next question, too, I had one more question, I hate to belabor the issue,

also, but if you are about to present the relative potency data of levo versus dex versus racemic bupivacaine in animals, that is exactly I think what we are looking for.

DR. GENNERY: Deborah, could you --

DR. HARDING: I'm Deborah Harding, pharmacology, Chiroscience. So, we have evidence that levobupivacaine and racemic bupivacaine are equipotent. And that is at clinically relevant doses in the rat, levobupivacaine, dexbupivacaine, and bupivacaine were found to be equipotent.

In a study by Gary Strickartz, looking at sciatic nerve block in the rat, he showed that with .1 ml of 0.25% for sciatic nerve block, levobupivacaine and bupivacaine were equipotent on both sensory and motor function.

And this dose is equivalent to, that should be approximately 1 mg/kg in the rat. That's about 50% of the clinical dose that was used in the brachial plexus study, and that's Study No. 6154, where about 0.4 mls of 0.5% per kg was used, that's about 2 mg/kg.

Gary Strickartz also looked at cutaneous analgesia in the rat and compared this with the dose used for infiltration for surgery in man. And so here, at clinically relevant doses in the rat, levobupivacaine, dexbupivacaine, and bupivacaine were found to be equipotent.

So, for example, with 0.6 mls of 0.075% for cutaneous analgesia in the rat, a similar potency was found, with also a similar duration of action.

And this dose that was used in these studies is equivalent to about 2 mg/kg in the rat, which again is similar to that used in the clinical dose for infiltration surgery, and that is for example, in Study 30428, where around 50 mls of 0.25% were given, and that is of the order of 1.8 mg/kg.

This is data from the literature, looking at comparing levobupivacaine and dexbupivacaine. The first study is on intradermal anesthesia in the guinea pig, and they compared levobupivacaine with dexbupivacaine.

And they showed that levobupivacaine at 0.125%, 0.25%, and 0.5% were equipotent, and that

levobupivacaine was 16% more potent than dexbupivacaine at the 0.25%.

In spinal anesthesia in rabbits, dexbupivacaine and levobupivacaine were found to have parallel local anesthetic dose response curves. Levobupivacaine was found to be 40% more potent than dexbupivacaine.

In corneal anesthesia in the rabbit, levobupivacaine and dexbupivacaine had similar activity.

A study done by Aberg in 1972 looked again at sciatic nerve block in frog and rat. And on potency found no difference between levobupivacaine and bupivacaine in vitro frog sciatic nerve, and in vivo in rat sciatic nerve.

Also looking at infiltration anesthesia in the guinea pig, levobupivacaine had a longer duration of anesthesia than bupivacaine, and it was significant at 0.25%.

Another study by Dhyre recently published, or fairly recently published, on infraorbital nerve block in the rat. He found here that the duration of

infraorbital nerve block was slightly lower at 0.125% for levo than bup, but at 0.25% and 0.5% -- that's a typing error there -- they were equipotent.

DR. HORLOCKER: Any other questions? We'll take more question then defer the rest for our discussion later in the afternoon. Dr. Parris?

DR. PARRIS: Winston Parris, Tampa, Florida. In pain management situations, one usually pre-treats the patients with benzodiazepines, either diazepam or midazolam, not only for sedation, but also for elevating their seizure threshold in the event of an inadvertent intravascular injection.

Did any of your, in your clinical studies, did you pretreat those patients with diazepam or midazolam, prior to determining your cardiotoxicity, and also your neurotoxicity studies?

DR. GENNERY: Well, I think in terms of the volunteer studies, they had no medication other than test medication at all.

DR. PARRIS: And so the lidocaine, the lidocaine test.

DR. GENNERY: Yes, well, the lidocaine

test was done one week prior to them going into the formal part of the study, but one of the requirements to the protocol is that they should have no other medication whilst participating in those studies.

So, the only agents they got were either bupivacaine or levobupivacaine, nothing else.

DR. PARRIS: What about the animal studies, did you --

DR. GENNERY: Sorry, which ones?

DR. PARRIS: In the animal studies.

DR. GENNERY: Well, Robert, can you --

DR. GRISTWOOD: Can I ask you to please repeat the question.

DR. GENNERY: What other medications were given as part of the animal study protocols, the whole animal models, I guess you are referring to --

DR. PARRIS: Yes.

DR. GENNERY: -- both the pig and the sheep. The anesthesia in the pig model?

DR. GRISTWOOD: That was pentobarbital.

DR. GENNERY: Pentobarbital was the anesthesia in the pig model, and the sheep were --

DR. GRISTWOOD: The sheep were not --

DR. GENNERY: -- conscious during the experimental phase of the study.

DR. HORLOCKER: Thank you. We'll just take a quick break and reconvene at -- I'm sorry, go ahead.

DR. ROBERTS: I'm sorry, one quick question. I had a question for Dr. Crews. You mentioned in your study that you had found some evidence of an improved cardiovascular and CNS profile.

Can you please give us the study numbers and whether those studies were ongoing at the time of NDA submission?

DR. CREWS: I would assume you are referring to my conclusion that, based on the data we have from the clinical safety, clinical trial database, that there seems to be evidence to support the fact that levobupivacaine may have less cardiotoxicity or CNS toxicity.

The studies that I am referring to with respect to CNS toxicity was the human volunteer EEG

study, MAO 400. The cardiovascular safety data would include the meta analysis from the four clinical trials that were listed.

They were CS 001, CS 005 -- I had it on my slide, but I don't recall the --

Yes. The meta analysis included the two pharmacology studies which were 004801, 012105, and then the clinical studies that were included in this with signal averaged EEG -- EKG data were CS 001, CS 005, 030632, and 030721.

The evidence for enhanced cardiovascular safety from that meta analysis being less effect on prolongation of the PR interval, and the additional data supportive of differences in CNS and cardiovascular effects are based on the response to the suspected intravascular injection data that I presented.

DR. ROBERTS: Thank you.

DR. HORLOCKER: We will take a ten-minute break and reconvene at 11:35.

(Whereupon, at 11:25 a.m., a brief recess was taken until 11:37 a.m.)

FDA Presentation

Summary of the Issues

DR. RAPPAPORT: Good morning, Dr. Horlocker, members of the Committee. My name is Bob Rappaport. I am the Deputy Division Director of the Division of Anesthetics, Critical Care, and Addiction Drug Products, and I am also the Team Leader for the Anesthetics Drug Group.

I want to thank the Sponsor for allowing us to give you a relatively short presentation today. And I have a couple of things I need to point out before we start.

The first is that, for the record, Dr. John DiMarco from the Cardiovascular Advisory Committee has been consulting with us during the review process, and is serving as a nonvoting member of the Committee today.

The other issue that I wanted to point out was a few places in the Sponsor's presentation where we hadn't had a chance to review the data, and the first of that is, obviously the dog resuscitation study.

The second is the pediatric study data presented by Dr. Guenther. And I want to also point out that the, I think it was six studies that Dr. Crews included in the meta analysis, we only received four studies in the integrated analysis that we reviewed. There's a little bit of difference there. I don't know if that's --

We are asking your help today in answering two questions. The first question is, Has the Sponsor done an adequate and appropriate job of evaluating the cardiotoxicity of their product?

The second question is, Would it be appropriate for the Agency to approve labeling for that product, which does not begin with a black boxed warning regarding the potential cardiotoxicity with the 0.75% concentration, particularly in the obstetrical patient?

The only purpose we have in asking these questions is to allow us to write labeling that provides for the safest and the most effective use possible.

We are in concurrence with the Sponsor

regarding the effectiveness of levobupivacaine, while the actual potency, in comparison to bupivacaine and other related local anesthetic agents, has not been fully elucidated in our opinion, it does appear to provide effective anesthesia in the settings which have been studied thus far.

The Sponsor claims equivalent potency to bupivacaine, however, their application contains a few instances in which levobupivacaine appears to be less potent than bupivacaine, and no absolute documentation of equivalence has been recorded in any setting.

You have heard an extensive and detailed presentation from the Sponsor. What we are asking you to consider now are a number of factors which have combined to prevent us from coming to a final conclusion on our own regarding the issue at hand.

The first portion of our presentation covers what we don't know at this time from the preclinical evaluations that were undertaken by the Sponsor at this Committee's recommendation.

Dr. Goheer, the Reviewing Pharmacologist for this application, will present that information.

That will be followed by comments from Dr. Roberts, the Primary Medical Reviewer for the application, and she will give you the Division's perspective on the safety data, and analyses submitted to the application, highlighting the areas where our interpretation differs from that of the Sponsor.

And the final portion of our presentation will come from Dr. Permutt, the Supervisory Biostatistician on this product. Dr. Permutt will address the important matter of the relative potency and toxicity of levo and racemic bupivacaine, which you all obviously are aware of already.

In answer to our first question, Has the Sponsor adequately evaluated levobupivacaine's potential for cardiotoxicity at the labeled dose, and if not, what further studies are needed?

You may conclude that enough data is available already, or that more is required. I would ask that if you choose the latter, you help us determine what more is required, and at what point we can allow the Sponsor to claim an improved cardiotoxic profile for their product, assuming of course that

their hypothesis is correct.

For our second question, Should the boxed warning that currently exists in the bupivacaine label, be applied to this product?

There are three possible answers. The first, have the black box for bupivacaine, for levobupivacaine, read just as it does for bupivacaine.

The second possibility is, make specific changes in the black box for levobupivacaine, and perhaps bupivacaine as well. An example of that would be, removing the reference to any specific concentration.

Finally, you can choose to recommend not using a black box at all for this product.

In considering your answers to these questions, I would ask that you be aware of two matters with which the Division must concern itself in our review of the labeling for this product.

The first is, we must provide a level playing field for all products with relatively equivalent safety and efficacy risk-benefit ratios, especially products in the same pharmacologic class,

and with similar mechanisms of action.

The second matter is, how our actions produce changes in the medical community, at times unintentionally. By not including a strongly worded black box in the labeling for levobupivacaine, and even possibly removing or changing the black boxed warning in the bupivacaine labeling, are we sending practitioners a message which may result in an increased risk to their patients?

We appreciate your assistance in helping us reach an appropriate conclusion regarding the labeling of this new product. And we will begin with Dr. Goheer.

Preclinical Cardiac and Neurotoxicity Issues

DR. GOHEER: Good morning, Dr. Horlocker, ladies and gentlemen. My name is Anwar Goheer. I am a pharmacologist at FDA.

To save time, I will not address the data already presented by Dr. Gristwood and Professor Mather. They have presented the data nicely.

As you know, the Sponsor claims that the

levobupivacaine is as effective as bupivacaine. Data presented by the Sponsor also indicate that the levobupivacaine had less cardiovascular toxicity than bupivacaine.

Bupivacaine is a racemic compound and it has been used for many years as a local anesthetic. At high concentration, it causes CNS and cardiovascular toxicity, hypotension, cardiovascular collapse, and ventricular arrhythmia have been reported in the literature.

Nearly two years ago, we had a meeting of this Advisory Committee on this topic. It was agreed that the data from the following studies are needed to compare the cardiovascular toxicity of levobupivacaine and bupivacaine.

These studies will help us to understand the direct effect on the myocardium and the CNS, and the role of the CNS on cardiotoxicities.

These studies will also show the relative ease of resuscitation in the animals. These studies are comparisons of the direct effect of levobupivacaine and the racemate on the CNS and the

heart, and conscious sheep, following closed, intra-arterial injection.

Specifically, we can divide that into two categories. Number one is the heart direct coronary artery infusions. In this study, the CNS performance was maintained.

Professor Mather has completed coronary artery infusion studies with the levobupivacaine, bupivacaine, and ropivacaine in sheep. The final reports have not been submitted to the FDA.

The second category was CNS direct carotid artery infusions with cardiac performance maintained. The intra-carotid and the resuscitation studies in sheep have not been started.

Number two was to simulate clinical resuscitation following bolus administration of a little dose.

According to the Sponsor, the experimental phase of dog resuscitation study has been completed. These are the preliminary data presented by Dr. Feldman this morning.

The final report of this important study

has not been submitted to the FDA. The data from these important studies are needed to conclude that levobupivacaine is less cardiotoxic than bupivacaine.

Conclusions. Animal studies show preliminary evidence of differential cardiotoxicity. That is levobupivacaine may have better cardiovascular safety profile than bupivacaine.

However, the main question that remains to be answered.

Question No. 1, what are the direct effects on myocardium and CNS and the role of CNS on cardiotoxicity?

Question No. 2, what is the relative difficulty of resuscitation in the animal?

We are waiting for the data from these important studies that I just mentioned. We would like to seek the expert opinion and comments from this Advisory Committee on this issue.

Thank you. And now I will invite Dr. Monica Roberts to present her clinical review.

Clinical Cardiovascular and Neurotoxicity Issues

DR. ROBERTS: Good afternoon, Dr. Horlocker and members of the Committee. My name is Dr. Monica Roberts and I am the Primary Medical Reviewer for this NDA.

I will be presenting to you the cardiovascular safety as I saw it, as submitted in the NDA. I will try not to repeat any of the specific data that was already presented by the Sponsor.

The clinical development program of levobupivacaine was specifically designed to evaluate the product's effects on cardiovascular function.

The Sponsor has designated five clinical trials and one integrated analysis of four of these trials to determine and compare the effects of levobupivacaine and bupivacaine, specifically on QT dispersion, and QRS intervals.

The integrated analysis included Study 004801, as you can see. In the remaining studies, I won't repeat them to you.

The analysis of the four separate clinical trials were designed with the following objective. To determine the effects on QT dispersion or QRS

interval, following exposure to study drug, the hypothesis being that levobupivacaine had little effect on cardiac electrical parameters.

Study 004801 was a double-blind, randomized, crossover study, and subjects dosed with intravenous bupivacaine, or levobupivacaine, to CNS symptomatology.

The primary endpoint was the difference in QT dispersion from pre-dose, to the maximum observed post-dose value.

The results show that the estimate of the treatment difference was -5.4 ms, which was not statistically significant.

Neither were the secondary endpoints, PR intervals, QRS intervals, and QT intervals, found to be statistically significant.

Study CS 005 was also conducted in a double-blind, randomized fashion, and it compared 0.75% levobupivacaine to the same dose of bupivacaine.

The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value; however, the QRS data were those upon

which statistical analyses were performed.

The results showed that the estimate of the treatment difference was -0.4 ms, which again was not statistically significant.

Study 030721 compared 0.25% levobupivacaine with 0.25% bupivacaine. The primary endpoint was the difference in QT dispersion from pre-dose to the maximum observed post-dose value. Statistical analyses were performed on the QRS data as well.

The results showed that the estimate of the treatment difference was -1, which was not statistically significant.

The last Study included in the meta analysis, Study 030632, compared 0.5% levobupivacaine and bupivacaine. The primary endpoint again was the difference in QT dispersion from pre-dose to the maximum observed post-dose value.

The results showed that the estimate of the treatment difference was -1.09, which was not statistically significant.

The second endpoints of PR intervals, QRS

intervals, and QT intervals were also not statistically significant.

Additionally, Study 012105 was submitted as evidence of cardiovascular safety, although not included in the meta analysis, was a two-phase analysis of the cardiovascular effects of levobupivacaine when administered intravenously in an open label fashion, followed by a double-blind, randomized, evaluation of the effects of levobupivacaine and racemic bupivacaine on myocardial depolarization, and re-polarization, as measured by QRS duration of a signal averaged EKG, and QT dispersion in healthy males.

In this Study as in the previous EKG study, subjects were dosed to CNS symptomatology. The objective of this Study was to compare the QT dispersion from a blinded review, as well as PR, QT, QTc, and signal averaged QRS durations, by dose.

The primary endpoints were the maximum positive change from pre-dose, using the end of infusion, 5 minute, 10 minute, 15 minute, and 30 minute time points for the QT dispersion and the

signal averaged QRS values for each treatment.

Secondary endpoints for the same time points were PR, QT, and QTc durations for each treatment.

The Sponsor concedes that there are no statistically significant changes from baseline in the primary endpoints, QT dispersion and QRS duration, or for the secondary endpoints, changes from baseline in the PR and QT intervals, between the two treatments, however while there did appear to be a statistically significant difference between the two treatments with regard to the change in baseline in the QTc, this endpoint was chosen prospectively to be secondary in nature, and was just one isolated finding among many other endpoints which were shown not to be statistically significant.

Dr. John P. DiMarco is the Director of Clinical Electrophysiology Lab and Associate Division Head, Cardiovascular Division, at the University of Virginia.

He consulted with the FDA on the evaluation of the cardiovascular safety of

levobupivacaine. I will defer to him to present his conclusions as an independent reviewer of these studies.

My search strategy for identifying the significant cardiovascular adverse events was to perform a head-to-head comparison of all reported cardiovascular adverse events in the levobupivacaine clinical development program.

The following data was obtained from the safety database, however the data from the safety update was not included in time for this meeting.

As you can see from this slide, there is very little difference in the percentage of cardiovascular events reported between the two groups.

Secondly, I separated the clinical trials according to category, and found the following similar results. In the obstetric population, there again, was -- we were not able to appreciate any difference in terms of the cardiovascular events that were reported.

Of interest, is the incidence of bradycardia, percentages being eight to zero in favor

of bupivacaine, however the number of patients in each group must be taken into consideration.

In the pain management population, again the two drugs are behaving similarly, however with the incidence of tachycardia, bupivacaine demonstrated a twofold increase in cases reported. Based upon this one isolated finding, however, one cannot conclude that there is clear evidence that bupivacaine in this case is less safe, either.

The analysis of the cardiovascular adverse events reported in the Peripheral Block Study demonstrated the same overall trend.

Finally, in the Pediatric Study, when patients received either levobupivacaine, or no local anesthetic at all, the cardiovascular adverse events occurred only in the levobupivacaine group.

Next, I chose one cardiovascular adverse event, namely, bradycardia, and gathered as much details of the surrounding episode as possible.

I chose bradycardia because it occurred with a fair amount of frequency; i.e., less than 5%, and it was associated with asystole on at least two

separate occasions.

The first episode occurred in a 66 year old male with a history of essential hypertension for which he took atenolol and naproxen for osteoarthritis.

He was scheduled to undergo a knee replacement. He received a T12 to L1 epidural with 10 mls of 0.125% levobupivacaine. It was given in divided doses.

As you can see, his pre-op EKG was significant for sinus rhythm, however his heart rate was 55, blood pressure was normal, and saturations as well.

Following drug administration, ten minutes following exposure, as you can see, his heart rate had dropped to 40 bpm. He subsequently was unarousable and had a flat line EKG. He was resuscitateable, however.

The sensory block at that time was found to be T6 to T7. It was said to have increased to T3 to T2, subsequently. One can conclude that this may represent the possibility of a high spinal, and

equally, one can conclude that this represents study drug effect.

The next case involved a 46 year old female with a history of GI reflux, anemia, and renal carcinoma, and also a pre-op EKG suggestive of mild bradycardia.

She was scheduled to undergo a radical nephrectomy and received a total of 12 mls of 0.75% levobupivacaine.

Inter-op course was significant for the occurrence of a pneumothorax. As they dissected the abdomen, they entered the diaphragm.

In the recovery room, however, as you can see, her vital signs were relatively similar to pre-op, and she complained of pain and received a bolus administration of 0.75% levo, followed by an infusion, and one hour following administration, she was complaining of nausea and as she vomited, she then went into asystole, however she also was resuscitateable.

Conclusions. Two conclusions are possible. One, that this represents a vasovagal

response, or two, that this represents drug exposure, the effects of drug exposure.

The next case involves the only death that occurred in this study, a 70 year old male with a history of GI disorder, scheduled for left hip surgery.

He underwent an epidural of 0.75% levobupivacaine bolus, followed by the study drug infusion, which in this case included the additional administration of clonidine.

His pre-op EKG was similar to that post-op, which demonstrated left ventricular hemi-block. Pre-op vital sounds were normal, however, one hour following administration of study drug, he demonstrated blood pressures of 50s to 60s, which remained so for the ensuing 27 hours of his hospital stay.

EKG, as I stated previously, showed a left axis deviation on discharge. The patient expired 11 days following treatment.

The one case that I would like to present to you of pediatric bradycardia, occurred in a five

year old male who had a history of enteritis, and surgical correction of an anal rectal abscess. He also had, in the past, myringotomy with tubes.

He was scheduled to undergo a left inguinal hernia repair, and received 0.5% levobupivacaine as an infiltration anesthetic. As you can see, his pre-op vital signs were normal for age.

Approximately one hour and 30 minutes following study drug administration, he was bradycardic and complaining of nausea and vomiting. This also resolved.

In summary, I would like to say that my conclusions are that there are unquestionably some amount of cardiotoxic effects associated with this drug, and I have not been able to find data in the NDA which would allow me to draw any final conclusions that there is a statistically significant difference between the two drugs with respect to the cardiovascular safety.

Potency/Toxicity, and Related Efficacy and Safety Statistical Interpretations

DR. PERMUTT: I'm Tom Permutt. I'm Team

Leader for Anesthetics in the Office of Biostatistics at FDA.

You have heard from my three colleagues about the three different kinds of data that we have to address the relative potency and toxicity of levo and racemic bupivacaine, and I want to talk about the rather difficult problem, I think, of putting these three kinds of data together and yes, we do think that potency is important.

Dr. Rappaport spoke briefly about the clinical efficacy data. Levobupivacaine was compared to bupivacaine, usually at the same doses, in several anesthetic techniques. Both were effective. In fact, both were approximately perfectly effective. The vast majority of the patients had their surgery with adequate anesthesia.

In very few studies, higher concentration of levobupivacaine as compared to bupivacaine, and again, not much difference in the response was seen. And again, this is because both were about completely effective.

We're in a flat part of the dose response

curve, so these studies are not sensitive assays of potency, they, as the Sponsor told you, they weren't meant to be. They are studies of efficacy and they show that levobupivacaine, like bupivacaine, was effective.

Dr. Roberts talked about the electrocardiographic data from several human studies, both observations of the clinical trials in patients and the special studies in volunteers.

Our interpretation of these, as Dr. Roberts says, is a little different from that of the Sponsor. Dr. Nimmo and Dr. Crews mentioned how very few statistically significant differences, but these were extracted from a rather large number of possible comparisons, and on the whole, my evaluation is that those don't represent a statistically significant difference in effect.

As Dr. Woosley commented this morning, you wouldn't expect to see effects, because humans were very appropriately not dosed to serious toxicity. So, again, you're in the flat part of the dose response curve. This time, the lower end.

We've got the animal toxicity data discussed by Dr. Goheer. And here, we do see differences between the two drugs. Milligram for milligram, as Dr. Savarese says, you see more toxicity with bupivacaine than with levobupivacaine, looking up and down.

You get a bewildering variety of percentage differences, or ratios, depending on what exactly it is you are measuring, as a toxicity, and quantitatively, the interesting comparison I think, as Dr. Savarese intimated earlier, is going across.

You see roughly equal toxicities at doses of levobupivacaine and of bupivacaine, in roughly a ratio of 1.3:1. More than 25%, not dramatically more than 25%, but more than 25%, less importantly than the ratio of 0.75% to 0.5%.

All right, so again, the question is how to put these three kinds of data together. And while studiously avoiding talking about potency, I think the impression that the Sponsor would like to leave us with, and which in fact is what I hope is true, is this. That the efficacy of bupivacaine and

levobupivacaine, the dose response with respect to efficacy are about the same.

And that there are differences in toxicity, that bupivacaine is more toxic -- and again, I've schematically drawn these rather far apart, but I remind you that the ratio is only something like 1.3 -- so that there is a better therapeutic index, if you will, better separation of effective doses of levobupivacaine, from here to here, and of bupivacaine, from here to here.

And I agree that the data are completely consistent with that hypothesis; that we haven't seen anything to controvert that hypothesis. The clinical efficacy data up here. The human toxicity data down here. And the animal toxicity data all in here, which is you know, were you actually see the separation.

I also don't see anything in the data that is not consistent with this alternative hypothesis, which is that the potency of levobupivacaine and bupivacaine, the potencies are different by about the same ratio as the toxicities are different, so that the therapeutic index of the two drugs is about the

same.

Again, here we have the human clinical data up here in a flat part of the efficacy curve of human toxicity data. And the separation here. But you don't see any separation here, because you don't have any data with which to see it.

If this is true, then to the extent that drugs are dosed to effect in clinical practice, levobupivacaine is not a safer drug. I think we can hope that it is, but I don't think that there is anything in the data that allows us to say at this point that we know that it is.

I was interested to hear at the end of the Sponsor's presentation, in response to comments, some comments on the animal potency studies. And I don't find them terribly reassuring, either.

I think that they suffer largely from some of the same problems as the human studies. You see no difference in effect, where you wouldn't expect to see any difference in effect, because you have maximal effects. And you don't get, you have really rather crude estimates of potency, which I think are not

sufficient to rule out the possibility of what we are talking about, which is a fairly subtle difference in the potency, on the order of -- you know, again, 20, 30, maybe 40%, which is what we think the difference in toxicities are.

So, again, I hope it's safer, but I don't see any reason at this point to know that it's safer.

Questions From the Committee

DR. HORLOCKER: I would like to thank the FDA for their concise and timely presentation. We'll take questions now. Dr. Savarese.

DR. SAVARESE: I think another key issue here that we should ask the Sponsors to give us more reassurance about is the relative potencies and toxicities of levo versus dexbupivacaine.

We didn't really get that kind of information from the presentation this morning.

DR. GENNERY: Well, we have clearly not studied dexbupivacaine in humans.

DR. SAVARESE: And I'm satisfied with animal, yes, I understand. I understand. Perfectly satisfied with animal data.

DR. GENNERY: I think I'll ask Dr. Gristwood if we could put back his summary slide, because there the table did distinguish between those studies looking at racemic, and those studies looking at dex.

And then, if Dr. Harding can just again bring those slides back where there is some summary information of where dex has been studied. We'll try and answer that question for you.

DR. GRISTWOOD: Okay, this shows the summary slide for the relative cardiotoxicities from the range of studies, the comparative studies that were carried out.

I think you can see here that we do have data both for dexbupivacaine compared to levobupivacaine, where we're seeing -- you can start off looking at the in vitro data where we have got sodium channel data, these large differences here between the two isomers.

The important comparison here between the racemate and levobupivacaine, and again, we're still seeing a big difference here.

If we look at the, again, coming down through the slides, having data both for levobupivacaine and the racemate, in both instances we're seeing differences between the dexbupivacaine and racemic bupivacaine.

In fact, the only study that in vivo that was looking at dexbupivacaine was the rat study, where the differences were huge, there were huge differences.

The sheep study, we have data for racemate versus levobupivacaine. The pig study, we compared racemate with levobupivacaine.

DR. SAVARESE: Okay, thank you. I apologize. I just didn't remember this column in this particular slide.

DR. GRISTWOOD: I think the dexbupivacaine data really helps to reinforce the racemate versus levobupivacaine.

DR. SAVARESE: That's what I'm looking for; yes, that's what I'm looking for. And also, your potency estimate for the three compounds, the dex, the levo, and the racemate is identical in terms of local

anesthetic potency. Is that not correct?

They do not differ significantly, the three different optical isomers, or mixtures of.

DR. GENNERY: This is the study we asked Dr. Strickartz to carry out on our behalf at Boston. And we have, for the purposes of this presentation, really only qualitatively talked about levo and dex, because we felt that probably the most focused discussion from a clinical point of view would be the relative comparison between levo and bupivacaine, and especially if we could relate what Dr. Strickartz did to a clinical type of dosage.

But the basic outcome from the study is that the two enantiomers and the racemate behave in a pretty equipotent sort of a fashion, both in the sciatic nerve model, and in his infiltration model.

DR. SAVARESE: Right. This is important, because in your basic contention with all of this data is that you have kind of removed the bad medicine, the dexbupivacaine, and left only the good stuff in there.

DR. GENNERY: Sure.

DR. SAVARESE: One more question about

human, you have not given dexbupivacaine to anybody, correct?

DR. GENNERY: Absolutely.

DR. SAVARESE: Does anybody here have any opinion on -- I mean, to me, it would be a very simple potency comparison to do a very simple peripheral nerve block procedure, you know, like an ulnar nerve block or something, comparison, just to verify to us clinicians that in humans, really, dexbupivacaine and levo have the same potency, and that reinforces further your safety contentions.

Does anybody? Yes, Rich?

DR. SMILEY: It would be a more -- I mean, assuming you wanted to find the difference, it would obviously be the best way to find the differences that exist, to compare the L to the D, rather than the L to the racemate, because obviously you're averaging two.

It's -- again, it's stating the obvious, but I'll reinforce what Dr. Savarese is saying, that if we wanted to really pin down that these are equipotent drugs, if that matters, and it may, in some kinds of studies.

There are other things using low doses where you could be overly-worried about the isomer's activity, would really pin that down. Those were very close. It would be hard to make a case if the racemate would be the different --

DR. SAVARESE: Yes, I mean, I think that's what we're asking for, is there that kind of a comparison in humans available?

DR. GENNERY: The study that Aps and Reynolds carried out in the 1970s was in fact one of the studies which gave us the encouragement to move forward, of showing equipotency.

In fact, they felt that they had shown that levobupivacaine was somewhat more potent than the racemate. I can't remember whether dex was included in that paper. Apparently, it was. Perhaps we could dig that out and reread that.

DR. HORLOCKER: Yes?

DR. JEAN: Lucy Jean, pharmacologist from FDA. In order to understand intrinsic potency, the study as proposed by Dr. Savarese is useful.

I would like to point out, the Sponsor

stated equipotency at 0.25%, however at the lower concentration, 0.125, there are differences in the potency. Perhaps the 0.25, we already reached 100% analgesic effect. In order to see a difference, why don't you study at a lower concentration, to establish the intrinsic potency?

Thank you.

DR. HORLOCKER: Can we have the lights up, please? I have a question for Drs. Roberts and Permutt. Certainly, the laboratory studies show a trend towards decreased cardiotoxicity and as Dr. Smiley mentioned during the break, if he was a pregnant sheep, he would like to receive levobupivacaine rather than bupivacaine.

DR. SMILEY: Whether I was pregnant or not, put it that way.

DR. HORLOCKER: Yet, we don't have definitive human studies demonstrating this. Is this a lack of power of the studies, that we just don't have enough? Are there trends that may become significant, or do we just not have clinically significant differences between these two drugs, the

way that they have been evaluated at this point in time?

DR. PERMUTT: Yes, I think it's that we don't have the right kind of studies. To really see the difference in potency, you would have to give less than what Dr. Smiley called, generous doses, and see what --

What we would be looking for is equivalent effects at less than 100%. It doesn't help us much with respect to potency to say that both the drugs were completely effective.

If they were both partially effective to the same degree at the same dose, that would help, but we don't really have that kind of study.

So, not so much the numbers that are lacking as the studies of different dose, dose ranging design.

DR. HORLOCKER: Could we do those studies safely in humans, or would it require such doses that we would be ethically not allowed to do that?

DR. SMILEY: Excuse me. Were you talking about toxicity or potency --

DR. HORLOCKER: Yes, the cardiotoxicity --

DR. SMILEY: Because he answered to potency, and your real question was about toxicity --

DR. HORLOCKER: Right.

DR. SMILEY: -- and I think the answer may be that there simply may not be endpoints in humans that -- I mean, the endpoints that you hoped for in the meeting a couple of years ago just don't seem to be real endpoints. Either they are different or they aren't the right endpoints.

DR. PERMUTT: I'm sorry, Dr. Smiley is quite correct. I misinterpreted your question, I was thinking about the question of relative potency. I agree with Dr. Woosley that it's probably impossible to study toxicity in humans meaningfully.

DR. HORLOCKER: Dr. Reves?

DR. REVES: I would agree on ethical grounds, impossible to study that. We could design very simply a relative potency study, I mean, Richard and I already designed one, but I mean, I don't think that would be difficult.

You'd start with low doses and you would

have a peripheral nerve, and you would see whether pain is equivalently blocked or not, and I think you'd step up and you'd see -- walk up the whole dose response curve, and you'd compare them.

So, I think that's possible. That's all I have to say.

DR. HORLOCKER: Yes.

DR. CARLISLE: The real question, though, is at a clinically effective equipotent dose, are the toxicities going to be accelerated, and that's the issue in terms of what we were supposed to deal with today, I believe.

DR. HORLOCKER: Dr. Smiley?

DR. SMILEY: Yes, well, the problem, and I know you know this, and the problem of course is, that's not exactly the question, because I think we all know that in clinically-used doses, the vast, vast, vast majority of the times, neither of these drugs is dangerous at all.

The problem is in that rare instance where you get a intravascular or some other abnormal absorption of the drug, mostly it's intravascular, so

that that's what -- I mean, I know, again, I'm stating the obvious, but it's important to get that out there.

It's not -- the difficulty the Sponsors have is that even at clinically-used doses, it's hard to show differences in toxicity because we don't have surrogate endpoints for the V-tach, V-fib arrests that you see with the massive overdoses.

DR. REVES: I would comment on the three cases that we do have of inadvertent intravenous absorption of the drug. It does -- two happen to be bupivacaine and one levo, and it appeared to my looking at it -- not having gone over the Case Report Forms or seen the EKGs or any of the other things -- it did appear in the three cases, that is, n = 1 for the study drug, that it seemed to be a little less toxic than the two others but, you know, what can you decide on three cases? But we do have those three to kind of look at.

DR. HORLOCKER: Any other questions? Yes, Dr. Savarese?

DR. SAVARESE: Yes, I think that's important. I'm glad that Dr. Reves made that

observation, because I was thinking the same thing. I think we do have to pay some attention to that, that there were to bupivacaine cases, where there was a severe reaction, and where there had to be a resuscitation.

Whereas, with levo, there was -- it's only one case, but that patient really didn't require anything except a little barbiturate, right? Is that correct? Yes?

I just wanted to go back to the potency comparison. Dr. Gennery, in that paper from -- now we're talking 25 years ago -- if the potency comparison is as you say -- I'm not familiar with the paper at all, but if that paper shows identical potency in humans -- is that correct?

DR. GENNERY: Yes, it was. Volunteers.

DR. SAVARESE: In humans? In human volunteers of an adequate number, then I think we can start to be content that the potencies of all three of these mixtures of isomers are --

DR. GENNERY: Can I -- Can I just --

DR. SAVARESE: Sure.

DR. GENNERY: -- bring two other bits of data to your attention --

DR. SAVARESE: Sure.

DR. GENNERY: -- which are in the NDA.

DR. SAVARESE: Sure.

DR. GENNERY: One is an ulnar nerve block study, where we compared three doses of levobupivacaine against a standard dose of bupivacaine. And demonstrated equal efficacy, equal potency.

And secondly, is an MLAC study, which is a rather complex algorithm for trying to determine minimum local analgesia concentration required to relieve pain in first stage of labor. And we have got a slide of that which Dr. Graeme McLeod can talk to.

DR. SAVARESE: Can I just ask you, when was that ulnar nerve block study done? Was that a recent study?

DR. GENNERY: Three years ago.

DR. SAVARESE: Okay.

DR. GENNERY: The MCLAC Study includes two comparisons; one where we -- which was ours --

comparing levobupivacaine and bupivacaine, and one from Dr. Linda Pauley in the Mayo Clinic, looking at ropivacaine and bupivacaine.

DR. McLEOD: Good afternoon. Dr. Graeme McLeod, I'm a consulting anesthetist from Langwell's Hospital in Dundee, Scotland. I am a clinical investigator with Chiroscience.

What I would like to do is address this issue regarding potency on a weight to volume basis, and there has been, as has been indicated by Dr. Gennery, a methodology used by several groups, used to indicate the relative potency between these drugs.

And we've only got the one slide here, but I'm just going to indicate the methodology. In fact, this is a double-blind, sequential allocation method, based on a methodology devised by Dixon and Massey.

It's a multiclinical algorithm, which was created whereby a standard 20 ml volume is given to patients and the dose of drug is dependent on the response of the previous patient.

In other words, the previous patient that has successful analgesia, as indicated by an MLAC

score of less than 10 ml after 30 minutes, then the concentration is reduced by 0.1%.

On the other hand, if the previous patient had had unsuccessful analgesia, then the subsequent dose to the following patient was subsequently increased by 0.1%, and that created what has been described by the studiers as a free floating mechanism. What it does is it derives effectively an ED-50 and an ED-95 for both drugs.

Now, what this indicates on the left side are the results by Lyons and Columnatal from Leeks in England, and what they have found is that the ED-50, the MLAC ED-50 for bupivacaine was .081%, and for levobupivacaine was .083%, giving a relative potency of .98.

And I have a graph in my laptop, if you want to look at it, that actually shows a dose response curve. And the dose response curve, goes from .06 to .12%, and in fact, the dose response curve is similar for both drugs. And more or less parallel.

Unfortunately, this study, the numbers were small, only 60 patients were ever treated, and

the confidence intervals were rather large, and therefore, the investigators could not see with confidence that there was no difference between the drugs.

And the study on the right, and I have to talk about it, it's on the slide, is a comparison by Linda Pauley using the same methodology, only in patients in whom had, were dilated up to 7 cm, and different end parameters were used; nevertheless, it does indicate a potency difference between ropivacaine and bupivacaine of .65, with an MLAC of bupivacaine in this Study of .093%, and for ropivacaine, of .156%.

DR. HORLOCKER: Yes, sir.

DR. PERMUTT: Dr. McLeod, I believe you said that confidence intervals for the relative potency were rather wide. Were they as wide as, say, 30%?

DR. McLEOD: No, they were about 15 to 20%.

DR. TOBIN: To follow-up on Dr. Savarese's question, I think the idea of understanding equipotency is important, and maybe we have sufficient

data, possibly not.

What I am more interested in is the illustration on the last slide that Dr. Permutt put up, which really showed what I think is the crux issue here, and it responds to what Sue said earlier, too.

What is the incidence of the cardiotoxicity at the efficacious dose, and then, follow-up with more data that we have discussed a little bit earlier this morning, of what is the resuscitateability of those very toxic or dangerous effects?

So, Dr. Permutt, if we go back to your last overhead, where you have the four curves, I think that's the best graphic illustration of the crux of what we're all asking for.

DR. SAVARESE: We could call that Dr. Permutt's last permutation. You've probably heard that before, a bunch of times.

DR. TOBIN: Once or twice. Assuming with the group of two curves on the left, that we are at 100% efficacy of the dose, which is what most of our clinical data suggests, or that we are very close to

that point, where those two curves converge, what I am most interested in is where are the beginning of the two curves to the right?

And are they immediately beginning underneath the convergent points of the two curves to the left, or are they actually potentially further to the left on this graph, compared with their current location?

And then, the separation between the toxic curves may have a great deal, greater ramification, but if the two of them both have the left foot of their curves exactly at the 100% efficacious dose, or so close to it, would it really matter if these two drugs are equally potent or not?

And I think it is the numerator over the denominator that becomes critical here, and unfortunately, without a power of 100,000 patients enrolled in a study, the Sponsor may never be able to give us exact comparisons of numerator over denominator, to our satisfaction.

But more concerningly, is the outcome of what happens in those toxic events, and I think to

address the potential resuscitateability in the whole animal model is critical for us to make a determination if one drug is actually safer than the other.

DR. PERMUTT: Just to clarify, I did not mean to suggest -- I crammed them onto the slide, but I did not mean to suggest that toxicity of either drug was beginning at approximately the dose as where we were getting complete efficacy.

As someone said earlier, bupivacaine has in general fairly wide therapeutic index, and I didn't mean to suggest otherwise, only to question whether levobupivacaine has an even wider one.

DR. HORLOCKER: Dr. Savarese?

DR. SAVARESE: Well, let me just ask this question. As a Panel, possibly where -- are we possibly satisfied by now that the local anesthetic potency of levo versus racemic bupivacaine is the same?

If we can assume that, then the key question is, what is the relative toxicity data that we have got from the animal studies, and I would like

to hear Dr. Mather's data again, and Dr. Nimmo's data again on the human intravenous toxicity, because those are the two key questions, I think.

DR. ROBERTS: May I make a point while we wait for the presentation? I would like to reiterate what Dr. Carlisle says. I think that the only way to really answer your question is to conduct a study in which equipotent doses were analyzed with respect to the toxicity obtained at acceptable doses.

I think that we have seen evidence of toxicity demonstrated at acceptable doses. We have seen anything from bradycardia and hypertension to asystole occurring.

So, I think if we had a study in which we analyzed both simultaneously, we may be able to answer that question.

DR. SAVARESE: I think one of the things that we are concerned about here is that -- my opinion is, is that the two drugs seem to give the same kind of clinical performance. And that's just clinical performance.

You're interested in safety here. We

don't see a difference in properly performed clinical comparisons, of a safety difference. But that's just, as we're saying, the lower end of the toxicity curve, the very lowest part of it. And what we are most concerned about is what happens if somebody gets an accidental overdose of one kind or another.

And that's just not going to be possible to perform clinical studies of that sort. However, the other thing is that, I don't agree with Dr. Roberts. I'm sorry to disagree with you, but I think that a lot of the stuff that we are seeing here is simply the side effects of the anesthetic drug, and it does not include -- or does not indicate a toxicity.

I hope that's not what you meant. Were you thinking that this was actually a symptom of toxicity of drug?

DR. ROBERTS: What I'm thinking is, we have not seen enough evidence to prove that it is not. Or that it is.

DR. SAVARESE: Well, again, I think we can -- I can, anyway, I'd like to ask the rest of the Panel to think about this. I can explain most of

these symptoms that were seen in the testing of the drug as just the consequences of a high block, or a relative overdose, or an error in judgment in dosage on the part of the investigator, or just unfamiliarity with the drug.

DR. JEAN: Perhaps in order to help this doctor over there, I would like to ask the Sponsor if you have the slide for peak study that you have a curve showing QRS effects?

If we use increased QRS interval as one of the cardiotoxic parameters, I would like to show you the shape of the curve. The separation between bupivacaine and levobupivacaine.

DR. GRISTWOOD: Okay, these are the data I showed earlier from the Reitz and Morrison pig intra-coronary artery infusion study, showing the increase in QRS duration times the dose of drug administered.

And this is the curve for bupivacaine, and the curve for levobupivacaine, here.

And making assessments of the difference in effects on the QRS duration, there was a 25%

difference at this level, with a 40 msec increase, and there's a 47% difference at the level of 90 msec increase in QRS duration. Does that answer your question?

DR. JEAN: Yes. Would that help him?

DR. TOBIN: I'm sorry, it doesn't help as much as I would like, because this is obviously the drug delivery into the coronary artery, causing this, and as Dr. Savarese says, it's the unintentional delivery of a small amount of drug to the intravascular system that is probably responsible for the side effects we are seeing.

Although the data is helpful, somewhat, I'm not sure I can quantitate it without knowing confidently that they are indeed equally potent. But just as importantly is, what is the outcome of a prolonged QRS of an extra 90 msec?

That in and of itself may not be sufficient to cause clinical symptoms. It frequently does. But, if these are not non-resuscitateable rhythms, then this is preliminary data and we still need to go on to resuscitateability from the

catastrophic cardiovascular collapse.

DR. SAVARESE: Could we also see Dr. -- Madame Chairman, if it's okay with you --

DR. HORLOCKER: It's fine.

DR. SAVARESE: -- Dr. Mather's comparative data, and then Dr. Nimmo's comparative data, because these are also comparative toxicity data, which are key. Just one or two slides which you think are important.

DR. SMILEY: John, can I just -- I get the sense that we are almost of a consensus; that the human data, for the reasons we have talked about, is not that useful for us. So, I'm not quite sure why you would want to see that again.

I thought we had more or less come to a consensus that, because there is no surrogate endpoint, the human, sort of subtoxic dose data just won't let us make any conclusions about the human, so I'm not -- what are you looking for?

DR. SAVARESE: Well, I'm looking for Nimmo's data at the highest dosage levels of each -- he's comparing milligram for milligram of the

comparative symptomatology in the two sets of volunteers.

I think they were the same people, wasn't this a crossover study? Is that right, Walter?

DR. NIMMO: The first study was a crossover study. The second one I presented was a parallel group study. But in the first one, you are right, they were crossed over.

DR. SAVARESE: Okay, so I mean the question is, just let's see that data one more time.

DR. HORLOCKER: The healthy volunteer data where they had delivered an infusion --

DR. SAVARESE: Yes.

DR. HORLOCKER: -- and stopped at the time of first CNS toxicity?

DR. SAVARESE: Yes. I think that --

DR. HORLOCKER: Do you have that slide?

DR. NIMMO: Yes.

DR. HORLOCKER: I actually have a little bit of problems with the human data, because the CNS toxicity occurred at the same, or not a statistically different, milligram difference, so that they occurred

at the same time; they really weren't that different; and within our 50 mg intravenous dose.

So, we haven't been able to really show that humans respond differently to levobupivacaine versus bupivacaine, so I agree.

DR. SAVARESE: That's my point. Not that the experiment is bad, but that I really think that our consensus is pretty clear on this one, that there is just not enough human toxicity data to make much conclusion with or without potency data. In the human.

DR. HORLOCKER: And the good news of course is that you could deliver 50 mg intravenously and not even seize; they only had, that was over several minutes' time, but that is reassuring at least for both local anesthetics.

DR. NIMMO: These are the data on stroke index, acceleration index, and the first study, which was the crossover study, and 14 volunteers, all volunteers experienced CNS effects; remember, the dose was stopped only when CNS effects occurred, except in the one volunteer who got to 150 mg of levobupivacaine

with no CNS effects.

DR. DiMARCO: Can I ask a question about this study? Your methods say that you had two people drop out because of a greater than 20% fall in cardiac output. Those are the people I'm actually most interested in.

Why did you have people, you know, why aren't they counted? That's a, that's the toxicity we're looking for, not these trivial changes in the range of normal.

DR. NIMMO: Correct. And these changes are in the remaining 12.

DR. DiMARCO: So, what happened in -- you know, can you describe what happened in those two people on bupivacaine, and one on L-bupivacaine who had a greater than 20% fall?

DR. NIMMO: The study was a first infusion administration to man study for levobupivacaine, and so we were concerned that what might happen when levobupivacaine was infused for the first time to human beings, and the BoMed was being used as an indicator of safety.

So that whenever there was a sustained in cardiac index, over two observations, then we wouldn't dose the patients again, the other volunteers again, rather.

DR. DiMARCO: Then, the other question I had was --

DR. NIMMO: They recovered rapidly, you see.

DR. DiMARCO: The other question is, when you did your testing with lidocaine -- I'm not an anesthesiologist -- when you did your testing with lidocaine, you went to what you thought was the onset of CNS toxicity.

Did you examine any of these measurements in those individuals, to see that what -- we usually think that lidocaine is relatively cardio-safe, did you look, are any of these changes just associated with the CNS toxicity, and unrelated to direct effects on the heart?

DR. NIMMO: In the lidocaine group, we only made safety observations, we did not measure --

DR. DiMARCO: So, you don't have any

measurements.

DR. NIMMO: No.

DR. HORLOCKER: Dr. Savarese, did you want additional information?

DR. NIMMO: Well, we are going to present the EKG results.

DR. SAVARESE: Yes, but again, the drop-outs from the study, they were dropped because they became hypotensive?

DR. SAVARESE: Their cardiac index dropped and was sustained for more than a minute.

DR. SAVARESE: Yes, and there were two drop-outs in the bupivacaine side, and one on the levobupivacaine side?

DR. NIMMO: No, there was one in each.

DR. SAVARESE: Pardon me? One in each? Okay. Go ahead, yes. Now you're going to give us the CNS data?

DR. NIMMO: Okay, in this study, remember, all volunteers had CNS symptoms, and these are the 12 who remained in the study, they had both infusions, and one can make the comparison in the stroke index,

acceleration index, between the two groups.

And there was a significant difference between the two groups with respect to the fall in stroke index, of which there are almost 11 ml/m², compared with 3.3 in the levo group.

And acceleration index, a reduction of 0.18 per second per second, compared with 0.06 for baseline in the levobupivacaine group.

That is the same data shown graphically. And then this group of volunteers. The PR interval was significantly prolonged in the bupivacaine group, but there was no significant increase from pre-dose in the levo group, although let me say, there was no difference between the two groups.

And also in this study, in the 12 volunteers, there was a significant increase in QTc only in the bupivacaine group, and not in the levobupivacaine group. The differences were not great, and there was no difference between the two groups here.

DR. DiMARCO: Yes, I mean, if you look at the deltas. You know, it's 22 +/-35 and 21 +/- 31.

It's hard for me to say that there's -- you know, to make anything about that. The magnitude of the delta is the same, starting from the same baseline. Maybe your statistics are different, but -- it's hard to say anything about that.

DR. NIMMO: And you remember, the next study, Dr. Savarese, was in 22 healthy volunteers, and they all had bupivacaine until the same side effects, and the dose range was 30 to 120.

They were then allocated randomly to a double-blind, parallel group study, to receive levobupivacaine or bupivacaine. And more intensive EKG observations were made.

And in this group, everybody in the bupivacaine group got CNS effects, but only 6 of the 11 in the levobupivacaine group got CNS effects, because the dose was cut from the previous bupivacaine infusion.

And here are the data from this study. The doses did not differ significantly. The Cmaxs did not differ significantly, and they were similar to the previous study.

The only statistically significant observation was in the prolongation of the QTc interval, in the volunteers who received more than 75 mg of test drug.

DR. SMILEY: There's obviously at typo on that slide, isn't there? Is it -- is the 12 should be a 2, or the 17 should be a 7? Because there are only 19 patients in the study, right?

DR. NIMMO: There were 22 patients in the study, and these are the standard deviations in the brackets.

DR. DiMARCO: Those aren't numbers, those are --

DR. SMILEY: Those aren't numbers?

DR. DiMARCO: Those aren't numbers of patients, those are maximum increases.

DR. NIMMO: These are the standard deviations in the brackets.

DR. DiMARCO: Those are milliseconds.

DR. SMILEY: So, how many numbers in each groups?

DR. NIMMO: There were seven in this group

and four, seven and four. And between these two groups, there was no overlap at all. All four in this group had a smaller QTc increase, than in this group.

DR. GENNERY: Is that sufficient, John, to see the data?

DR. SAVARESE: That's the cardiovascular data, but I think your point was that -- I mean, I myself, personally, am fairly convinced about the differences, particularly with respect to myocardial contractility between the two that you showed, those graphic differences. They are certainly -- you can't ignore them.

But you said that those two groups of people each received enough of either bupivacaine or levobupivacaine, one or the other, to get to CNS symptomatology?

DR. NIMMO: Yes, in the first study, yes.

DR. SAVARESE: In the first study. In this study, all of the bupivacaine volunteers got to CNS symptomatology, and only half of the levo people?

DR. NIMMO: Yes.

DR. SAVARESE: Well, I think that's

important, too.

DR. SMILEY: Well, but that also could be explained by 20% lower potency, and they just missed the -- remember, you're going right to the borderline of toxicity with bupivacaine. If levo happened to be a little less potent, that's exactly the results you'd see.

You would see fewer of them reaching CNS toxicity on the second time.

DR. SAVARESE: Yes. So, I agree with you. Potency is key question and this is all under the assumption that they are the same potency.

I think we're going to need maybe a little bit more reassurance of potency identity, in order to shore up this data.

I also would like to ask Dr. Mather to go over his, because that -- your slide of convulsant dose -- I'm specifically thinking of that one, where there is a clear separation of convulsant doses. Could you just go over that data and explain that to us again?

DR. MATHER: We should have the summary

slide that puts together the convulsant doses with respect to the fatal doses. I think this might help clarify issues as well.

The point about the slide is that we are looking at the main convulsant dose of levobupivacaine and bupivacaine, and seeing the separation between them.

At the same time, you can see the mean fatal dose. And the ratio then exhibited between the convulsant and the fatal doses, is in the order of three for levobupivacaine, compared to two for bupivacaine.

I think this is an important issue in itself. There has been some controversy in the literature of which you may be aware, of the role of the central nervous system in inducing arrhythmias, and I think this is a significant issue in its own right.

There is no doubt that arrhythmias can be induced, stereo-selectively, and it's been demonstrated with the R and S enantiomers of bupivacaine. The stereo-selectivity plays a role with

injection of these agents. So, the role of the central nervous system and the cardiovascular system can't be underestimated in this case.

So, the point about this is, I think, that a margin of safety in the central nervous system, which are convulsant levels, also may be conveying a margin of safety in the cardiovascular system.

I wouldn't want to speculate too loudly or to too wide a public audience at the moment about the mechanisms involved in this, but a case has come to mind of the epileptic patients who have sudden cardiac death, etcetera.

But, placing the simple interpretation of the numbers. There is a margin of safety in both issues there, central nervous system and cardiovascular death. Does that sort of clarify the point you wanted?

DR. SAVARESE: There's a specific slide you showed. It's a graphic comparison of convulsant dose after IV infusion of bupivacaine versus levobupivacaine. And there is a clear separation of the two, and I think we should look at that again.

DR. HORLOCKER: Dr. Mather, on your previous slide for fatal dose, is that to mean the cardiac collapse? So, essentially, you were calculating the cardiac collapse over CNS collapse ratio that we're used to discussing.

DR. MATHER: They were Dr. Santos' data and, yes.

DR. REVES: It's a fatal arrhythmia, right?

DR. MATHER: These are convulsant doses, per se. Is this the data you wanted to --

DR. SAVARESE: Yes, that's the one I wanted to look at.

DR. MATHER: Right. There are individual animals, and then the mean and the 95% confidence intervals of the group means.

DR. HORLOCKER: Again, are these statistically significant?

DR. MATHER: Yes, they are.

DR. SAVARESE: I think, looking at the individual data on the left is what strikes me, is that there is absolutely no overlap even of

individuals there.

DR. MATHER: Well, there is one overlapping value, but, yes --

DR. SAVARESE: Oh, the lowest one on the --

DR. MATHER: Yes, the lowest one. There is also one very low one in the bupivacaine --

DR. SAVARESE: Right. Right.

DR. WATCHA: I think the confidence intervals on the right show it much clearer.

DR. MATHER: Again, the failure of the confidence intervals to overlap I think is impressive. Can I expand on that any further for you?

DR. SAVARESE: Well, you've had loads of experience doing studies like this.

DR. MATHER: Yes, I have.

DR. SAVARESE: Could you put these into a context with other local anesthetics, for example?

DR. GENNERY: Indeed, I could. The values for lidocaine will be approximately 300 mg. The values for ropivacaine will be almost identical of those for levobupivacaine. Slightly higher, but

almost identical on the upper edge of the levobupivacaine.

When it comes to the fatalities, then the same order pertains. So, lidocaine, 350 would be a round number. Ropivacaine, approximately 140 would be in that range, going down as low as 100. Something in that range.

So, the bupivacaine in all cases is the lowest on the ranking of those four commonly used local anesthetics.

DR. SMILEY: Can I ask for clarification on that? Just based on the numbers? Dr. Mather, on the numbers you just threw out there, would imply that in fact as clinically used, both levobupivacaine and ropivacaine would be, quote unquote, safer than lidocaine. Because therapeutically, lidocaine is used at four times the dose. And you're talking about ratios of 2, 2.5 to 1.

DR. NIMMO: The lethal dose on the same scale for lidocaine is approximately 1500 mg --

DR. SMILEY: Oh, the lethal. No, this is just convulsant dose. Okay. Fine. But as far as

seizures, though, that's all you're concerned about.

DR. NIMMO: As far as seizures, yes, it's interesting, and again, if you look at the dose for lethality compared to that for seizures, the value for lidocaine is slightly lower that you would predict on the potency ratio.

In the case of fatality, the value for bupivacaine is about twice as toxic as you would predict on the basis of that.

DR. SAVARESE: I think, just to further question you about this, that the remark you just made, plus something that you may have implied or even come out and stated during your presentation was that you think there may be a kinetic difference the two, maybe explaining some of the CNS differences that you see? Is that true?

DR. NIMMO: I wouldn't --

DR. SAVARESE: Could you go ahead and talk about that some more?

DR. NIMMO: I could talk about this some more, certainly. I've done some fairly subtle pharmacokinetics by way of mass balance calculations

of the amount of drug and its flux across the blood-brain barrier, and into the myocardium.

It turns out that there is no discernible difference between the R and S enantiomer of bupivacaine, and their rate of uptake through the blood-brain barrier, into the brain.

There is a subtle difference, a small difference, with respect to the heart. And in fact, there is actually slightly less S enantiomer of racemic bupivacaine gets into the heart at the peak effect, compared to the R enantiomer.

The mean value is approximately 92% with a confidence interval of about 4 or 5%. So, it's statistically significant. It's small, but it's all in the same direction. It's all saying, lower intrinsic toxicity on the heart, and a slightly lesser uptake into the heart.

Small difference. Statistically significant. Subtle, but all in the same direction.

DR. HORLOCKER: Yes, sir. This is the last question, I'll break for lunch.

DR. GOHEER: My question is to Professor

Mather. You have completed the intra-coronary artery infusion in the sheep.

DR. MATHER: Yes, I have.

DR. GOHEER: Would you like to say something about this?

DR. MATHER: I can't find my crib notes, I'm afraid, so I will talk from memory. The story is that we infused doses into the coronary artery in a parallel group, randomized, blinded manner, in which the coding was broken after the analyses had taken place.

We started with the injections at 2.5 nominal mg and increased by 2.5 nominal mg until either a maximum of 12.5 mg, or a lethal outcome ensued.

The animals were prepared in exactly the same way for exquisite measurement of cardiac dynamics. The injection was made into the bifurcation of the left anterior descending of the left circumplex coronary arteries, in a retrograde manner, to get the maximum degree of mixing of drug, as it was injected.

The broad outcome was that injections of

levobupivacaine, five out of seven of the animals in the cohort died during the studies. The bupivacaine, four out of six died. For ropivacaine which was included as a comparative, four out of six died.

The mean lethal dose for all of them was almost exactly 22 micromolars with a small standard deviation and there was no statistical difference between the three values of the lethal doses, nor of the frequency of deaths occurring in the series.

The results were surprising, and contrast somewhat with the differences with intravenous dosing. The differences between intravenous dosing where much larger differences between the potencies of the drugs were revealed.

My hypothesis for this, and I draw the attention to the word, hypothesis is, that the greatest difference between the drugs is in the central nervous system activity, and I believe that the activity of the central nervous system acts to coincide with the direct effects of the drugs on the heart to give a greater bias.

So, I believe in my preparation, which is

the only preparation of a single dose that is performed in a conscious animal, the intrinsic differences in cardiac toxicity between the drugs is much smaller than one would predict from the intravenous toxicity.

And the principle difference is revealed by the manifestation of the central nervous system effects feeding back onto the heart.

DR. HORLOCKER: Thank you. We will adjourn for the morning session now and reconvene at 2:00.

(Whereupon, at 1:04 p.m., the Advisory Committee Meeting was recessed, to be reconvened later the same afternoon.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:00 p.m.)

Committee Discussion

DR. HORLOCKER: If everyone would take their seats, we will start the afternoon session. I believe we have already covered a significant part of the discussion earlier today, but what I would like to again remind the Advisory Committee on, are the two questions that the FDA has asked us to address.

And these are, specifically, has the Sponsor adequately evaluated levobupivacaine's potential for cardiac toxicity at the labeled dose, and if not, what further studies are needed?

Secondly, should the boxed warning that currently exists in the bupivacaine label be applied to this product?

Now, what I would like to do is throw a real wrench in the whole discussion here, and let's discussion number two first, because when the black boxed warning was placed in 1983 around bupivacaine, anesthesia practice was much different than it is today. Specifically, we don't inject the whole dose

at once, we use a test dose. We inject incrementally and aspirate incrementally.

And so we don't see the same problem with racemic bupivacaine that was reported in Albright's Study. And there have been others on this Advisory Committee Panel that met in March of 1997, and those that discussed ropivacaine in 1996 that have said, perhaps we don't need the boxed label warning on bupivacaine.

Now, if we don't need the boxed label warning on bupivacaine, then certainly, regardless of whether the potency of levobupivacaine and bupivacaine are identical or not, it wouldn't matter and we wouldn't need the boxed label warning on levobupivacaine or bupivacaine.

So, I would actually like the Committee to address this issue first. Would we like to rescind the black boxed warning on bupivacaine? Dr. Smiley?

DR. SMILEY: Do we -- I hate to say this, but do we have a copy of that black boxed warning to put up there, because as I remember -- I mean, I've read it many times, but before --

DR. HORLOCKER: In fact, we have one in our packet and -- does anybody have an overhead?

DR. SMILEY: -- because the -- the point I wanted to make is that, while we would all agree that bupivacaine is a potentially dangerous drug. I agree with you about changes in practice, at least in epidural anesthesia, for the most -- at least at academic centers.

But, I think that if there were -- if one were to write the black box warning now, it would be so different than what is in that black box, that I think that, I believe that that black box is not really relevant to current practice, and doesn't conform with current scientific information, either.

Whether a special warning for this class of drugs is needed, is a slightly different question, but if you were asking me whether that black box would be put on bupivacaine now, the answer is almost certainly, no, because it really is not in conformance to what I understand to be the problems with using these drugs as anesthesiologists.

DR. HORLOCKER: In fact, what I would

suggest is that we actually look at the labeling for bupivacaine and also for the way the warning was worded for ropivacaine when it was approved in 1996, and that there still are some very strong statements, all in capital letters, that say that this is a drug not to be used at high concentrations in obstetrics and under certain circumstances.

And as you are saying, perhaps this is the way the warning would be worded, should it be wordsmithed today.

So, if we could get copies of those two labels, I think that would help us.

DR. ASHBURN: They're in the big black --

DR. HORLOCKER: Right. They're also in the -- at the very beginning of the blue -- you can see that the black box warning pertains to 0.075% bupivacaine in obstetrical use. It has no other real applications as pertaining to a surgical or pediatrics, or other applications of regional anesthesia.

And again, this label states what the facts were at the time. That there had been cardiac

arrests and difficult resuscitations and deaths that occurred in patients that have received, presumably large intravascular injections of 0.75% of bupivacaine.

Could I have the ropivacaine label, the beginning of it, where it discusses the use in obstetrics?

DR. ASHBURN: It's the last tab in the large blue --

MS. REEDY: We don't have that on a slide, but it's the 1996 tab in the blue briefing package.

DR. HORLOCKER: I can read the beginning of it. This is under the Noropin labeling, under warnings. And in capital letters, the warning is stated, "For Cesarian Section, the 5 mg/ml solution in doses up to 150 mg is recommended. As with all local anesthetics, Noropin should be administered in incremental doses, since Noropin should not be injected rapidly in large doses, it is not recommended for emergency situations where a fast onset of surgical anesthesia is necessary.

"Historically, patients reported to have

a high risk for cardiac arrhythmias, cardiac circulatory arrest, and death when ropivacaine was inadvertently rapidly injected intravenously."

So, if you recall from the transcript of the ropivacaine discussions, this was a very difficult decision for the Advisory Committee to make at this time. This was their compromise, to still state the facts as they were historically related to bupivacaine, and during the ropivacaine discussions, as with levobupivacaine, had no true data showing whether these patients would still be at high risk or not, and so they wanted to put the historical perspective in the label, and just state the facts as they existed then.

Dr. Smiley, did you want to?

DR. SMILEY: Well, I think that is a much fairer statement of the issues. None of us would question that local aesthetics are dangerous, and that some are a little more than others.

So, that would probably, again, starting from scratch, I think that would be we would be at. I do understand, or I am starting to understand, some

of the implications of removing black boxes, and having very similar drugs, and none of us would argue that levobupivacaine is fundamentally a very different drug from bupivacaine.

Not having a black box on one, having it on the other is slightly different than if this was a brand new drug class. I'll stop there for now.

DR. HORLOCKER: I'll interject then, also, that, if we do not place the black box warning on levobupivacaine, we will have to, more than likely, evaluate or reassess whether we want to remove it from bupivacaine, also, because they will -- the manufacturers no doubt will submit a --

So, this really is a timely discussion, that we will have at one point in time or another.

DR. SMILEY: But there's a big difference between, as I understand it, between putting a black box on something, and simply not having it as an indicated use.

DR. HORLOCKER: Correct.

DR. SMILEY: I mean, none of us are claiming that it's indicated to use 0.75% for Cesarian

Section, or frankly where I think the next bupivacaine death will come will not be in C Sections, where incremental injections are done, but rather in nerve blocks, where that's not as possible, when there's just a needle sitting there.

So, that's my fundamental objection to the black box warning, is it's not warning about the right thing. The problem is, giving any patient a sudden, large dose of any of these drugs, and yes, maybe bupivacaine is a little worse, so it actually has this incredibly powerful message about slightly the wrong subject.

DR. HORLOCKER: Could I get a member of the FDA to actually discuss with us, what the medical legal implications of the black box labeling is, and also, the warnings, the way they are worded; for example, with the ropivacaine drug? What do they mean, what do they infer?

DR. MCCORMICK: I don't think it's actually written in stone or in the regulations, you know, what the medical legal implications are. Certainly, if something is contraindicated in the

warning section, whether it's in a box warning, at the front of the label, or in the warning section of the label, the Sponsor certainly cannot advertise, promote its use.

It's really up to a practitioner to decide how he or she is going to use a product. I can't specifically speak to the medical legal implications, because that's really outside of our realm.

I would think that a practitioner would be taking on a great risk, certainly if he or she had a complication with a product, if it was specifically contraindicated in the warning section of the label.

DR. HORLOCKER: Well, as I understand it, the Sponsor is not seeking 0.75% levobupivacaine for use in obstetrics, correct?

DR. GENNERY: That's correct. We've done those studies and we're not asking for that indication, at that concentration, at the moment.

Could I ask, if you don't mind, if Dr. David Birnbach speaks to this issue, because we have been working with David on how best to approach this issue, and I would like to ask if he can just address

it?

DR. HORLOCKER: Dr. Birnbach.

DR. BIRNBACH: Thanks. I'm David Birnbach. I'm an Associate Professor at the College of Surgeons, Physicians and Surgeons at Columbia University.

I am also the President of the Society for Obstetric Anesthesia and Parenecology. More important to this discussion, I am Director of Obstetrics Anesthesiology and St. Luke's Roosevelt Hospital Center in New York City, that has a very large and high risk population of pregnant patients.

I have been in discussions with Chiroscience for several years, because as the fourth point there shows, I believe, as do many practicing obstetric anesthesiologists, that we need to do studies, that there is a need for a new epidural agent in obstetrics, and that 0.75% levobupivacaine might be such an agent.

I can't say that it is such an agent, no studies have been done; however, I would like to address the fact that if a black box warning is put on

this drug, it would just about invalidate any possibilities of the studies occurring, or of a practice changing for use of that better drug.

There are three or four points, I only have a very few number of slides, probably for the first time in my life, and I would like to discuss several issues.

First of all, the recent animal studies do not support the decision to put a black box on 0.75% bupivacaine for obstetrics. And they surely don't support putting a black box on obstetrics for 0.75% levobupivacaine.

In 1983, the data in those days -- and this was predominantly animal data -- suggested that pregnant patients were far more sensitive to the effects of bupivacaine than nonpregnant patients.

This was an American disease. Patients didn't die of 0.75% cardiotoxicity from bupivacaine, in any other country than the United States. And the presumption, especially on the part of anesthetists in the U.K., was that it was the practice of anesthesia in the United States, not the drug.

You can kill a patient with any local anesthetic, if you administer it inappropriately. And in obstetrics, inappropriate would be, putting 25 to 30 mls through the epidural needle, without a test dose, without waiting and incrementally dividing the dose.

Recent animal studies, and Professor Mather showed us this morning, Alan Santos' studies, and this is something that I think we should discuss for a few seconds, the recent studies do not support the differences in cardiotoxicity between pregnant and nonpregnant sheep.

That was central to the original black box warning just for obstetric patients. After all, obstetric patients were more sensitive to the effects of local anesthetics. If obstetric patients aren't more sensitive, than perhaps you should be thinking about a warning of 0.75 for everyone, or no warnings.

The second point that I would like to make is that levobupivacaine is, we think, less cardiotoxic than bupivacaine. And more importantly, our practice today is dramatically different than our practice was

20 years ago, and it is 20 years ago next month that Albright first came forth with his patients who had cardiotoxicity with 0.75% bupivacaine.

So, Alan Santos in 1995, in the first of his new studies, said the systemic toxicity of ropivacaine, this was a ropivacaine study, and now it's been duplicated for levobupivacaine, is not enhanced by ovine pregnancy, but neither is that of bupivacaine.

Now, this is about the strongest statement that a researcher. Now, this is about the strongest statement that a researcher can make, because he invalidated his own studies, and those of Dr. Morashima in publishing this. And in so doing, he discussed in the discussion section, that the present state of the art of chief research was not anywhere near where it was 20 years ago.

And doing his studies today, with the sophistication that he was capable of, he could not find any difference in cardiotoxicity between pregnant and nonpregnant sheep.

Now, if we look at the best database for

maternal deaths, if we are going to assume that mothers are more susceptible to the effects of epidurals, the best would be the U.K., the Continental Inquiries Into Maternal Mortality of England and Wales.

And the most recent data we have is the 1970 to 1987 data. During that period of time, 139 mothers died in the U.K., and of these, only 11 received epidurals. And of those, one died of untreated hypotension; five died of total spinal anesthetics after spinal; one died of cardiac disease, she had critical aortic stenosis and was given a one shot bolus drug; one died of complications of PIH, including seizures, and one had an amniotic fluid embolism which was found on autopsy.

Not a single death during that entire period of time was due to local anesthetic toxicity, with an epidural, as we are worried about, that somehow the practitioner will give a big bolus, no testing, and it will go intravascularly.

Now, I inferred that our practice is not what it was 20 years ago. We now as a rule

incrementally divide our doses. And the current standard of care in the United States, is in obstetrics, not to give bolus drugs.

I did a search of every textbook, and every single textbook, both of anesthesiology and obstetric anesthesiology, and that includes five in the United States, all say clearly and incontrovertibly, that a dose must be fractionated in obstetrics.

Number two. The switch has occurred several years ago. The vast majority of practitioners are now using multi-orifice catheters. And two recent studies by Norris and colleagues in St. Louis have shown that aspiration of a multi-orifice catheter has a greater than 99.5% chance of reliably detecting intravascular placement just on aspiration. That is nowhere near the case with single orifice catheters.

So, 1983, the only catheters available were single orifice catheters. More importantly, we now have standards for regional anesthesia practice in obstetrics, and in the main operating room. Things that we didn't have 20 years ago.

Now, if you look at Albright's cases, and again, there was some question about Albright's publication of these cases, this was an editorial. There was some concern that Albright was jumping the gun, and incriminating a drug rather than the practice.

If you look at Albright's cases, all the deaths -- and they were not all due to bupivacaine 0.75%, there were some due to epidacaine as well. None of the 11 were resuscitated appropriately.

As a matter of fact, in four of them, there was no anesthesiologist present. So, in 1999 standard of care, that would not be a problem, because we are present during regional anesthetics. We teach incremental boluses, and we have resuscitative equipment immediately available.

Last, there was a decreased use of epidurals for elective Cesarian Sections, and we are using epidurals more and more for a select group of patients, and that would be a high risk group of patients.

And that brings me to the last point,

which is why I, as a practicing obstetric anesthesiologist, and representing OB anesthesia as President of SOAP, believe that there is a need for a different epidural agent.

The options that we have right now, if you have a severe preeclamptic patient, there are only four options if you want to do it under a slow, controlled, regional anesthetic, which is what all practicing obstetric anesthesiologists want to do.

We don't want to give a general anesthetic. These patients have oral-pharyngeal swelling, or difficult intubations, or full stomachs. And so we are left with a choice. There is 2% lidocaine plain, and we tend to use somewhere between 20 and 25 ml to get a block for Cesarian Section, and that is a toxic dose of lidocaine in a patient who has a risk factor for seizure.

You can lose 2% lidocaine with epinephrine, and it has been reported, a case report three years ago in Regional Anesthesia by Hadzich and colleagues, demonstrated that they were able to double the diastolic blood pressure in a patient who was

already at risk for seizure, by giving an epinephrine-containing solution.

The block worked. It was in the epidural space, but there is an intravascular absorption of epinephrine and it is relatively contraindicated in a severe preeclamptic patient. You can use 3% chloroprocaine and the block will come on almost instantly, like a spinal, but we don't the luxury of a slow controlled block.

Or, you can use 0.5% bupivacaine, which is more or less what many of us do, and to put it in lay terms, that is a wimp of a drug. 0.5% bupivacaine for Cesarian Section does not give the solid block that many obstetric anesthesiologists are looking for, which has caused many to look for options.

And one of the options that three textbooks discuss is the mixture of lidocaine with bupivacaine. No data to support that that makes it any safer than using either of the drugs alone.

There are select groups of patients who would benefit from having the ability of the anesthesiologist to use a stronger agent in the

epidural space, that allowed us to have a slow controlled epidural block.

Right now we don't have such an agent. I'm not advocating that Chiroscience be given permission to go out and advertise that 0.75% levobupivacaine is safe and effective for Cesarian Sections, especially not in sick patients.

What I am advocating is, that we need to do the research. And the only way we are going to do that is to look realistically at why the black box was put there 17 years ago, and whether it needs to be there today.

And as a practicing obstetric anesthesiologist, my opinion is that it does not.

DR. HORLOCKER: Dr. Watcha.

DR. WATCHA: A question for you, sir. Are there such studies underway, planned?

DR. BIRNBACH: The planning is underway. The studies are not underway.

DR. WATCHA: Okay. This is a committee that has been asked to look at a drug, to approve a drug. If there are patient populations that are not

covered adequately by the current plan, then I think we need to get back the data, because already today, we have got a lot of material where the data is incomplete. Where the data is present with the -- without -- the FDA doesn't seem to have any of the data.

If we are going to be looking at this aspect of it, we need to come back here with the data.

DR. BIRNBACH: We're not, my understanding is that Chiroscience is not applying at this point for the use of 0.75% in obstetrics. And these are studies that can easily occur. They would take several years to carry out. And they can occur, once levobupivacaine is on the market, if it is approved.

It does not need to be approved for use in obstetrics. On the other hand, if the black box warning is there, it will contraindicate the use, medical legally, and I believe that your statement is correct, that no practitioner, if that black box is there, would dream in this medical legal climate, even if it was a better drug, of using that drug.

It would, more to the fact, preclude the

studies. Because if a black box warning appears, how many patients will allow that drug to be used as part of a study?

If there were evidence that levobupivacaine caused cardiotoxicity, if there were evidence that the practice today, like it was 20 years ago, put patients at risk, then it would be different.

What I am saying is, that this conversation should be separated from the question about levobupivacaine and whether or not it should be approved.

This is the conversation about whether or not the warning needs to preclude its use right now, and I believe that the evidence doesn't support, at this juncture, putting that warning on.

DR. HORLOCKER: I think Dr. Birnbach has given compelling evidence why we really don't need the 0.75% racemic bupivacaine black box warning, as Dr. Smiley was saying, that really the toxicity is going to occur with a large injection, single injection, probably with a peripheral nerve block, rather than with a continuous catheter technique where we can load

it incrementally.

I would like to get back to the actual discussion about racemic bupivacaine, because it will easily facilitate the rest of our discussion, regarding levobupivacaine. What are the concerns, considerations, of the Advisory Committee regarding the removal of the black box warning of racemic bupivacaine? Dr. Parris?

DR. PARRIS: I feel, if it were to be removed, in the general population of our lay colleagues, out of academic institutions, that would give the impression that it is safe, or it is certainly not very cardiotoxic.

I think Dr. -- the last speaker, made a very persuasive argument for not having the black box attached to the levobupivacaine package insert, but I'm a little uncomfortable, because what happens if you do have a -- for example, you're doing a Biers Block, and when you release the tourniquet, you're putting a large amount of local anesthetic into the circulation.

Of course, if you do good practice, you

should reinflate the cuff to prevent that, but what happens if the cuff fails? What happens if you are doing an intercostal nerve block where the levels, the blood levels are highest? What happens in those situations?

DR. HORLOCKER: But again, I would like to remind you, the black box warning pertains to 0.75% bupivacaine in obstetrical use, so that's why it really is -- it's related to a small subset of patients, and it has nothing to do with a Biers Block, or a single dose injection.

DR. PARRIS: But my point is that --

DR. SMILEY: That was precisely my point.

DR. PARRIS: That's the point. That's the --

DR. SMILEY: That was mine.

DR. PARRIS: -- practice was the same. I mean, in those days, 20 years ago, there as more tendency to give a large bolus, and that is analogous to releasing the local anesthetic after a Biers Block, or through an intravascular injection.

DR. SMILEY: That was precisely my point,

is that, I believe that the black -- no one reads them, anymore. I mean, this drug has been -- bupivacaine has been around for a long time, nobody reads that black box anymore.

In fact, if they did, it would be counterproductive, because the implication is that the problem with bupivacaine is that pregnant women have cardiac arrests, if you do it wrong.

That's not the problem. The problem is, if you give too much of it, and you get a blood level real fast, however you manage to do that, with a Biers Block, with an interscabian block that goes into the jugular vein or carotid artery, with an epidural catheter or a needle that's in vessel, you may kill somebody.

And yes, you may kill them easier with bupivacaine than with lidocaine, and it may be more difficult to resuscitate, and pregnant women are more difficult to resuscitate, no matter why they arrest. But that's a different issue from any particular drugs.

So, my point is that, that's -- if you

need the black box, and I don't think you do. I think you need anesthesiologists trained in anesthesiology, but if you needed a black box, that wouldn't be the black box warning.

The black box warning would be, don't give it intravascularly. I mean, I've had a little more time to write it, but it wouldn't be, don't use this drug, this concentration.

It wouldn't focus on concentration, because it's dosed, also. We know that also. It's not 0.75%, it's how many milligrams are in the blood, how many nanograms/ml are at the concentration?

I know most of you know this, but I think it's important that -- I mean, you're making a very good point, that you know, if you do a Biers Block with this drug, and think it's not toxic, because it doesn't have a black box, and give a ton of drug and then take the tourniquet off a few minutes early, or an hour early, yes, you may have a problem, but that's not what the black box says, anyway.

So, it should just be, you know, you don't know how to use local anesthetics.

DR. PARRIS: Another, just a follow-up to this. Local anesthetics today are not only used by trained anesthesiologists. In the realistic work of pain medicine, there are neurologists; there are radiologists doing nerve blocks.

And they don't have the same sophisticated knowledge of the pharmacokinetic properties of the drugs as anesthesiologists are supposed to have. They just look at the package insert, and that's their basis.

DR. HORLOCKER: But again, that black box wouldn't assist them with that decision-making process, since it only is applying to the obstetrical population. Dr. Reves?

DR. REVES: I actually had written, even though it's not perfect English, what I was thinking, as you said you hadn't written it, and mine would be a warning that says, animal studies demonstrate CNS and cardiac toxicity that is dose-related, thus equal volumes of higher concentration will be more likely to produce toxicity. Something along those lines.

I would remove the black box for both

drugs.

DR. HORLOCKER: Okay. Dr. Carlisle?

DR. CARLISLE: I'm still a little concerned about the whole issue of resuscitation, and I actually disagree with our last discussant, in that, he implied that, had there been adequate efforts at resuscitation, with the bupivacaine episodes, that these patients would all have been resuscitated.

And I'm not sure that we actually have evidence that that is true. In fact, we have, we are working under the assumption that these patients have a very difficult to resuscitate rhythm, and we have seen no evidence that that's not true, today, with either of these drugs.

DR. HORLOCKER: Dr. Ashburn?

DR. ASHBURN: She beat me to the punch. I think, because I think that, as Dr. Reves was saying, one of the important issues is that a drug of higher concentration given in equal volumes is going to lead to higher, or the potential for higher systemic doses, but the other issue is, is that there is some evidence, at least the presumption, that

individuals who do have a malignant arrhythmia with bupivacaine are harder to resuscitate.

And that seems to be, if you are going to black box, those are the issues, or those are the warnings, however it is communicated, and I must say, I'm not so sure that I've seen data, other than animal data, that show that levobupivacaine is any different. And we certainly have seen no data with regard to the ability to resuscitate, once a critical event has occurred.

And with regard to the last talk, there were a couple of contraindications that actually brought -- at least a statement that was made on the first slide that said, local anesthetic toxicity studies in animals do not necessarily predict what will happen in humans.

That was one of the bullets on the first slide, which of course, if you believe that, then all the data on cardiac toxicity that was presented by the Sponsor, would be immediately suspect, with regard to the cardiac safety claims of this product, compared to the other.

So, I don't know which argument the Sponsor would like us to believe, because those bullets seem at least to me to be in a bit of contradiction.

DR. HORLOCKER: Dr. Watcha.

DR. WATCHA: A question for the FDA. You get reports of toxicity of various drugs, again, data incomplete and not everything that is reported.

Since that black box was put in, have we had additional reports of 0.75% bupivacaine toxicity for non-obstetric patients?

DR. MCCORMICK: That's a good question. I thought you were going to ask about obstetric patients, and I was going to make the point that we are not seeing that anymore.

We'll have to go back and look at that. We don't have that information, offhand, but that's a good question.

DR. WATCHA: And the second question correspondingly is, you may not put in a black box warning, but we could certainly put in something along the lines of which the other folks have mentioned, so

that we do have a warning, but not something that will prevent investigation of this drug for the full obstetric anesthesia, and that to me would seem to balance what we as a Committee need to do, is to balance the risks and benefits of this.

DR. HORLOCKER: Dr. Tobin?

DR. TOBIN: Teresa, if I can read from the large binder that you sent to us in the materials. This is the transcript from many years ago, and there's a relation regarding, what is the black box for, and let me quote from this. This is page 257.

"Special problems, particularly those that may lead to death or serious injury may be required by the Food and Drug Administration to be placed in a prominently displayed black box.

"The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning, in the absence of clinical data."

Well, considering the toxicity of all the drugs that we use, everything could wind up in a black box. I'm certainly, again, in agreement with my

colleagues that there is a need for a prominent warning here.

But I caution us not to forget the lesson of history here, that if we have had a diminution in the reports of toxicity from 0.75%, I cannot be confident that that is because of the change in anesthetic practice versus the diminished use of that drug.

So, I think we have to be very cautious about saying, it's safe and we can go ahead and eliminate the black box. I'm certainly willing to accommodate and go towards a strong warning that doesn't necessitate the black box, but maybe bold print.

And I liked some of what Dr. Reves had said earlier, something along those lines, but I think we can't just assume that by history, the change in practice is the reason that we have seen decreased morbidity and mortality.

DR. HORLOCKER: Dr. DiMarco, could you summarize the cardiac toxicity data between the two drugs as you have done your evaluations?

DR. DiMARCO: Yes, I think actually, as a cardiac electrophysiologist, all the drugs I use does have a black box, because they're all pro-arrhythmic, and that's -- you start off with that approach.

I was asked specifically to compare a few things, and I'll start with the preamble that I think the Sponsor had a very difficult job, because what they are trying to do is in an ethical situation with nondangerous doses and normal volunteers are in clinical use, look at a very rare event that usually occurs with what would be a massive dose, overdose, or a poisoning due to an inadvertent injection or too rapid absorption.

However, when I looked at those things, let's look at the normal volunteer studies, what the Sponsor calls contractility changes, I was a little unconvinced by those for, one, I couldn't tell whether they were related to CNS effects on the heart.

There are changes in heart rate, there are changes in blood pressure. Even the changes that are seen are relatively small and the differences between the drugs are quite minor. So, I wasn't impressed

that there was hard evidence that there were changes in contractile function at that period of time.

The electrocardiographic changes are interesting that they look at, and I think that I'm particularly worried by Dr. Woosley's statement earlier today, where he said where he reanalyzed them and found even the changes that are reported here, weren't present because of a different method of analyzing the QT interval.

And that's, I didn't have that information when I did the report, but even so, the changes that are seen, really didn't achieve statistical significance. They're very small.

Some of the things that are of interest are for example, there is one study that shows a change in the PR interval, but if you look at the Sponsor's slide where he is looking at his meta-analysis of the ECG review, the two studies that use the highest doses didn't show a change in the PR interval, so you would think that that would be the place where you would see the most effect.

So, I really wasn't convinced that in the

studies that were shown to me, there were major changes in the cardiovascular profile of the drugs, because there really weren't, you couldn't demonstrate them at these doses, even if they were there.

The final thing I will say, and I didn't say this in my report is that, you know, in looking at these compounds, the toxicity that you are seeing, and that's been described in the literature, really looks to me like a Class 1 antiarrhythmic drug overdose.

That's where we get non-resuscitateable arrhythmias. That's where you get reflex tachycardias, which because of use-dependence make the arrhythmias -- make the electrophysiologic effects more pronounced. You can't defibrillate because you have got changes in defibrillation threshold, and you have adverse hemodynamic effects.

And so, I'm not sure that the QT interval --

DR. SMILEY: Do you have any suggestions about what to do about it when it happens?

DR. DiMARCO: Well, you know, everything's -- we don't resuscitate them well, either. You know,

people have tried things, but the literature, really, there are a few positive reports with hypertonic saline. There is some negative reports. So I'm not sure, in the resuscitation studies which are using Bretyllium, which is something that you might think is an ischemically-mediated re-polarization phenomena, may be in a different direction.

And I think the final statement that Dr. Mather had, that when he gives it directly to the heart, he doesn't show a change, suggests to me that at least something other than just differences of the two drugs specifically on the heart have to be operational.

DR. HORLOCKER: Dr. Rohde. Comments on black box warnings on either or both levobupivacaine and bupivacaine.

DR. ROHDE: My feeling is that they are not needed.

DR. HORLOCKER: Ms. Connolly?

MS. CONNOLLY: I would say I would be in agreement with --

DR. HORLOCKER: Use the microphone,

the lines of what people I think are saying is, that I don't think we need a black box, specific black box warning anymore, but there should be a modified warning about dose adjustments and total dosage advice, rather than the black box thing, which I think is -- you know, it's overly-dramatic and overly-simplified, and based upon too many -- too little information.

DR. HORLOCKER: Dr. McCormick, would you like us to take a formal vote for the removal of the black box warning of bupivacaine? Would that be helpful to you all now?

DR. MCCORMICK: Yes, it would. Actually, if I may make a point of protocol. I believe we had a period of public comment --

DR. HORLOCKER: Oh, I'm sorry.

MS. CONNOLLY: Perhaps before we have the vote, we should invite members of the public to --

Open Public Hearing

DR. HORLOCKER: Yes. Thank you very much. We did just jump right past the open public hearing, because I earlier had assumed there would be no other

-- is there anyone from the audience that would like to speak? I apologize for the breach in protocol. Thank you.

Committee Vote

DR. HORLOCKER: All right, at this time then let's take a formal vote among Committee members on the removal of the black box warning of bupivacaine, and the placement or actually it's for the removal of the black box warning on levobupivacaine, also, so which, if either of these drugs, would you want a black box warning on? Dr. Reves?

DR. REVES: I wasn't raising my hand to speak.

DR. HORLOCKER: No, we're going to go around and vote. It doesn't matter whether you raised your hand or not.

DR. REVES: I think we probably should do them separately, but I would say --

DR. HORLOCKER: Okay, we could do them separately.

DR. REVES: But I'm for not putting one on

levo, and taking off the one on bupivacaine.

DR. PARRIS: Before we vote, Madam Chairman, are you, in removing the black box from bupivacaine, and not putting it on levobupivacaine, are you at the same time suggesting that we have language in the package insert, recommending that --

DR. HORLOCKER: It would probably be very similar to that with ropivacaine that has a strong warning in capital letters. This would be up to the FDA to formally develop the labor.

But, correct. There would be not a lack of warning or a lack of use of common sense with dose and concentration.

DR. PARRIS: Okay.

DR. MCCORMICK: May I just make a point?

DR. HORLOCKER: Yes, Dr. McCormick.

DR. MCCORMICK: An that is that, before we do take any action on the bupivacaine label, which we haven't gotten really specifically recently studied, we would certainly want to go back and look at all of the adverse events that have been reported to us.

DR. HORLOCKER: Okay. Would you still

prefer to have us at least make our --

DR. MCCORMICK: I think it would be useful to hear your opinions. Definitely.

DR. HORLOCKER: Okay. Dr. Smiley?

DR. SMILEY: Yes. I would remove that black box warning from both drugs.

DR. HORLOCKER: Okay. Dr. Carlisle?

DR. CARLISLE: I would remove the black box warning and replace it with strong language in incremental dosing.

DR. HORLOCKER: Both drugs?

DR. CARLISLE: Both drugs.

DR. HORLOCKER: Okay. Dr. Ashburn?

DR. ASHBURN: I agree.

DR. HORLOCKER: Okay. Dr. Watcha?

DR. WATCHA: As above. Agree. For both.

DR. HORLOCKER: Dr. Tobin?

DR. TOBIN: I agree for both.

DR. HORLOCKER: Dr. Rohde?

DR. ROHDE: Yes.

DR. HORLOCKER: Removal for both, or?

DR. ROHDE: Well, one doesn't have it,

right?

DR. HORLOCKER: Okay. It's inferred, unless we take it off. Ms. Connolly?

MS. CONNOLLY: And I again, that which currently exists.

DR. HORLOCKER: Use the microphone, please?

MS. CONNOLLY: That which currently exists, I agree to be removed.

DR. HORLOCKER: Okay. Dr. Savarese?

DR. SAVARESE: Again, one more point of information to make sure I understand, I mean I'm sure I do, but we're talking about a more ropivacaine-like label, correct?

DR. HORLOCKER: Right. For lack of a better analogy, but, yes.

DR. SAVARESE: Okay, I agree with that, and I also favor the no black box for either of the two.

DR. HORLOCKER: Dr. Parris?

DR. PARRIS: The two.

DR. HORLOCKER: I vote for removal for

both. Okay, let the minutes note that it was a unanimous vote.

(Whereupon, the Committee having been polled on the previously-noted proposal, returned a unanimous vote.)

Let's move on to Question No. 1, because this one also does have some significant labeling inferences. Even though both drugs may end up without black box labeling, there still is the possibility that there could be an advantage to using levobupivacaine because of a potential decreased cardiac toxicity. So, we really still need to address this issue.

"Has the Sponsor adequately evaluated levobupivacaine's potential for cardiac toxicity at the labeled dose? If not, what further studies are needed?"

Dr. Reves, would you like to make your comments?

DR. REVES: Well, I think we discussed the difficulties in doing a sort of dose finding study on toxicity in humans.

The animal data are persuasive that there seems, that there certainly is dose-related toxicity, and moderately persuasive that there's a difference between these two drugs, that begs the question of whether there is equal -- if they are equipotent.

But I think we'll never get the perfect human toxicity study, so I think they've done as much as is reasonable to learn about this.

They are at the flat end of the curve, but that's where they have to be by the IRBs.

DR. HORLOCKER: And just as a reminder, the previous Advisory Committee had requested that the Sponsor document at least a 25% increase in safety over bupivacaine in a clinical study, is the way that they had previously set the goals for the statement to be able to support an increase in safety.

DR. REVES: I think they showed it in the animals and not in the humans.

DR. HORLOCKER: Dr. Smiley?

DR. SMILEY: I agree completely. I think we are, I suspect we're in tremendous consensus on the human studies being difficult and unpersuasive, and

that the animal studies are moderately persuasive.

DR. HORLOCKER: Dr. Carlisle?

DR. CARLISLE: I'm still troubled by the lack of the resuscitation data, but in terms of CNS toxicity, I agree that I think the animal data is moderately, are moderately persuasive.

DR. HORLOCKER: Certainly, one of the options that this Advisory Committee has is to wait until the resuscitation data are available, before we make our final assessment of this.

We can consider that in our vote, also, when we come around again, because those data are critical, but perhaps enough data already exists to still make the statement. Dr. Ashburn?

DR. ASHBURN: I think, based on the question, the way this question is worded with regard to -- I guess it depends on what you are looking for.

If it's just cardiac toxicity with regard to this particular local anesthetic agent, I think, yes, the studies are sufficient.

Is it sufficient to claim superiority over bupivacaine, that I'm less sure of. And even

understanding the difficulty in human trials versus animal trials, that at least in my mind is a little more problematic.

And I think that even when the current study is done with regard to resuscitation, it seems to me that an n of 6 in each study group with regard to resuscitation is insufficient to have enough statistical power to be able to identify whether or not the animals, there is any difference in the study drug.

So, even though the statistical analysis has been completed, I would say that I think an n of 6 is insufficient to be able to really go home on animal studies, whether or not these drugs are going to be different when that study is done.

DR. HORLOCKER: We could of course request additional studies and if I remember correctly from the ropivacaine discussions, there is a different resuscitateability, depending on which animal model is selected.

And so, using an alternate model might also give us additional data, and so there is that

possibility.

DR. ASHBURN: I concur.

DR. HORLOCKER: Dr. Watcha.

DR. WATCHA: One of my concerns, Madame Chairman, has been the fact that we really do not even know which of the groups those patients -- those animals were.

We try to make decisions on incomplete data, inadequately presented and summarized data, and if we need to have another meeting to come back and see all the data properly, whether we have a chance to review the data before the meeting, that would be fine, too. We are making decisions on data that is incomplete and inadequate at present.

And again, with regard as mentioned before, with regard to certain patient populations, we have no data on it.

DR. HORLOCKER: Excellent points. Dr. Tobin?

DR. TOBIN: I think the Sponsor has provided sufficient data in the animal studies to indicate that levobupivacaine is at least as safe as

the current racemic mixture.

However, I think there is insufficient data, once again, pointing to the resuscitation studies, to demonstrate superiority of whether or not the morbid events do occur, and whether or not resuscitateability is indeed better in the levobupivacaine group. And I strongly encourage them to go back and increase the size and power of those studies.

Secondly, I would like to echo what Dr. Watcha has said, which is that we do not know the potential age-related toxicity of this drug, and we know of some toxicity with bupivacaine in the young human patients.

And I would like to encourage them to consider a developmental model, as it is clear that bupivacaine is in widespread use in the pediatric population, including the newborn.

In the Sponsor's or in the FDA's prepared proposed package insert, there is incomplete reference to pediatric indications, and I would like to be sure that even the data that we are presented today are

recognized that they only included infants greater than age six months, and that the potential indication of ages zero to 18, it is not appropriate.

DR. HORLOCKER: I also concur that the lack of resuscitation data is worrisome, and if I were the Sponsor, I would actually want to get that data out so that you could claim a true superiority, if one exists, over bupivacaine.

I would hope that if the data, if this drug is released without that data, that the label would actually reflect that and say that, while there may be decreased cardiac toxicity, the resuscitateability between this drug and bupivacaine is unknown at this point in time, because I think we really have to do, as others have mentioned, state the facts as they exist today, and as someone has earlier said, what we don't say is as important as what we do say.

And so, we have to stress what we know and what we don't know, and the label could always be amended as that data come in, or the drug could be held until we get those data. And it could be

included at that point in time. Dr. Rohde?

DR. ROHDE: One thing seems to me to be perfectly clear, we could search forever and never exhaust all the possible subgroups where we might find one drug being superior to the other.

So, it seems to me, and that's not really the issue. The real issue is what the Sponsor has presented, which is pretty convincing, except for the resuscitation data.

I would like to see for something like this a good follow-up by FDA in terms of drug surveillance, because that's the only way that you'll get data on all these possible subjects, particularly the ones that are going to be very, very small.

It might take ten years before data will come in on these groups, and if it does, and it's not a drug for that subgroup, that's fine, but that should not penalize the rest of the population for whom this might be very beneficial.

DR. HORLOCKER: Ms. Connolly.

MS. CONNOLLY: As the consumer representative, I definitely think that the animal

models did show a trend toward CNS toxicity and cardiac toxicity at the labeled doses.

However, I do have a concern that the human volunteer studies did not adequately show gender differences. One study was all male, and the other studies said 22 healthy volunteers, but did not break it down according to gender.

I am also concerned, too, that we need more studies with regard to the pediatric population. And the lack of resuscitation follow-up study.

DR. HORLOCKER: Dr. Savarese.

MS. REEDY: Are you saying that the potential for cardiac toxicity is adequately --

MS. CONNOLLY: Has been adequately addressed. Yes.

DR. HORLOCKER: Dr. Savarese?

DR. SAVARESE: Well, I guess my first point is, remember that again, we're doing all of these toxicity comparisons under the assumption that the anesthetic potency is the same.

And my question is, do we have enough data to make that assumption, or to make that conclusion?

As far as I know, there have been only a couple of comparative studies of potency in humans, I'm talking about humans.

My feeling is that there should at least be one or two more simple comparative studies; you know, simple nerve block comparisons of the two drugs to establish that they are equipotent, beyond any shadow of a doubt.

And then with that data in hand, then all I would need is the improved IV toxicity data with respect to resuscitation. I think we're all waiting for that.

And the only other possible thing that might be needed is a little bit more IV toxicity data in humans. The sort of study that Walter Nimmo presented. But that's a small number of subjects, and well, I don't know how much more of a chance you want to take in injecting more drug into people, but maybe just pushing it a little bit further, beyond where you did.

I'm not saying I would insist on this. This is just what I'm suggesting.

DR. HORLOCKER: In summary, then, would you actually vote to withhold approval of the drug until those studies are done, or would you just make strong recommendations for the Sponsor to perform these evaluations in the future?

DR. SAVARESE: Oh, I think, yes. I think they could be done as post-approval. Yes, I don't say we should hold up approval at this point, no.

DR. HORLOCKER: Dr. Parris?

DR. PARRIS: Following up on this, some of the indirect cardiotoxicity studies have not been reflected in the Sponsor's presentation.

For example, drug interactions. There are some drugs that interact with others and thus render them more cardiotoxic than when administered alone.

In the presence of hepatic dysfunction, the metabolism may be altered, thus elevated in the blood levels, and making a tendency for more cardiotoxicity.

I am not suggesting that we should hold up, but I think these ongoing studies should be reflected, either by surveillance of the FDA, or by

more -- And they may be already there, but it should be presented.

I think Ms. Connolly addressed the issue of a sexual, I think an ethnic distribution. For example, what is the effect on African-Americans with sickle cell disease? Or there may be -- you know, so I think that should be represented.

And one final comment. About ten years ago, I did some work on bupivacaine-induced muscle atrophy. And I had difficulty getting that study published in the United States. I did a sabbatical in Holland, and I came across 13 cases of muscle atrophy, and that's why the Europeans don't like bupivacaine.

And there may be a relationship between muscle atrophy and cardiac toxicity. I don't know. So, maybe we should look at muscle atrophy in patients, following peripheral nerve blocks.

And one final comment, I think the last discussant alluded to a British study that was performed between 1970 and 1987, suggesting that there were very few reports of local anesthetic toxicity.

I have a little experience in the British

system. Between that period, there was not much local anesthetics administered via epidural. It was primarily by a spinal, because of the Woosley and Rowe disaster of 1954. So that would not be a fair statement to make, to make the inference that there was diminished level of local anesthetic toxicity.

DR. HORLOCKER: Dr. McCormick, are there any clarifications that you would like the Advisory Committee to make at this time, or do you have further questions?

DR. JEAN: Lucy Jean, FDA. I would like to ask Dr. Savarese about his recommendation concerning the potency. In animals, there are two valid in vivo rat studies testing the efficacy, as far as I know, and then there is an in vitro frog sciatic nerve preparation.

In your recommendation, are you referring to animal or human studies, that you would like to see as a Phase 4?

DR. SAVARESE: Human, not animal.

DR. JEAN: Thank you.

DR. HORLOCKER: All right. Are there any

other questions or comments? Yes, sir?

DR. GENNERY: If I wonder if I can address one or two of the concerns that are being raised, and just perhaps give a picture as to how some of these things are being addressed?

First of all, with regards to pediatrics. We have actually set up and are underway the studies that we agreed to two years ago. Recruitment in some of them has been a bit more difficult, a bit slower than we had perhaps hoped, but two of those studies are now complete.

The others are ongoing and as of today, something over 150 children ranging from the ages of two weeks up to 12 years have had levobupivacaine administered by peripheral block, by caudal injection.

DR. WATCHA: Unfortunately, in the material that was given to us we have statements that they were incomplete, that the data is not complete, and we are trying to make some decisions, where we're getting statements, written statements as part of our read-out, that says that we don't have that data yet.

DR. GENNERY: All I'm trying to do is to

provide you with reassurance that we committed to the program, and we are doing the program.

DR. WATCHA: Okay.

DR. GENNERY: Secondly, with regards to hepatic dysfunction, we have set up and we are running a study in patients who are having substantial partial hepatectomy for secondary tumors. And we are giving them -- their epidural anesthesia is with levobupivacaine, and their postoperative pain management is with levobupivacaine and Fentanyl.

Now, this is a very complex protocol. We're looking at long-term kinetics, and metabolic changes over that period of time, up to about five days postoperatively. It's going to take a long time to do this protocol, but it is underway, and we hope it will provide very high quality science at the end of the day.

I think those are perhaps the two outstanding issues. If there are any others, I would obviously be happy to try and address them.

DR. HORLOCKER: Are there any other questions?

I just have one statement for the Advisory Committee members then, you don't have to bring all of these books back. Kathleen will send them to your address that they have on file, so that you can leave them at your seat and the FDA will take care of it.

I'd like to thank the Sponsors --

DR. MCCORMICK: May I have --

DR. HORLOCKER: Oh, I'm sorry.

DR. MCCORMICK: Excuse me, may I -- I just have one point to make. Firs to fall, I would like to thank the Committee for a very informative and very helpful discussion today. I think we have clarification of where we need to go with this at this point.

I would like to ask a question of the Sponsor, and that is, if you could clarify for us where these resuscitation studies do stand, and whether we can expect them as a Phase 4 commitment?

DR. GENNERY: With regard to the dog study, the experimental phase is done and that very preliminary data was presented this morning.

The current status is that we are

analyzing the plasma concentration data. That is being carried out at the moment. We are working very closely with Dr. Feldman to get that study completed, fully analyzed, and fully written up, as a final report to file with the Agency, just as soon as we can.

DR. MCCORMICK: And with regard to pediatrics, do you have plans for exposure down to the newborn?

DR. GENNERY: We hope to be able to present the next pediatric clinical trial report to you within the next few weeks.

DR. MCCORMICK: Thank you.

MS. REEDY: I am going to give you a little exercise. First of all, thank you very much for coming. I hope you enjoy our meeting room. And this is an excellent Committee, I've really enjoyed working with you. I'll pass that on to Karen.

Any of the background materials you would like to take with you, you are welcome to do so. If you would like them shipped to you, put them on the table with your name plate on top of them. If you

would like us to shred them, put them on your chair, please, and we'd be glad to do that, too.

DR. WATCHA: If you want some of them, and if you want the others shredded --

DR. HORLOCKER: Dr. Tobin, did you have one more comment?

DR. TOBIN: Yes, Terese, to the Sponsor. Could I encourage you to at least examine the possibility of doing a toxicity resuscitateability study in a newborn animal model?

It comes to mind, the neonatal piglet or the beagle, because I think in the circumstance, we as the pediatric affiliates here, must applaud the FDA for insisting upon pediatric examination of a drug before it comes to market, since children have always been orphan consumers.

But, without exaggeration, I will tell you that it is an extremely common practice in academic medical centers to use continuous infusion bupivacaine.

This has resulted in significant toxicity, which is now multiply reported in the journals. I

would like nothing better than to have a better drug to use in these small children, to give them perioperative pain and stress relief, as I think it is actually beginning to show improvement in survival with certain diagnoses.

DR. HORLOCKER: Okay. Dr. Tobin, did you have a specific model in mind?

DR. TOBIN: Either the neonatal piglet, which is used in cardiopulmonary resuscitation work, or in the newborn beagle.

Adjourn

DR. HORLOCKER: I would like to thank the Sponsor, the members of the FDA Panel, and my Advisory Committee members. You have all done an excellent job. Thank you. This meeting is adjourned.

(Whereupon, at 3:05 p.m., the 87th meeting of the Anesthetic and Life Support Drugs Advisory Committee was adjourned.)

CERTIFICATE

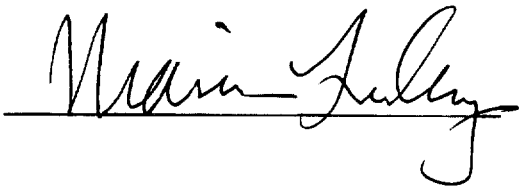
This is to certify that the foregoing transcript in the matter of: 87th Meeting of the Anesthetic & Life Support Advisory Committee

Before: DHHS/FDA/CDER

Date: January 12, 1999

Place: Rockville, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.



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TOTAL OCCURANCES: **16,331**
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CASE SENSITIVE

NOISE WORD LIST(S): **NOISE.NOI**

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WORD RANGES @ BOTTOM OF PAGE

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