IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 11-5048 and 12-2928

WARNER CHILCOTT CO., LLC, Plaintiff, -vs- LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants. WARNER CHILCOTT CO., LLC, Plaintiff, -vs- WATSON LABORATORIES, INC., Defendant.	TRANSCRIPT OF PROCEEDINGS TRIAL

Trenton, New Jersey
October 7, 2013

B E F O R E:

THE HONORABLE JOEL A. PISANO
UNITED STATES DISTRICT COURT JUDGE

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October 7, 2013.

THE COURT: Good morning.

THE CLERK: All rise.

THE COURT: Welcome everybody.

Now, there are a lot of people here. Let's see. I made my own list. We're going to be trying a case about validity. Is that correct?

MR. PAPPAS: Good morning, George Pappas.

That is correct.

THE COURT: As a result, as I understand it, having read the trial briefs, the defendants bear the burden of proof.

MR. PAPPAS: That is correct, your Honor.

THE COURT: So why don't we have them go first and introduce themselves and we'll get moving.

MR. PAPPAS: Very well.

MR. GREEN: Robert Green on behalf of the Lupin defendants.

THE COURT: Mr. Green.

MR. KOCHANSKI: Paul Kochanski, Lerner David, on behalf of the ANDA holder, Amneal Pharmaceuticals of New York City.

THE COURT: I have your substitution of attorney, Mr. Kochanski. I've signed it. Where is Mr. Kennedy?

MR. KOCHANSKI: Mr. Kennedy is not here today, just

I'm here today.

THE COURT: I haven't seen him for awhile. I've signed your order, welcome.

You and Mr. Kennedy will be representing Amneal?

MR. KOCHANSKI: Yes.

MS. CONFOY: Karen Confoy for the defendants as well.

THE COURT: Now, who is Mr. Kinkade? Is he with you?

MS. CONFOY: Your Honor, he is not here today, neither is Heather Kumo, but they may be here.

THE COURT: Filling from time-to-time as local counsel, okay.

Mr. Green, who do you have with?

Miss Szeliga is here. I see you.

Who is Miss Borg-Breen?

MS. BORG-BREEN: Caryn Borg-Breen.

THE COURT: Mr. Wezowski.

MR. WEZOWSKI: Good morning.

THE COURT: Miss Tyrus.

MS. TYRUS: Good morning.

THE COURT: Miss Parekh.

MS. PAREKH: Good morning.

THE COURT: You're all from the same firm?

MR. GREEN: That is correct, your Honor.

THE COURT: Great.

Now, we have Warner Chilcott. Miss Betz is here.

MS. BETZ: Good morning.

Cynthia Betz from McCarter & English.

THE COURT: Mr. Pappas, good morning.

Mr. Block.

MR. BLOCK: Good morning, your Honor.

THE COURT: I just wrote them down in the order I have them here.

Mr. Elikan.

MR. ELIKAN: Mr. Elikan, your Honor.

THE COURT: Nice to see you.

Mr. Sonnenschein.

MR. SONNENSCHEIN: Good morning, your Honor.

THE COURT: Mr. Kennedy.

MR. KENNEDY: Good morning, your Honor.

THE COURT: Where is Mr. Conde?

MR. CONDE: Good morning.

THE COURT: Mr. Cobb.

MR. COBB: Good morning, your Honor.

THE COURT: Who is everybody else?

MR. CONDE: Mr. Jason Leonard and Miss Mary Alice Hiatt.

THE COURT: We'll try to make your stay efficient and as pleasant as possible.

Defendants bear the burden of proof on this so it seems they ought to go first. Does anybody object to that?

MR. PAPPAS: No objection, we agree.

MR. GREEN: Fine with us.

THE COURT: I've read your trial briefs, I have the patent, I have the complaints and the pleadings.

Why don't you tell me how the case is going to be tried, how long you think it will take, what you expect to happen and then we'll get into it.

MR. GREEN: On behalf of defendants, we have three live witnesses. We would expect those to be completed by first part of Wednesday and we have deposition designations for two witnesses. If your Honor desires to have those played, we presently believe that that would be probably no more than an hour and a half of total time.

We've had a conversation with plaintiff's counsel here and we believe that it's quite likely that with the exception of one of plaintiff's witnesses, we can probably be done by Thursday.

THE COURT: With the entire case?

MR. GREEN: With one exception of Dr. Darney who is going to testify on behalf of plaintiffs. As I understand it he's not available until Monday. It's possible, if things move along with the speed we are currently predicting, we would have Monday through Thursday, Friday a down day and resuming with the last day of trial.

THE COURT: How about Mr. Kochanski, what about you,

do you have a presentation?

MR. KOCHANSKI: We're following Lupin, so we we're not going to add anything to it.

THE COURT: Mr. Pappas.

MR. PAPPAS: I agree with Mr. Green's statement. The schedule, we wouldn't necessarily know this, but in the early trial preparation, we agreed their witnesses would go this week and ours would go next week.

We do have two live witnesses ready to put on when the defendants close their case. Our best estimate is that will go through Thursday afternoon, so Friday may be an open day simply because initially when the trial schedule was set and the estimate of witnesses, Watson was a defendant and they had a case, we will be prepared to start -- last time I checked Monday is a federal holiday.

THE COURT: So it is. The most important one I might add, Columbus Day.

MR. PAPPAS: Yes. So we have assumed, although the state of affairs in Washington such as they are now, I'm not really sure what's going on, but we've assumed, at least for planning purposes, unless you tell us that Monday will be a holiday, we'll be begin with Dr. Darney on Tuesday, he'll be quite extensive and Dr. Kagan after that and maybe some deposition testimony, we're not sure.

In any event, we certainly will be able to finish

before Friday of next week, which was the time set aside. That's basically the schedule, your Honor.

THE COURT: We have three live witnesses and some depositions from Lupin?

MR. GREEN: Yes.

THE COURT: And two live witnesses and perhaps --

MR. PAPPAS: Four. We have two this week that will be ready to put on. Once we recognized that the schedule may speed up, we got the witnesses -- we were able to get two of the witnesses from week two into week one. We'll move it as fast as we can.

THE COURT: Whatever you need by way of scheduling, you'll have no lack of cooperation from us. I don't have anything else scheduled for the courtroom unless something comes in, so however the testimony goes, whatever is most convenient for you folks, let us know and we'll be happy to accommodate you.

In terms of having an open day on Friday, I think all of us can benefit from that, we all have other things to do and otherwise you tend to ruin my reputation besides. It's okay with me if Friday is dedicated to other things. Maybe you folks can get home for the weekend. We have Monday off, so.

MR. GREEN: We would enjoy that I think if possible.

MR. PAPPAS: Your Honor, I think Mr. Green and the

parties had agreed that we can do brief openings, limited to 45 minutes so I think Mr. Green will open, I'll open and then I believe you're going to call Dr. Barnhart. Is that correct?

MR. GREEN: That's fine.

MR. PAPPAS: He's in the courtroom so we're ready to go.

THE COURT: I participated in a panel discussion on Thursday afternoon in Chicago as a matter of fact. One of the questions that was put to us is how should parties best present deposition testimony, do we want the transcript just handed up or do we want it made or read into the record, et cetera. I think every judge on the panel agreed that the most effective way to present is to actually play it or read it somehow, that the simple mailing it in technique doesn't get the kind of attention that it should get because it's part of the testimony in the case, so I think you're right about the way you want to go forward.

MR. PAPPAS: Very well, your Honor.

THE COURT: Okay.

MR. GREEN: If I may pass up copies of the demonstratives we'll be using in the opening.

Good morning, your Honor. Robert Green on behalf of the Lupin defendants.

We'd like to begin by giving you a little background on the witnesses that you will hear this morning that will be

virtually of top-level background because during each of their depositions, during each of their periods of testimony, of course, they will be giving you detailed information regarding the backgrounds.

If I can start first with Dr. Kurt Barnhart. Dr. Barnhart is presently the vice chair, clinical research for the Department of Obstetrics and Gynecology. I need to get this correct. That's at the University of Pennsylvania. The last time I introduced Dr. Barnhart to Judge Chesler, I said he was from Penn State and I still have not quite lived that down with Dr. Barnhart. It's the University of Pennsylvania, not Penn State.

His testimony here today is going to be directed toward giving the Court background information with respect to combination oral contraceptives, which is a sub matter of the present litigation and he will address the prima facie case of obviousness that the defendants plan to present.

His testimony will also encompass rebuttal testimony for witnesses that your Honor will, obviously, not have heard at that time. It winds up being we have Dr. Barnhart here, we have an agreement with plaintiffs, we will simply address that so to the extent Dr. Barnhart's testimony is a bit extended, it's an attempt to also address the testimony that we expect your Honor to hear from Dr. Darney, potentially Dr. Kagan and Dr. Thisted and that will come after the initial presentation

THE COURT: Miss Breen, is that what you like to be called?

MS. BORG-BREEN: Caryn Borg-Breen. It's a hyphenated name.

THE COURT: Yes, I know that. I didn't know if you wanted both.

MS. BORG-BREEN: It's actually my husband's last name.

THE COURT: How are you?

MS. BORG-BREEN: I'm doing pretty well, your Honor. At this time, Lupin would call its first witness, Dr. Kurt T. Barnhart.

THE COURT: Dr. Barnhart.

MS. BORG-BREEN: He is a board certified obstetrician and gynecologist who will be presenting testimony on behalf of Lupin supporting prior art.

Permission to approach?

THE COURT: Sure.

K U R T B A R N H A R T, sworn.

THE COURT: Good morning, sir.

THE WITNESS: Good morning.

Can I clarify two important things before we start?

THE COURT: Wait until Miss Borg-Breen gets back. What have you given here?

MS. BORG-BREEN: We have two binders of exhibits and

a copy of the presentation I just handed up.

DIRECT EXAMINATION BY MS. BORG-BREEN:

Q May it please the Court, good morning, Dr. Barnhart. Could you please introduce yourself to the Court?

A Sure. Good morning.

My name is Kurt Barnhart. I'm a professor of obstetrics and gynecology and epidemiology, learning how to use a microphone, at the University of Pennsylvania in Philadelphia.

MS. BORG-BREEN: Can you please bring up DTX108A.

Q Dr. Barnhart, if you could just identify this document for the Court?

A So this is a copy of my curriculum vitae, dated 8/13.

MS. BORG-BREEN: At this time we'd like to move DTX-108A into evidence.

THE COURT: However you want to do this easiest is the best way. In terms of what you're introducing into evidence, if there's an agreement on what it is, just tell me there's an agreement this is admitted and it's in evidence. In other words, you don't necessarily have to go through the drill with every document.

MS. BORG-BREEN: Okay. Would you prefer we just move them into evidence?

THE COURT: Are they all accepted? Are all of these exhibits in by consent?

MR. ELIKAN: It's a very thick two binders. I can't imagine there's going to be a problem.

THE COURT: Why don't we just -- I'll tell you what, disregard everything I just said.

There is no objection, this is in evidence.

MS. BORG-BREEN: Thank you, your Honor.

Q Now, Dr. Barnhart, could you please briefly summarize for the Court your educational background?

A Certainly. I'm currently now at the University of Pennsylvania in Philadelphia, but my journey there was including my undergraduate training at Tufts University in Boston. I went to medical school at Mt. Sinai School of Medicine in Manhattan.

I moved to Philadelphia to do my clinical training and obtained a masters of science degree, also University of Pennsylvania. That's what the MSE stands for, clinical epidemiology and biostatistics.

Q And what is clinical epidemiology and biostatistics?

A Epidemiology is the study of health trends or health statistics. Clinical epidemiology is bringing that to how it might interact with a specific patient, and biostatistics is expertise in statistics but mostly relevant to biology or clinical trials or clinical research.

Q And are you board -- are you board certified?

A Yes, I am. I'm board certified in both obstetrics and

gynecology, as well as the subspecialty reproductive endocrinology and infertility, which basically deals with human reproduction and the hormones that are involved in reproduction, both aiding a woman to help get pregnant and aiding a women to help prevent pregnancy.

Q Are you a practicing clinician?

A I am. I am part of a faculty practice called Penn Fertiity Care at the University of Pennsylvania.

Q What is the focus of your clinical practice?

A My clinical practice makes it easier focuses on gynecology as opposed to obstetrics. My focus is on treating women for their reproductive needs, including helping them get pregnant, helping them avoid pregnancy, dealing with other gynecologic problems, menopause, fibroids, things like that.

Q What percentage of your clinical practice focuses on family planning?

A Probably about 25 percent of my practice would be dealing with family planning directly. However, the hormones are used in oral contraceptives and used commonly for other disorders as well and also interacts with my expertise in fertility in general.

Q Do you prescribe oral contraceptives to patients?

A Yes, I do.

Q Do you conduct clinical research?

A I do. Approximately at least half of my job is to

oversee or conduct clinical research in the field of contraception, early pregnancy and fertility treatment. And that work has been funded over the last 15 to 20 years by the National Institute of Health, as well as by some pharmaceutical companies and also includes both a lot of my own ideas.

Q Have you had any involvement in oral contraceptive clinical trials?

A Yeah. I've had a long history of working with contraception in general, using the same hormones in non-oral routes as well as in developing -- in studying oral contraception as well.

Q Do you have any publications related to your research?

A I do.

Q Approximately how many?

A I think the amount of peer-reviewed publications is in the order of 160 or 170 and probably a third or so of that is directly related to family planning and contraception.

Q Do you hold any editorial positions?

A I do. I am the associate editor for the journal called Fertility and Sterility which focuses on actually my specialty, which is both helping women get pregnant and prevent pregnancy. I held that position for a year and I'm also the former associate editor of a journal called Pharmacoepidemiology and Drug Safety.

Q Dr. Barnhart, do you consider yourself to be an expert in obstetrics and gynecology and clinical epidemiology and biostatistics?
A Yes, I do.
MS. BORG-BREEN: At this time, your Honor, we would like to offer Dr. Barnhart as an expert in the field of obstetrics and gynecology and clinical epidemiology and biostatistics.
THE COURT: Any objection?
MR. ELIKAN: No objection, your Honor.
THE COURT: Do you have any questions?
MR. ELIKAN: No.
THE COURT: Your name is?
MR. ELIKAN: Mr. Elikan.
THE COURT: You are?
MR. BLOCK: Mr. Block, sorry.
Q Please bring up JTX-1.
Dr. Barnhart, do you recognize JTX-1?
A I do. This is the cover page for my understanding is the patent that we're discussing here in this litigation.
Q This is the '984 patent?
A It is.
MS. BORG-BREEN: At this time we move JTX-1 into evidence.
THE COURT: 107?

MS. BORG-BREEN: JTX-1.

THE COURT: You need to keep your voice up. I'm having trouble hearing you. Mr. Elikan is having trouble.

MR. ELIKAN: No objection.

MS. BORG-BREEN: I will certainly do my best to speak louder.

Q Dr. Barnhart, have you formed any opinions regarding the '984 patent?

A Yes, I have.

Q And what is your opinion?

A My opinion is based on the prior art available to the person of ordinary skill, that this patent would have been obvious, the claims in this patent.

Q Have you formed an opinion regarding who the person of ordinary skill in the art is that's relevant to the '984 patent?

A Yes, I have.

Q And do you have a demonstrative you prepared to summarize this?

A Yes.

So my definition of a person of ordinary skill was a physician who understood women's health or specialty training in gynecology, had some experience in understanding the development and research in oral contraception and, of course, also had experience in administrating or evaluating those

opening argument, which is correct. That's the endogenous estrogen the woman makes. The higher the follicle gets, the more estrogen the woman is making in her own body and competing with the estrogen in the pill. When it's suppressed again, you've got a rise and then a fall. You've got a fluctuation.

So if you can limit the fluctuation, because you're limiting the follicle growth, not only are you making the pill more effective, you're making bleeding control better and you're also eliminating side effects that are associated with this estrogen fluctuation. So the goal might have been to make a safer pill, but it clearly is well understood by people in the art that you're not only fixing efficacy, you're improving cycle control and you're improving and lessening side effects.

Q Dr. Barnhart, can you identify some exhibits, some trial exhibits that support what you have been saying about this 24-4 regimen?

A Yeah. So this isn't just my opinion and this is not something that's novel or not taught. This is very well understood.

I put a number of references on the slide to give you that information. For example, under the day seven graph, there's a DTX-477 and DTX-507, which are articles in the literature in the late '90s that describe the problem with the

21-7 pill regimen. It's known ten years before this that the 21-7 might not be optimum.

Then there was a lot of work supported in these other literatures under the four-day pill-free interval. I can read them, DTX-433, 445, 481, 484, 505, 520, 530 and 531 as well as JTX-10 which are, again, examples and not an exhaustive list of a discussion of what the benefits would be to improve the oral contraception by making a shorter hormone-free interval.

Some of these papers, like the ones I bolded, have actual data to show that this is a benefit to the pill. Some of them are widely-publicized review articles saying a menu, a road map saying there are four ways we can improve this pill-free interval. We can shorten it, I'll get to in a second, we can add estrogen to it.

This is exceedingly obvious and well discussed in the physiology, biology, medical literature about the oral contraceptive pill and again, all -- again, I can quote each data, but all in the '80s and '90s, well before the patent-in-suit. This is not new information.

MS. BORG-BREEN: At this time, your Honor, we move DTX-477, 507, 433, 445, 481, 484, 505, 520, 530 and 531 as well as JTX-10 into evidence.

MR. ELIKAN: No objection, your Honor.

THE COURT: Okay.

Q Dr. Barnhart, we discussed at the beginning of your

A They noted in their review that the Pearl Index was the highest or the worse or highest pregnancy rate, unintended pregnancy rate for Lo Loestrin than they had seen before or that they had approved, I should say. I don't know what they've seen.

Q Can we have page two of this document?

Is this the portion of the document where the FDA talks about Lo Loestrin having the highest Pearl Index of any oral contraceptive previously approved?

A That's correct.

MS. BORG-BREEN: Your Honor, we have nothing further for Dr. Barnhart at this time.

THE COURT: Okay.

Let's take a short break.

THE CLERK: All rise.

(Recess.)

K U R T B A R N H A R T, previously sworn, resumes the stand.

THE CLERK: All rise.

THE COURT: Have a seat.

CROSS-EXAMINATION BY MR. ELIKAN:

Q Dr. Barnhart, I handed up binders containing exhibits that will potentially be used in the cross-examination.

Now, Dr. Barnhart, this isn't the first time that you have testified in a patent case, correct?

A That's correct.
Q So you're testifying in this case on behalf of Lupin that the patent-in-suit is obvious, right?
A Correct.
Q This is, in fact, the third time in two years that you you have opined on behalf of Lupin in a trial that an oral contraceptive patent was obvious, right?
A I think -- the first time I was retained was Watson, but I ended up with Lupin, you're correct, but yes, so I have been involved in three trials.
Q In one of those trials, the one you alluded to, at trial you testified on behalf of Lupin that a patent covering the oral contraceptive Ortho-Cyclen would have been obvious at the time of the invention, right?
A That's correct.
Q And you also testified for Lupin that a patent held by Teva covering the Seasonique regimen would have been obvious at the time of invention, correct?
A I think the Court agreed.
Q So you did testify in that case that the patent was obvious?
A Yes.
Q And those three matters are the entirety of the patent cases in which you've testified at trial, right?
A That's correct.

Q So while you've testified time after time after time that patents covering oral contraceptive regimens would have been obvious, you've never testified that any patent covering oral contraceptive regimen was not obvious, right?
A The only three times I testified -- I looked at other patents. The only three times I testified were I concluded they were obvious, yes.
Q And so you never testified that a patent was not obvious covering oral contraceptive?
A I've not testified in court to that affect, no.
Q Dr. Barnhart, can you keep your voice up as much as possible?
A I'll do my best.
Q Thank you so much.
Let's talk about break-through bleeding, shall we?
A Sure.
Q Okay.
You're aware of literature generally saying that as estrogen doses decline, bleeding problems increase, right?
A As a general point, I don't disagree with that but obviously we need to know what we're talking about 21-day pills or 24-day pills because most of that literature is referring to 21.
Q You understand you're on cross-examination now and you're going to be answering my questions?

A Did I not answer your question?
Q I just want to make sure your answer is you are aware of literature saying generally that as estrogen doses decline, bleeding problems increase, right?
A Again, as a general proposition yes, but it's more complex than that.
Q And you've, in fact, written that low dose estrogen combination oral contraceptives have higher rates of bleeding pattern disturbances, right?
A Since you're referring to my record, yes, I was referring to 21 day seven pills when you low dose the estrogen, you can increase the -- might increase the bleeding.
Q Can we have PTX-351?
This is your article, is it not, Dr. Barnhart?
A Yes.
Q The Chapter 8 Contraception, you're one of the authors, right?
A Yes.
Q Can we turn to page 16 of 32?
If you can highlight the bottom of the first paragraph of page 16?
You see in this paragraph that you wrote, so while COCs containing 20 microgram EE may be theoretically safer, this has not been proven and low dose estrogen COCs have higher rates of bleeding pattern disruptions. Is that right?

A Right. That's what I just said.
Q Did I read that correctly, sir?
A Yes.
Q At least in that sentence, you didn't qualify it and say 20 microgram EE products or low dose estrogen COCs have, in general, higher rates of bleeding, except for 24-4 regimens?
A I didn't need to because three sentences above it I refer to the Cochran review, which I know and if anyone looked at it, reviewed evidence which was basically was confined to 21-day contraceptive.
Q I'm just asking you about that sentence right now and you agree you didn't put a qualification in it?
A You restrict me to that single sentence, no, there is no qualification in that single sentence.
Q Okay.

The sentence immediately above, you wrote, compared to the higher estrogen pills, several COCs containing 20 microgram EE resulted in higher rates of early clinical trial discontinuation overall and due to adverse events, such as irregular bleeding as well as increased rates of bleeding disturbances, both amenorrhea or infrequent bleeding and irregular, prolonged frequent bleeding or break-through bleeding or spotting, right?

A That's what that sentence says.
Q Your words, Dr. Barnhart?

A Yeah. I actually want to go back to the sentence you said I didn't qualify.

THE COURT: Hold it, hold it.

Dr. Barnhart, I'm going to ask you to simply listen to the question and answer it. If you start volunteering and qualifying things, this will be a long arduous process.

THE WITNESS: Fair enough.

Q In effect, you would agree with the statement that there is evidence that a 20 microgram EE, there is an increase in incidents of menstrual irregularities compared to higher estrogen dose pills, right?

A That statement is true and referenced appropriately to say where I'm getting that information, correct.

Q And you, in fact, agree, the lower you go in estrogen dose, the more problems you might have with cycle control, right?

A I listened to your question. You said the lower the dose, the more problems you might have, yes, that's true. You might have more problems.

Q You would agree with me as well that women sometimes complain about unscheduled vaginal bleeding while on an oral contraceptives?

A Yes.

Q You've, in fact, seen that in your own practice?

A Yes.

Q You would agree that there are many reasons why women find unscheduled bleeding disturbing, right?
A Yes.
Q Unscheduled bleeding can be uncomfortable in an emotional sense, right?
A I suppose.
Q Well, in fact, it is, right? You know that?
A I don't know what you mean by uncomfortable emotionally.
Q Can we have the OTC trial transcript, page 396, line six through 11.

Sir, I'm showing you your trial testimony from the Ortho Tri-Cyclen Lo case.

"QUESTION: It's uncomfortable?

"A, I don't think it's painful if that's what you're asking me.

"Uncomfortable, I didn't say painful.

"ANSWER: Well, it can be uncomfortable in an emotional sense, yes.

Those were the questions and those were your answers?
A Okay, yes.
Q They were?
A They were.
Q Unscheduled bleeding or break-through bleeding and spotting can be disruptive to a women's sexual life, right?
A Yes.

Q You've, in fact, written about the importance of cycle control?
A I have.
Q You've written that the majority of women and men avoid sexual relations during vaginal spotting, right?
A Correct.
Q And you've written that your data collected by you demonstrate that the majority of men and women avoid sexual relations during both menstruation and vaginal spotting, right?
A Those sound like my words, correct.
Q You agree that many couples may discontinue a contraceptive method because of its affect on sexual frequency or enjoyment, right?
A Yes.
Q You would agree with me as well that unscheduled vaginal bleeding, while taking an oral contraceptive, is one of the more common reasons for oral contraceptive discontinuance?
A I would agree with that.
Q And you recognize Dr. Darney, about whom you testified before, as a leader in the field of contraception, right?
A Yes.
Q And can we have PTX-82, Mr. Brooks?
I'm showing you, sir, a Clinical Guide For Contraception, third edition, Speroff and Darney.

Can we turn to page 94?

And right under the first paragraph, Mr. Brooks, if you can highlight it, please.

Do you see that Dr. Darney wrote, "A major continuation problem is break-through bleeding. Break-through bleeding gives rise to fear and concerns. It is aggravating and even embarrassing. Therefore, on starting oral contraceptives, patients need to be fully informed about break-through bleeding."

You agree with that, right?

A I do.

Q And can we turn to the fifth page of this, Mr. Brooks? If you can blow up the date?

This was published in 2001, right?

A Yes.

Q Part of the prior art, that the person of ordinary skill in the art would have been aware of in 2005?

A Yes.

Q Not from the '70s or '80s, but from 2001, right?

A Yup, yes.

Q You would agree that a POSA, a person of ordinary skill in the art -- can I use the acronym POSA? Would you understand I mean the person of ordinary skill in the art?

A I understand.

Q Would you agree that a POSA in 2005, would have thought

that the most rational approach to prescribing is skilled to recommend an OC that provides a good cycle control?
A Sure.
Q Now, you testified during your direct examination about a slide deck that was discussing the results of an ACOG survey, right?
A I did.
Q That's the American College of Obstetrics and Gynecology?
A Correct.
Q Can we have Barnhart demonstrative 52, please?
This was your slide, taken from that slide deck, right?
A Yes.
Q This is Barnhart 52.
Now, you pointed to a couple of lines here, the highlighted one concerning sample availability, right?
A I did.
Q And two lines above it, patients ask for it, right?
A Yes.
Q You culled out both of those in your direct examination?
A I did.
Q But you didn't mention the first line, did you, cycle control?
A No, I didn't.
Q And this is about asking doctors the factors of

importance to them when selecting a prescription contraceptive, right?
A Correct.
Q And as to cycle control, it's way up there on that list in the number one position, right?
A It is.
Q And there's some commentary underneath that you also didn't mention during your direct examination, right?
A That's correct.
Q And it says, sir, "cycle control appears to, by far to be the most important factor when selected a prescription contraceptive," right?
A I agree with that.
Q You agree with it, but you didn't mention it during your direct examination, right?
A I didn't have a reason to.
Q Now, you've given testimony that a person of ordinary skill in the art, POSA, would have shortened the steroid-free interval and added unopposed estrogen to a 21-7 regimen to compensate for a potential loss of cycle control in efficacy associated with lowering estrogen dose, right?
A I did.
Q But you would agree with me, sir, that a POSA in 2005, would not have believed that an ineffective 21-7 regimen would necessarily become effective by shortening the steroid-free

interval, right?
A That, I'm not trying to quibble, but it would depend on what we meant by effective and why.
Q Can we have Mr. Brooks, Lo Lo dep, 246,24 through 247,9?
(Transcript is played.)
Your words, sir?
A I think I'm saying the same thing now. It's a broad statement but I don't disagree with it.
Q At your deposition?
A Correct.
Q And do you remember telling me as well that if estrogen in the -- the estrogen dose in the combination phase is not contraceptive, you've got a bad pill?
A Say that again, I'm sorry.
Q If the estrogen dose in the combination phase is not contraceptive, you've got a bad pill?
A I believe -- I don't know if I said that or not, but I believe that.
Q You remember telling me as well that the estrogen dose, the ethinyl estradiol dose and in the estrogen-only phase is not growing to compensate for a low dose estrogen in the combined phase if that dose is insufficient?
A Again, I don't remember the exact words, but that's a true statement. I agree with that.
Q On an unscheduled bleeding, you would agree with me that

unscheduled bleeding is more common on progestin-only pills, like the mini pill, as opposed to combined oral contraceptives, right?

A Yes.

Q That's reported in the prior art?

A Yes.

Q Including the prior art that you've considered in this case?

A Correct.

Q Now, you spoke about very briefly, about the '394 patent on your direct examination, right?

A I did.

Q But you didn't mention that it also discussed progestin only pills, right?

A I didn't mention that, no.

Q Can we have JTX-10, Mr. Brooks, column two, lines four through ten?

Do you see that in the '394 patent, you see this statement, there are contraceptive preparations that comprise progestin only. However, the progestin-only preparations have a more varied spectrum of side effects than do the combined preparations, especially more break-through bleeding. As a result, the combined preparations are the preferred oral contraceptives in use today.

Do you see that, sir?

A I see that.
Q And do you agree with that?
A Yes, it's got a reference of 1982 and I don't disagree with that in the broad sense.
Q It continues to be true today?
A Yeah, I think it still does. Progestin only has more break-through bleeding than a combination estrogen, progestin.
Q It's also less effective than the combination oral contraceptive, right?
A Are you asking me a different question, not what was said here?
Q I'm asking you about the progestin-only pill, the mini pill?
A That's debated.
Q Your view is that progestin-only contraceptives are generally less effective than combined oral contraceptives, right?
A In very briefly, in the perfect sense, that's a true statement, but in the real world, they seem to overlap.
Q You, in fact, have written that statement, haven't you, sir?
A Yeah, I'm not disagreeing with that. I'm just giving a little more detail.
Q And you've also said that because as few as one missed pill can decrease efficacy, they are generally less effective

than combined oral contraceptives?
A Yeah.
Q You wrote that in the prior art, right?
A Agree.
Q And I think you mentioned in your direct examination the mini pill is not administered in a 21-7 regimen, right?
A That's correct.
Q It's administered continuously?
A Meaning everyday, yes.
Q Every single day, no placebos, no hormone-free interval, right?
A That's correct.
Q And it's important to take the progestin-only pill, like Micronor, at the same time everyday, right?
A Yes.
Q And mini pills don't inhibit ovulation 100 percent of the time?
A I explained that earlier, I agree with that, yes.
Q Probably closer to 50 percent?
A That may be correct.
Q It is correct, that was what you told me, right?
A I don't have the number committed to memory but that doesn't sound unreasonable.
Q Why don't we we have the Lo Lo deposition testimony, 195, 17 through 24.

Says 50 percent of the women? I don't know the answer off the top of my head, but I was referring to some people consider reliably 50 percent, other people consider reliably a hundred percent. I'm not saying it's not 100 percent, it's probably, probably closer to 50.

Your words to my question, sir?

A Yeah. Yes, I'm saying the same thing now.

Q Okay.

You also discussed a slide, slide 45. Could we have that?

You recall discussing this during your direct examination?

A I do.

Q You testified about 22 different approved products that contain either norethindrone or norethindrone acetate in the years between 1973 and 2005, right?

A That's correct.

Q That's where the number 22 comes from, it's counting those products?

A That's correct.

Q Now, not all of those products are distinct formulations, right?

A That's true.

Q So if we look at your slide 36, you've listed in this and several following slides, those formulations, right?

A That's correct.
Q And if we look at numbers four and eight, they both contain norethindrone at one milligram and 35 micrograms of ethinyl estradiol, right?
A That's correct.
Q And in a 21-7 regimen. So those regimens, Ortho-Novum 1/35 (21) and Norinyl 1 plus 35, they're the same formulation?
A That's correct.
Q You've made no attempt to avoid double counting in coming up with this number 22, right?
A I just counted from the exhibit that Dr. Darney gave of approved contraception.
Q You haven't made any effort to strike out regimens from your 22 that are duplicates?
A No, you counted products, not formulations, correct.
Q You haven't de-duped the formulations?
A I don't think I know what de-duped means.
Q You have taken out the duplicates?
A No, I have not.
Q Okay.
Now, what we can do is count the numbers of the approved regimens containing norethindrone acetate over the last 20 years using these slides, right?
A I'm sure you could.
Q You can do that, you got the slides and am I, in fact,

correct, that between 1985 and 2005, there was one approved oral contraceptive containing norethindrone acetate, that's Estrostep, right?

A Say that again, I was looking at the table. There's one containing?

Q On Barnhart-38, you disclose the one, the single example of an approved oral contraceptive, approved during the last 20 years containing norethindrone acetate, right?

A You're not including norethindrone?

Q I think my question was perfectly clear.

Norethindrone acetate?

A I'll trust your math. I have to look at the chart to see, but I trust if that's what you're saying that it's true.

Q So you can look at your slides, Doctor, if you still have them in front of you.

It's one example, 20 years, one example of an approved oral contraceptive using norethindrone acetate, right?

A With the restrictions you gave, I guess I'll agree with you.

Q Estrostep actually increased the total estrogen dose as compared to Loestrin 1/20, right?

A It did. By virtue of its name, it stepped up the estrogen, yes.

Q So the first pill that's administered in Estrostep is Loestrin 1/20, correct?

A Correct.
Q And that's administered for five days?
A Yes.
Q And then the estrogen content goes up?
A That's correct. My understanding of that pill is that was designed to be a more natural mimic of the cycle, hence the Estrostep was stepping up estrogen.
Q So more estrogen than Loestrin 1/20?
A Yes.
Q I want to talk about some of the general principles that you use in your medical practice.
You're familiar with the philosophy called evidence-based medicine, right?
A Yes, I am.
Q And that's a philosophy according to when you try to make medical decisions informed by data derived from actual research, right?
A Correct.
Q And you're a proponent of evidence-based medicine?
A I am.
Q And you try to follow the hierarchy that's laid out by the principles of evidence-based medicine in your clinical practice?
A That's correct.
Q And you believe that a POSA would have shared your view

on the importance of evidence-based medicine, right?
A Yes.
Q And the primacy of data in the practice of medicine?
A Is that a question or statement, I'm sorry?
Q Right?
The POSA would have shared your view on the importance of evidence-based medicine and on the primacy of data in the practice of medicine, correct?
A Yes.
Q And POSA would generally have tried to adhere to the tenants of evidence-based medicine, correct?
A Yes.
Q And evidence-based medicine posits a hierarchy of evidence, right?
A Correct.
Q And in that hierarchy, randomized clinical trials are generally believed to provide the best evidence, right?
A Correct.
Q This is sometimes called level one evidence?
A That's correct.
Q Level two evidence typically consists of observations, correct?
A Loosely put, observational type of research.
Q Observational trials or research?
A Yes.

Q And level two evidence is less informative than level one evidence?
A Less informative? It's more subject to not reflecting the truth so it can be lower on the hierarchy, yes.
Q You have less confidence in the outcome if it's supported by level two evidence than if it was supported by level one evidence?
A Yes. Slightly different way, you have less confidence that the answer is not influenced by bias or chance, yes.
Q There's also level three evidence, right?
A There is.
Q That's sometimes called expert opinion?
A Often called uncontrolled observation or expert opinion, yes.
Q And level three doesn't have level one or level two evidence or data to support it, right?
A Yes.
Q As a general rule, the person of ordinary skill in the art would give more weight to level one or level two evidence than level three evidence, right?
A Assuming the evidence was available on all those levels, yes.
MR. ELIKAN: Your Honor, we're reaching a new part of the cross. I'm okay with stopping now as sort of the bottom line.

THE COURT: Does anybody object to stopping now?

MR. GREEN: No, your Honor.

MR. ELIKAN: I would just ask that you instruct the witness that he shouldn't talk to counsel now that he's under cross-examination.

THE COURT: Don't speak to anyone about your testimony, Dr. Barnhart, and we'll see everybody tomorrow.

What time do you want to get started tomorrow? Let's try to be out here at 9:15.

MR. ELIKAN: Thank you.

(Trial adjourned until Tuesday morning, October 8, 2013 at 9:15 a.m.)

October 8, 2013.

THE CLERK: All rise.

THE COURT: What can we expect today? We have continued cross of Dr. Barnhart and then what, Mr. Green?

MR. GREEN: Then the defendants will call Dr. Jesse David. He will talk about the patents as we discussed yesterday, precursor to the commercial success discussion.

THE COURT: Okay.

MR. GREEN: Then I believe at that point, your Honor, we expect Dr. Sims to testify, but he will not be available until tomorrow, so we may have a short day today.

THE COURT: Okay.

By way of schedule, there's a weekly judges' meeting on Tuesdays at 1:00, so I'd like to attend, at least in the interest of self-defense. So let's try to go until about 11 or so and then take a short break and go somewhere just before one and see where we are. Okay?

MR. GREEN: Sounds good. Thank you.

Where is the witness?

K U R T B A R N H A R T, previously sworn, resumes the stand.

CROSS-EXAMINATION CONTINUES BY MR. ELIKAN:

Q Good morning, Dr. Barnhart.

A Good moring.

Q Let's talk a moment about your oral contraceptive

prescription habits, shall we?
A Sure.
Q Setting aside the refills, you don't prescribe oral contraceptives for contraception purposes very often, right?
A Correct, not very often. Most of the time people refer to me for other reasons.
THE COURT: Move the microphone.
THE WITNESS: Sure. Move me.
THE COURT: Okay.
Q And the number of prescriptions you write, varies from month-to-month?
A I'm sure.
Q In some months it's only a couple of times?
A That's probably true.
Q That is true, right?
A I guess so, yeah.
Q And never do you prescribe a lot more than ten times per month, right?
A I'm answering your question restricting it to new women walking in the door for contraceptive purposes, but with that caveat, yeah, that's sounds right.
Q Let's turn now to the '394 patent.
JTX-10.
Now, as of April, 2005, there were no commercial embodiments of the '394 patent, correct?

A That's true.
Q Can we have JTX-10 on the screen, column three, lines 37 through 45?
Focusing your attention on that portion that's on the screen, Dr. Barnhart, the '394 patent discusses providing a combination of estrogen and progestin for 23 to 25 consecutive days of a 28-day cycle, correct?
A Correct.
Q And at column four, lines 48 through 50, the patent states a preference for administering a combination of estrogen and progestin for 24 days specifically, followed by four days of placebo, right?
A That's what the screen says, yes.
Q And, Dr. Barnhart, if you'd like, I think you have the same thing on your screen as is shown there so you don't have to crane your neck.
A I appreciate that.
Q Okay.
Now, the '394 patent contains broad potential dosage ranges for estrogen and progestin, right?
A I believe that's true.
Q And looking at column three, lines 37 through 45 again, we see a description of a range of estrogen from one to 35 micrograms of ethinyl estradiol, right?
A That's correct.

Q And a range of one to 35 micrograms of ethinyl estradiol represents a 35-fold difference between the highest and the lowest estrogen values, right?
A I guess that's mathematically correct.
Q That is mathematically correct, right?
A Yeah, I was thinking it overestimates. When you start with one, it makes the percentages seem pretty high.
Q It's a 35-fold difference?
A Yes.
Q And it describes a range of progestin in that same passage of .25 to ten milligrams of norethindrone acetate for 23 to 25 days, right?
A It does.
Q And a range of 250 micrograms to ten milligrams represents a 40-fold difference between the highest and the lowest norethindrone acetate values, right?
A Yes.
Q And you would agree with me, sir, that a POSA, a person of ordinary skill in the art, in 2005, would have understood that not all regimens encompassed by these ranges would be contraceptively effective?
A I would agree with that.
Q For example, a POSA, in 2005, would not have believed that a 24-4 regimen with 250 micrograms of norethindrone acetate and one microgram of ethinyl estradiol would be

contraceptively effective, right?
A I agree.
Q Even though such a regimen would fall within the scope of the regimens claimed by the '394 patent?
A Yes.
Q And in your opinion, that's because that's a very low dose of estrogen and it may not be synergizing with the progestin dose?
A And the progestin dose is low as well, yes.
Q That's true for a variety of the prior art patents that you have looked at, they encompass ranges that are not necessarily contraceptively effective, right?
A Yes.
Q Now, your reasoning in the Ortho-Tri-Cyclen Lo case was that a POSA would make only one change at a time in developing a new oral contraceptive regimen, correct?
A Generally, yes.
Q And in that case, you opined that it would have been obvious for one of ordinary skill in the art to start with the Ortho Tri-Cyclen regimen in generating a new regimen, correct?
A Yes.
Q And then to make only one change at a time so as to determine the results of a specific change?
A Yes.
Q And that's because in science, it is easier to determine

the result of a specific change rather than to make a multiplicity of changes and attempt to determine the attribution of the results to each specific choice?

A I agree.

Q And it's your opinion here as well that a POSA developing a new contraceptive would want to proceed one step at a time?

A That would be a logical thing to do, yes.

Q And that's because if you start modifying two and three and four things at the same time, you don't know whether your intended modification had the effect you expected or not because it's confounded or buried or, perhaps, compensated by other changes that you made, right?

A Absolutely.

Q And when developing a new regimen, there's even more motivation to go slowly, because if you change two things, you won't know whether your idea of changing one of them was good or bad?

A I agree.

Q And because there's always a gamble in a new product?

A I agree.

Q Of course, this problem would be compounded if you make more than two changes, right?

A Yes.

Q Now, you agree with me that when looking to develop a new oral contraceptive, it's logical to start with a regimen that

it had already been proven to have efficacy and acceptable cycle control, right?
A I agree.
Q And that it would be logical to start with a regimen that was commercially successful?
A That would be logical.
Q Let's talk about the '490 patent now.
JTX-12.
Now, in your direct examination, you testified about similarities between the '490 and '940 patents?
A I did.
Q And you had a demonstrative about that, Barnhart slide 30.
Can we have that on the screen please, Mr. Brooks?
That was the slide, right?
A Correct.
Q And because of the similarities, in your view, POSA would read the '940 and '490 patents together?
A I don't know what you mean by reading them together.
Q They would look at them together and examine the similarities just as you did in your slide?
A Yes.
Q Okay.
Let's start with the '490 patent at JTX-12, column three, lines 44 through 47.

Do you see, sir, that the patent says the inventors stated that the object of this invention is to make available a combination preparation with an estrogen content that is as low as possible in each individual dosage unit, but also with a low total hormone content per administration cycle?

Do you see those words, sir?

A I do.

Q Now, the '490 patent also has an example, right?

A Yes.

Q That's the one and only example in this patent, correct?

Can we have, Mr. Brooks, column five, line 50 through column six, line 47.

Do you see that, Dr. Barnhart?

A I see it.

Q That's the one and only example in this patent, correct?

A Culled out like Example 1, yes, but on the column right next to it, it gives you other examples without culling them out in that kind of table.

Q It's the only thing designated and specified as an example, right?

A The only thing with a title of Example.

Q And in that only example in the patent, the order of administration consists of 23 or 24 days of combination pills.

Do you see that, sir?

A I do.

Q Followed by four or five days of unopposed estrogen?
A Yes.
Q And now, let's look at the next column, column six.
Do you see lines 35 through 43, that the inventor specified estrogen dosages, 20 micrograms in the first combination phase for five days, right, Dr. Barnhart?
A That's correct.
Q Twenty-five micrograms in the second combination phase for seven days?
A Yes.
Q And 20 micrograms of ethinyl estradiol in the third combination phase?
A I see that.
Q And so in this example, the inventor's describe giving 20 microgram ethinyl estradiol in the first phase, 25 in the second and 20 in the third, right?
A Yes.
Q But there is no point in the combination phases in this example where the ethinyl estradiol dose is less than 20 micrograms per day, correct?
A In this table, no.
Q I'm sorry?
A In this table, there is not.
Q So while the patent talks about an ethinyl estradiol dose of 15 to 25 micrograms, right, that's the ethinyl estradiol

dose that you mentioned yesterday?
A That's correct.
Q In the only example in the patent, the lowest ethinyl estradiol dose in the combination phase is 20 micrograms?
A I agree with you that's what they put in the table, yes.
Q And in the example, the inventors also didn't provide the same dose of estrogen in the combination phase as in the unopposed estrogen phase, right?
A Again, in that example, they did not.
Q Now, in the example that we have been looking at, the progestin is either Levonorgestrel or Gestodene, correct?
A That's correct.
Q And that's not surprising because the '490 patent specifically calls out Gestodene and prefers Levonorgestrel, right?
A I believe those are the words they use, yes.
Q Now, in column four, there are other progestins listed, correct?
I'm referring now to column four, lines 53 to 62.
A Yes, and also in column five there are.
Q In column four, we see Gestodene, Levonorgestrel, Desogestrel, 3-Keto Desogestrel, Gepirone, Cyproterone acetate, Norgestimate and norethisterone, correct?
A That's correct.
Q And in column five, line 40, the patent says, of the

above-mentioned gestagens, for the first hormone component Gestodene is to be emphasized, also Levonorgestrel is preferred, right?

A I see that, yes.

Q Those are specifically culled out?

A That's correct.

Q In the list of progestins that we looked at in column four, norethindrone acetate does not appear?

A No, I went through that yesterday. A person of ordinary skill would understand that norethisterone is --

Q You understand that you're going to have to answer my questions?

Norethindrone acetate is not in that column?

A Those words are not in that column.

Q It says, norethisterone.

Yesterday you said that was a British spelling of norethindrone acetate, right?

A I think I might have said something like that, yes.

Q You misspoke, right? Norethindrone and norethisterone are equivalents, correct?

A Yes.

Q Okay.

And norethindrone and norethindrone acetate are chemically distinct, right?

A Yes, they are. One has an acetate group and the other

A Yes, often in scientific --
Q Cartoon?
A That's a word we use scientifically all the time to show it's not data, it's an example.
Q Cartoon was the word you used, sir?
A That was the word I used.
Q Let's talk about the '050 patent now.
Can we have DTX-3 and four, Mr. Brooks?
You discussed this yesterday as well, correct?
A I did.
Q Can we have column two, lines 47 through 49?
A Which DTX is this, I'm sorry?
Q DTX-384.
Do you see that at column two, lines 47 through 49, it says, "The present invention relates to chewable palatable oral contraceptive tablets for administering an oral contraceptive agent to human females"?
A That's correct.
Q And the inventor stated, and now I'm at column three, lines 55 through 60, "In principle, virtually any oral contraceptive agent used in human medicine could be employed in accordance with the principles of the invention. The oral contraceptive agent may be an estrogen, a progestin or combination of an estrogen and a progestin."
Do you see that, sir?

A Yes.
Q So this patent isn't about a particular or particular regimen, it's about making any regimen chewable, correct?
A I believe that's true.
Q Now, you pointed to a table in column four providing dosage ranges for contraceptive hormones. You put that on your slide 41, correct?
A I did.
Q Can we have slide 41?
And you focused on a phrase that the dosage of the oral contraceptive agent employed would tend to be that conventionally used in the art for the particular oral contraceptive agent selected, right?
A That's correct.
Q And underneath, you put a table from the patent?
A Yes.
Q Let's look at the ranges on the table.
Do you see there's a column under the heading Broad?
A Yes.
Q Can we blow that up, Mr. Brooks, ethinyl estradiol portion.
The broad ranges, one to 75 micrograms, correct?
A Yes, it is.
Q And 75 micrograms was greater than the ethinyl estradiol dose approved in any oral contraceptive in more than 30 years,

right?
A That's true.
Q And at the bottom end of the range is one, which is a dose that's never been used in a combined oral contraceptive that was marketed, correct?
A I assume that's why they call it a broad range, yes.
Q So there's nothing conventional in the broad range about one microgram or 75 micrograms, correct?
A Well, the conventional doses are in that broad range.
Q One in 75 are not conventional doses, sir?
A Correct. The range is conventional, but the extremes are not.
Q And the preferred range is also provided in this table, correct?
A Yes.
Q And for ethinyl estradiol, it says 20 to 50 micrograms, right?
A That's correct.
Q And do you see that the patent has six different examples, right?
A Okay.
Q At column nine, line 63, that's part of the Example 1.
Do you see that, do you have that, Dr. Barnhart?
A Yes.
Q Do you see that the ethinyl estradiol dosage is 35

A That's also correct.
Q Or with 15?
A In that table, that's correct.
Q Let's turn to the Mircette and the '724 patent now, okay?
A Sure.
Q Now, Mircette is the commercial embodiment of the '724 re-issue patent that you discussed yesterday, right?
A Yes, it is.
Q JTX-14.
A Thank you.
Q Now, Mircette was itself a modification of the 21-7 regimen known as Mercilon, correct?
A That's correct.
Q Mercilon provided a daily dose of 20 micrograms ethinyl estradiol in the 21 days of combined administration, correct?
A That's correct.
Q And 150 micrograms of the progestin Desogestrel?
A That's also correct.
Q The only difference between Mercilon and Mircette was that Mircette modified Mercilon's seven day hormone-free interval by adding five days of unopposed estrogen at the end of the regimen?
A That's correct.
Q So in Mircette, first there's a combination for 21 days?
A Correct.

Q And then two days of placebo?
A Yes.
Q Five days of unopposed estrogen?
A Yes.
Q But the makers of Mircette didn't use unopposed estrogen, they didn't use this modification process to reduce the dosage that's used in the combined phase below 20 micrograms, correct?
A You're asking me about the motivation, I'm sorry?
Q I'm not asking about motivation.
The makers of Mircette didn't use this modification process to lower the dosage of the combined phase for estrogen below 20 micrograms?
A No, they kept the dose the same.
Q And they also didn't use a shortened steroid-free interval to reduce the estrogen dose in the combined phase below 20 micrograms?
A No, they did not.
Q Now, you say that it would have been obvious to provide the same level of unopposed estrogen in the combined and the unopposed estrogen phases, right?
A I did.
Q But you would agree with me that the makers of Mircette did not do that?
A No, they didn't.

Q They put 20 in the combination phase and then ten in the ethinyl estradiol-only phase, correct?
A That is what they did.
Q And as of 2005, Mircette was the only marketed combination product in the world that provided unopposed estrogen in a combination oral contraceptive?
A It was the only one on the market, yes.
Q So as of 2005, there was no marketed combination oral contraceptive that provided the same dose of estrogen in the combination phase as in the unopposed estrogen phase?
A Yes.
Q And you're not aware of any prior art discussing the advantages of keeping the estrogen dose the same in the combination and the estrogen-only phases?
A The only prior art that describes keeping it, refers to keeping it the same would be they want to minimize the fluctuation of estrogen in the cycles, that has been mentioned, but no one's ever said, to answer your question directly, no one ever said keep it the same for biological reasons.
Q There is no prior art discussing any advantages of keeping the estrogen dose in the combination and estrogen-only phases the same?
A Sorry. The specific to your question, no, there was just no art of keeping them both similar to minimize fluctuations.

Q No art, that was the answer to my question?
A With the qualification I gave, yes. There was no art.
Q And you said it would have been obvious to provide unopposed estrogen immediately after the combination phase?
A That's what I said.
Q Dr. Pasquale, the named inventor in the '724 patent didn't do that?
A No, they chose to put the placebo first.
Q And as of 2005, there was no marketed oral contraceptive that provided unopposed estrogen immediately after the combination pills and before the placebo pills, right?
A I believe that's true.
Q Mircette has the placebo pills before the ethinyl estradiol-only pills?
A That's correct.
Q And you've never urged your patients to reverse the order of the pills in their Mircette packages and take the ethinyl estradiol-only pills before the placebo pills?
A I don't think so.
Q Let's talk about the so-called pill scare.

Now, you spoke yesterday about a so-called pill scare and testified that a POSA, a person of ordinary skill in the art, would not have been -- would not have pursued Desogestrel and Gestodene, correct?
A That's what I said.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 11-5048 and 12-2928

WARNER CHILCOTT CO., LLC, Plaintiff, -vs- LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants. WARNER CHILCOTT CO., LLC, Plaintiff, -vs- WATSON LABORATORIES, INC., Defendant.	TRANSCRIPT OF PROCEEDINGS TRIAL

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Trenton, New Jersey
October 9, 2013

B E F O R E:

THE HONORABLE JOEL A. PISANO
UNITED STATES DISTRICT COURT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

S/Joanne M. Caruso, CSR, CRR
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October 9, 2013.

THE CLERK: All rise.

THE COURT: Good morning.

Have a seat, relax.

What shall we do?

MR. BLOCK: Your Honor, plaintiff calls Raymond Sims.

THE COURT: Mr. Sims.

R A Y M O N D S I M S, sworn.

THE COURT: How are you, sir?

THE WITNESS: Fine.

MR. BLOCK: Good morning, your Honor.

THE COURT: Mr. Block, go ahead.

DIRECT EXAMINATION BY MR. BLOCK:

Q Good morning, Mr. Sims.

A Good morning.

Q Could you please tell the Court by whom you are employed?

A I am employed by Charles River Associates, which sometimes goes by CRA for short.

Q And what type of organization is CRA?

A CRA is an international business and economic consulting firm. We provide consulting and advisory services to a variety of clients.

I have a number of different areas, functional practices like economics, finance, competition, intellectual property and we have industry practices like chemicals and

life sciences. I am in the intellectual property practice.
Q If I could direct your attention to plaintiff's exhibit 127, which Mr. Brooks will put on the screen, but whatever is easier, it's also in the binder of exhibits.
Could you please identify exhibit 127 for us?
A Yes. That's a copy of my CV.
MR. BLOCK: Your Honor, I offer plaintiff's exhibit 127.
THE COURT: Who is on this case for the defense?
MR. GREEN: No objection.
THE COURT: This witness is your problem, Mr. Green?
MR. GREEN: It's mine, your Honor.
Thank you.
Q And, Mr. Sims, what is your position at CRA?
A I am a vice-president in the intellectual property practice.
Q And how long have you been a vice-president in CRA?
A Well, technically since 1999.
Q Why do you say "technically"?
A Well, I was a managing director at a small consulting firm that focused on specializing in intellectual property consulting starting in 1999 through 2004.
In 2004, our firm became a part of, in fact, became the intellectual property practice of Charles River Associates and my time of service dates back to when I started with that

other firm in 1999.
Q What is or what was the name of that other firm?
A That firm was Intecap, Intellectual Capital.
Q Could you please tell the Court generally what are your responsibilities at CRA?
A Yes. My responsibilities are primarily to provide consulting assistance to clients in the area of intellectual property, all facets of intellectual property. I have been in licensing negotiations, valuation of intellectual property for a variety of purposes, in developing strategies for commercializing intellectual property and I have been involved in litigation matters such as this.

And in each of those areas, in each of those facets, what we do, what I do is look at the markets for, for the products that are covered by or embody the patents that are at issue to try to assess how much value -- how much of the value of the product is contributed by the patents.
Q And how long have you been consulting in the intellectual property area?
A For about 25 years, dating back to the late 1980s, when I was with Price Waterhouse.
Q So you did intellectual property consulting while at Price Waterhouse?
A Yes. I started my career at Price Waterhouse. I started working, focusing on intellectual property again in the late

'80s when I was a partner at Price Waterhouse and eventually became the partner in charge of the firm's national intellectual property practice.

Q And so then did you do intellectual property consulting at A.T. Kearney, which is the next place, as I understand it, where you worked?

A Yes. In fact, I was actually recruited away from Price Waterhouse to start an intellectual property practice at A.T. Kearney and so I was the head of the intellectual property practice for that firm and also the co-leader of that firm's economic consulting group.

Q Mr. Sims, do you have any advanced degrees?

A Yes, I have a master of business administration from the Kellogg Graduate School of Management which is at Northwestern University at Evanston, Illinois.

Q Sir, where did you attend college?

A My undergraduate degree is from the University of Calgary, which is in Canada.

Q Mr. Sims, have you given any presentations or published any or authored any publications on intellectual property topics?

A Yes, both. I've authored articles that have been published and also given presentations on matters relating to intellectual property.

Q In your work at CRA, have you been asked before to

analyze the issue of commercial success of a patented invention?

A Yes, I have.

Q And how many times, approximately, have you been retained in a patent case to analyze the issue of commercial success of a patented invention?

I guess I should say in a patent case where the issue was the validity or invalidity of the patent.

A Okay. Well, in that context of an invalidity claim, probably about ten or so times, but obviously I look at commercial success of products and patents in the context of patent litigation for determination of royalty damages, for example, but in the context of invalidity, probably about ten times.

Q Have you been re -- have you looked at the issue of commercial success of a patented product where validity of the patent was in question in cases involving pharmaceutical products?

A Yes.

Q And do you know how many times?

A I think probably five or six.

Q Have you ever given testimony before in a case involving the commercial success of an oral contraceptive in a case where validity was an issue?

A Yes, once.

Q I'm sorry, you said once?
A Yes, once.
Q What case was that?
A That was a case involving Loestrin 24. It was between Warner Chilcott and Mylan, I believe.
Q Was that at deposition?
A It was at deposition, yes.
Q And who are you retained by in this case?
A Warner Chilcott.
Q And what were you asked to do?
A I was asked to analyze the information available and to determine whether Lo Loestrin, which is the product that I understand embodies the claims of the patent at issue here, the '894 patent, whether that is a commercial success, is and has been a commercial success.
Q Sir, you said the '894.
Did you mean the '984 exhibit?
A Yes, dyslexic.
Q You and I both, we are both dyslexic.
A Okay.
Q You mentioned that you testified once before on behalf of Warner Chilcott.
Are the Warner Chilcott retentions a major source of revenue for CRA?
A No, they're very small. Certainly well under a percent,

probably under two-tenths of a percent of total revenues for the year.

Q Has CRA ever been retained in a matter where Warner Chilcott was an adverse party?

A Yes, we have.

Q Do you know if CRA was ever retained by a generic pharmaceutical company?

A Yes, we have done work for generic companies as well.

MR. BLOCK: Your Honor, based upon his education, training and experience, we offer Mr. Sims as an expert in intellectual property research and analysis regarding whether a patented product is a commercial success.

MR. GREEN: No objection.

THE COURT: Thank you, Mr. Green.

Go ahead, Mr. Block.

Q Mr. Sims, did you prepare a demonstrative slide to summarize the topics you'll be covering today in your testimony?

A Yes.

Q Can we have slide Sims-2?

Mr. Sims, can you please tell the Court generally the topics we'll be covering and we'll discuss them in more detail.

A Sure. The first topic is to look at Lo Loestrin and determine how it has performed and whether it would be

characterized as a commercial success in the oral contraceptive market.

Then, secondly, to take a look at that performance and that success and determine whether it was driven by primarily by the patents, patented features or whether there was some other factor that was primarily responsible for that success.

Q And are there any assumptions, Mr. Sims, that you are making about the product, Lo Loestrin, vis-a-via the '984 patent?

A Yes.

Q And if we can please have the next slide, slide Sims-3?

Could you please tell the Court what those assumptions are?

A Yes. They are as reflected here. That my assumption is that Lo Loestrin is a commercial embodiment of the oral contraceptive regimens that are claimed in the '984 patent, and that the safety, efficacy and tolerability of Lo Loestrin derived from that regimen, and by safety, efficacy and tolerability, I mean the medical side effects and the benefits of using that regimen.

Q And what is the basis for making those assumptions?

A Primarily it's based on Dr. Darney, the technical expert in this case.

Q And did you review Dr. Darney's report?

A I did review Dr. Darney's report, yes.

Q And going back to slide Sims-2, how do you -- in general, how do you go about analyzing the performance of a patented product in a marketplace?

A Well, you look at the performance of the product, primarily starting with the prescriptions, the volume of prescriptions and the sales revenue and how that product performed relative to other competitors in the marketplace.

Q Could you please tell the Court what types of materials you considered in performing your analysis in this case?

A Yes. I looked at financial information that was produced by Warner Chilcott relating to Lo Loestrin. I looked at information relating to the market, prescriptions, not only for Lo Loestrin, but other competing products, oral contraceptives in the market. That was produced by a third party. We did some of our own independent research.

I read deposition transcripts and I read the expert reports of Dr. Darney and Dr. Kagan and that's the information that I utilized to reach my opinions.

Q So turning to the overview of the oral contraceptive market, did you prepare a slide summarizing your findings regarding this market?

A Yes.

Q If we can please have slide Sims-5?

And before discussing what you found about the market, let's define the market.

What products are you including in the "OC market"?
A The OC market, oral contraceptive market consists or comprises all combination oral contraceptives using estrogen and progestin and, in addition, there are two products, the NuvaRing, which is a vaginal ring that also uses estrogen and progestin, and the Ortho Evra patch, which is a transdermal patch that also uses estrogen and progestin.

The reason that those two products are included in the market, there's a couple of reasons. Number one, they use the same estrogen and progestin.

Number two, they're prescribed in the same way and they have the same cycles as the oral contraceptives.

And, number three, Warner Chilcott considers them to be competing products, products for which if there's a prescription written for NuvaRing or Ortho Evra, that's a prescription that wouldn't be written for Lo Loestrin.
Q And what is the basis for concluding that the OC market has a stable or shrinking market size as reflected on slide Sims-5?
A Well, that's from looking at the prescription data in the market, publicly-available prescription data.

The market has actually stabilized somewhat in the last couple of years, but over the last six or seven years, it's declined from about 89 million prescriptions per year in 2007, to about 84 and a half million in 2012.

That decline is sort of slow, but it's still declining year over year slightly.

Q How do you know this, Mr. Sims?

A I know it from looking at the prescription data that was produced in this case, IMS prescription data.

THE COURT: What does that stand for?

THE WITNESS: You know, I'm not sure it stands for anything, to be honest. It's a third-party company that gathers and provides, actually sells data to companies in the pharmaceutical industry.

It gathers prescription information, some information relating to sales, information relating to some of the marketing spans of the companies, that it gathers through its own sources and it reports that back to the industry.

THE COURT: So it defines the universe of prescription numbers in the OC market?

THE WITNESS: I'm not sure what you mean by "it defines." It reports whatever a company would ask it to report. It gathers all of the information relating to that market and it will provide you a report as a company that whatever information you request.

So if you want prescriptions in the OC market, it will provide that information. If you want prescriptions in some other area, antibiotic market, it will provide that information.

THE COURT: Is it considered reliable in the industry?

THE WITNESS: It is considered reliable. It's really the best information available. Virtually every pharmaceutical case that I've ever been involved in, whether litigation or not litigation, the companies use and rely on data from IMS in order to have a sense for what the market is.

THE COURT: Thank you.

Q And what is the significance of the market, the OC market size being stable or shrinking, to your analysis in this case?

A Well, that means that the market is not growing, so there are a number of competitors, competing products competing for those prescriptions and so since the market is slightly declining, any new product coming into the market, in order for it to make sales or have prescriptions written, is going to have to take prescriptions away from another product.

The pie is only so big and the pie is actually shrinking, so if Lo Loestrin gets a piece of that pie, some other product or other products by definition are going to have a smaller piece of the pie.

Q And the second bullet on slide Sims-5 says, "highly competitive."

What is the basis, Mr. Sims, for saying that the OC market is highly competitive?

A Well, partly because of the fact that the market is

shrinking, as we just said. It's stable or shrinking. It's not a growing market so you can't just get in and take advantage of a market that's taken off.

So the fact there's a limited number of prescriptions and it's declining. The fact that there are well over 100 individual products that are prescribed or are being used, 40 plus regimens that are used and prescribed in the oral contraceptive market, so there's a lot of competitors, a lot of products that are used.

It's a prescription-only market. The product has to be prescribed by a physician in order to be purchased so that makes it a little more difficult to make sales.

And there are other branded and promoted products in the market, so of those 40 plus regimens, some of those are branded and are promoted to physicians.

A large part of the market, in fact, the majority of the market is low-cost generics that are well established and been around for years and they're priced substantially lower so there is price competition in the market as well.

That's also reflected by the impact of the formulary placement because the generic products are not only cheaper for the pharmacies to buy, but they're also cheaper for the patients in terms of co-pays that they have to pay at the pharmacy.

Q And did you prepare a slide with some examples of

products that are in the OC market?
A Yes, I did.
Q If we could have slide Sims-6?
You mentioned that there were hundreds of products and then over 40 regimens.
Could you please explain to the Court the difference between products and regimens?
A Well, there may be more than one product that is used with the same regimen. So, for example, there could be a branded product and a number of generics for that same product, but these -- so these are the regimens that are individual or distinct regimens that are used in the OC market.
Q When you said "these," you're referring to the regimens?
A On this exhibit.
Q Which is slide Sims-6?
A I can't read it.
Q Yes.
A Yes, slide six.
Q And what you mentioned that some of the -- there are other products in the OC market, branded products that are being promoted to physicians.
Which ones on slide Sims-6 were being -- were or are being promoted to physicians contemporaneous with Lo Loestrin being promoted to physicians?

A During this period, over the last couple of years, the products that are bolded or either bolded or are in color, so BeYaz, Generess, Loestrin 24, Lo Loestrin obviously, Natazia, Ortho-Tri-Cyclen Lo, Safyral and Yaz were all promoted, branded and promoted products.

Q And why have you highlighted in color, in addition to Lo Loestrin, why have you highlighted in color BeYaz, Generess, Natazia and Safyral?

A Because those are products that were introduced at about the same time as Lo Loestrin. So they were launched into the market at about the same time, within six months of Lo Loestrin.

Q And if we can go to the next slide, slide Sims-7, could you, for the record, tell us when those products that you just mentioned were launched?

A Yes. So as this indicates, Natazia was launched in July of 2010; BeYaz was launched in October of 2010; Lo Loestrin and Safyral were both launched in January of 2011; Generess was launched in May of 2011.

Q And going to the next slide, Sims-8, let's talk about the prescriptions for Lo Loestrin.

Q Forgive me for asking the question, but why are the number of prescriptions informative as to whether Lo Loestrin is a commercial success?

A Well, because the number of prescriptions reflects the

demand for Lo Loestrin, a demand for the product.

Physicians write prescriptions and those prescriptions are filled in the marketplace, at pharmacies. The indication is that there are a lot of physicians prescribing, writing a lot of prescriptions for Lo Loestrin.

Q And did you prepare, Mr. Sims, a demonstrative showing what your analysis -- what you found about Lo Loestrin's performance in terms of total prescriptions?

A Yes, I did.

Q Could we please have slide Sims-9?

What did you find with respect to Lo Loestrin's total prescriptions?

A Well, I found that the number of prescriptions, the total prescriptions has been significant and it's been steadily increasing since the launch of the product in January of 2011.

In January, there were about 1500 prescriptions that first month. That increased after a year to about over 125,000 prescriptions and by January of 2013, two years into the market, over 225,000 prescriptions.

So there have been a substantial number and it's been steadily increasing over the first two years of the product in the market. And there have been over three million prescriptions written, filled for Lo Loestrin since its launch in January of 2011.

Q This slide ends at January, 2013.

Why is that?
A Well, because at the time we prepared the report, we only had data for a limited time period, through the first quarter of 2013. This particular data only went through January of 2013.
Q And what is the source data upon which slide Sims-9 is based?
A This is based on IMS data that was produced in this case.
THE COURT: Excuse me.
Is this worldwide or American market?
THE WITNESS: This is U.S.
THE COURT: Thank you.
Q And, Mr. Sims, if you can please look at PTX-168, it's easier to do it in the book.
Do you recognize this document?
A Yeah. This is a schedule from my report and it is the schedule that basically summarizes the IMS data that was produced in the case.
It has the information for each year starting in October of 2005, going through January of 2013.
MR. BLOCK: Your Honor, I offer plaintiff's exhibit 168.
MR. GREEN: No objection, your Honor.
THE COURT: All right.
Q Mr. Sims, did you also look at new prescriptions or

NRX's?
A I did.
Q And what is an NRX?
A NRX is a new prescription, so it's not a refill. It's either a new patient or it's a new prescription for an existing patient. So it's a re-authorization of a prescription, perhaps, after an annual examination, but it's a point in time, it's a prescription that's written where there's a decision being made by the physician specifically to prescribe that product.
Q So does IMS track or record NRX's separately from total prescriptions?
A Yes.
Q And am I right that NRX's are a subset of the total prescriptions for a product?
A That is correct, yes. Total prescriptions includes all new prescriptions.
Q And did you prepare a slide summarizing your findings about the NRX's for Lo Loestrin?
A I did.
Q Could we please have slide Sims-10?
And, Mr. Sims, what did you find with respect to the new prescriptions or NRX's for Lo Loestrin?
A Well, I saw similar patterns as we did with the TRX. Again, they have been substantial, significant and steadily

increasing since the launch of the product in January of 2011.

For the new prescriptions, obviously in January, they were all new so it's still about 1500 prescriptions. In January of 2011, by -- sorry, by January of 2012, that number exceeded 50,000 and by January of 2013, that number exceeded 90,000, so there's been a steady increase in the number of new prescriptions for Lo Loestrin since its launch.

Q And what is the source data for slide Sims-10?

A Again, it's the NRX prescription data reported by IMS that was produced in this case.

Q And, Mr. Sims, if you could please look at PTX-162.

Do you recognize this exhibit?

A Yes. That, again, is a schedule from my expert report that is a summary of the IMS NRX data for the OC market from October of 2005 through January of 2013.

MR. BLOCK: Your Honor, I offer plaintiff's exhibit 162.

MR. GREEN: No objection.

THE COURT: Any objection?

MR. GREEN: No objection.

THE COURT: These numbers, Mr. Sims, is that -- that's in prescriptions, these are not dollar amounts?

THE WITNESS: No, these are the numbers of prescriptions, that's correct.

THE COURT: Thank you.

Q Mr. Sims, we can talk about dollar amounts.
Did you also look at sales revenue from Lo Loestrin?
A I did.
Q Can we have slide Sims-11?
And --
THE COURT: Excuse me.
If you can look at 162, do you have that?
THE WITNESS: You know, I was trying to find it in my binder here.
Yes, I have it.
THE COURT: So this is the total U.S. contraceptive market monthly new prescriptions by product, right?
THE WITNESS: Correct.
THE COURT: So for 2005, I'm just trying to understand the methodology here. For example, we have the first page is 2005, and it shows October through December?
THE WITNESS: Correct.
THE COURT: It has a total on the bottom line, total contraceptive market of 6.4 million?
THE WITNESS: Correct.
THE COURT: What is that?
THE WITNESS: That is the total number of new prescriptions that were --
THE COURT: So for October of '05, there were 2.2 million new prescriptions?

THE WITNESS: Correct.

THE COURT: And where is Lo Loestrin?

THE WITNESS: Lo Loestrin was not introduced until 2011. If you go back -- actually, I don't have the other -- if you go back to page seven of that exhibit, you'll see Lo Loestrin is about the sixth.

THE COURT: That was the 1500 that you told us about?

THE WITNESS: Correct.

THE COURT: I see. Thank you.

MR. BLOCK: Thank you, your Honor.

THE COURT: Forgive me, this is the first time I'm seeing these tables so I'm trying to get this.

MR. BLOCK: Thank you.

Q Your Honor asked about sales revenues so let's talk about sales revenue for Lo Loestrin.

Did you prepare a demonstrative summarizing your findings about Lo Loestrin's sales revenues?

A Yes, I did.

Q Can we please have slide Sims-12?

Can you please tell the Court, Mr. Sims, what you found with respect to Lo Loestrin's sales revenue?

A Well, I found, as I would have expected based on the prescriptions, that, again, the sales were significant and steadily increasing for the most part over the first two years the product was in the market.

The net sales were a little under ten million and in the first quarter of 2011, and increased to over 50 million, just over 50 million the first quarter of 2013.

Over the first 27 months that Lo Loestrin was in the market, it generated over $250 million in net revenues for Warner Chilcott, about 200 of those in the first two years and based on this information and based on other information that I've seen, it would appear that the sales in 2013 are going to probably be about 250 million as well, if they continue on this.

Q What do you mean by "net sales"?

A Net sales are the grows sales less deductions for things like cash discounts, wholesaler fees, returns and Medicaid reimbursements, things like that.

Q And what data is slide Sims-12 based upon?

A This is based on financial information that was produced by Warner Chilcott in this case.

Q And if we can please look at exhibit PTX-220?

Mr. Sims, do you recognize plaintiff's exhibit 220?

A Yes. This is the first page of it, but this has grows and net sales for Lo Loestrin for the years 2011 and 2012 and then --

Q Mr. Brooks, can we please have the next page of plaintiffs exhibit 220?

A Right. So now you can see it by year. This is for 2012,

the quarterly sales. We also have quarterly sales for 2011 in this same exhibit and also -- well, I guess it's another exhibit for 2013.

Q So if we can quickly look at plaintiff's exhibit 221, do you recognize plaintiff's exhibit 221, Mr. Sims?

A Yes, this is the same information for the first quarter of 2013.

Q So it came in two increments?

A It came in two increments, yes. Two separate documents.

MR. BLOCK: Your Honor, plaintiff's offer exhibit 220 and 221.

MR. GREEN: No objection.

THE COURT: Where it says "grows sales", 63,272 --

THE WITNESS: That's millions. These are in thousands.

THE COURT: I'm sorry, it says it right there, forgive me.

Q And, Mr. Sims, you said that based on other information about sales -- I'm sorry. Start that over.

If we go back to slide Sims-12, that ends at the first quarter 2013.

Why is that?

A Because, again, at the time we prepared this report, that was the only information we had available.

Q Do you know, has Warner Chilcott publicly reported

results of Lo Loestrin sales for the second quarter of 2013?
A Yes, they have.
Q And what were the reported net sales for Lo Loestrin for the second quarter of 2013?
A $59 million according to their 10-Q report.
Q So is that an increase from the first quarter?
A Yes, it was just under 52 million for the first quarter and it's 59 million for the second quarter, so it's continuing that upward trend.
Q Do you know how Lo Loestrin's prescriptions and sales revenues compare to Warner Chilcott's prelaunch projections for the product?
A Yes. They exceeded the prelaunch projections.
Q How do you know that?
A Well, I know that for a couple of reasons. Number one, I read it in the deposition transcript of a sales -- a brand manager for the Loestrin product for Warner Chilcott, but I also confirmed it by looking at projections in a prelaunch Brand Plan and comparing those projections with the actual sales.
Q Did you prepare a demonstrative comparing the projection to the actual performance of Lo Loestrin?
A Yes, I did.
Q Can we please have slide Sims-13?
What did you find with respect to how Lo Loestrin

actually performed versus Warner Chilcott's prelaunch projections?

A Well, as I indicated, they exceeded their prelaunch projections.

On the left, in the purple, is the number of prescriptions and in the prelaunch projection, Warner Chilcott expected that it would have about, I think it was about 265,000 prescriptions. In reality, there were more than 700,000 prescriptions filled for the product in 2011.

As it relates to revenue, Warner Chilcott was projecting revenue of about $24 million. In reality, in the first year, 2011, it generated revenue of about $62 million.

So it far exceeded its projections based on its prelaunch expectations.

Q And the revenues are net sales revenues?

A Those are net sales, yes.

Q And what is the significance of the fact that Lo Loestrin exceeded its prelaunch forecasts?

A Well, Warner Chilcott launched the product with expectations. I mean, it believed that the product would be a success and it had expectations to warrant or justify launching the product.

Its actual sales exceeded those expectations. It was more successful than Warner Chilcott expected or anticipated at the time or before it launched the product. So it's done

better than it expected.
Q Given the amount of Lo Loestrin sales, Mr. Sims, does it surprise you that at least two generic companies are seeking FDA approval to sell generic versions of Lo Loestrin?
A No, it doesn't surprise me at all. Obviously, they want to get a piece of those sales.
Q The next slide, Sims-14, I think the next subtopic on performance is Lo Loestrin's performance versus the competition.
How do you go about analyzing that?
A Well, we've seen the actual, the absolute prescription numbers so we know what they are.
The question is, how do they compare with other competitors? What we do is look at the share of the market that Lo Loestrin has relative to those other competitors.
Q Did you prepare a demonstrative summarizing your findings about market share?
A Yes.
Q Can we please have slide Sims-15?
Mr. Sims, what did you find with respect to Lo Loestrin's market share in the first 27 months since its launch?
A Well, I found that, again, similar to the number of prescriptions, since the market is actually declining, just as the numbers of prescriptions have been growing, the market

share has been growing as well. It's been significant and growing.

It started, obviously, very low in January of 2011, and the new prescriptions, which are in the purple bars, have -- sorry, the total prescriptions, which are in the purple bars, the market share has increased to a little over three percent, 3.2 percent of the total OC market by January of 2013.

For new prescriptions, which are the new prescriptions being written, the share of those new prescriptions has increased to almost four percent of the total market for new prescriptions.

Q Given your analysis of this market, is it common for a product to have a market share of over three percent?

A In this market, no, there are very few products that have a share of over three percent. As I indicated earlier, there are over 100 products.

In fact, in March of 2013, there were 144 products for which there were prescriptions filled.

Q And where does Lo Loestrin rank in terms of the market share out of those 144 products, in terms -- is it the first, the second?

A Well, I think it's the seventh. It's in the top ten. There are, I think, my recollection is that there are -- of those 144 individual products for which prescriptions were filled, there were six products that had more than, more

prescriptions filled in total than Lo Loestrin.
Q And what is the source of the data that you're depicting on slide Sims-15?
A That is from IMS data that was produced in this case.
Q And is this also based on the schedules from your report that we've looked at already today?
A Yes. I do have a schedule that contains this information. Yes.
Q Mr. Sims, does a product have to be the number one product in a market in order to be a commercial success?
A No, not at all. I mean, that doesn't make any economic sense at all. There could be, in any give market there could be a number of products that are successful. It would be ridiculous to say that in the automobile market, there's only one successful product. Clearly, there are many and just about any given market, there are more than one successful product.

Any product that is in the top, one of the top selling products, generates over $250 million in sales in a two-year period and is on track to generate 250 million in the next year, I think would be considered a success, even if it's not number one.
Q Did you do any other assessment of Lo Loestrin's performance versus the competition?
A I did. I also looked at Lo Loestrin's performance

relative to those other four products that were introduced at about the same time.

Q Why did you look at that?

A Well, because those products, as I said, were introduced at about the same time and they were competing for prescriptions just as Lo Loestrin was, trying to take prescriptions away from other established products in the marketplace.

Q And did you prepare a slide summarizing your findings about how Lo Loestrin compared to those other products?

A I did.

Q Could we please have slide Sims-16?

What did you find, Mr. Sims, with respect to Lo Loestrin's performance as compared to that of Safyral, Natazia -- Natazia, Generess and BeYaz.

A Well, I found Lo Loestrin outperformed each of those products. In other words, the number of prescriptions that were written and the share of the market it attained was significantly greater than each of those other four products that were introduced at around the same time.

For example, this data reflects the number of prescriptions and the share in the 24th month after introduction. So it's sort of on a comparable time period.

In the 24th month, Lo Loestrin had generated or achieved about a three percent share of total prescriptions.

BeYaz was substantially lower than two percent. Generess was just over one percent. Natazia and Safyral were well under one percent.

So Lo Loestrin was about twice as the number of prescriptions and shares BeYaz; almost three times Generess and over ten times Natazia and Safyral, far exceeding their performance.

Q And what does this -- what does that finding mean with respect to how Lo Loestrin's doing in the market?

A Well, again, these are all products that were introduced, being promoted to physicians for prescribing and the indication is that those physicians believe that Lo Loestrin -- they preferred Lo Loestrin for their patients over the other four products that were introduced at about the same time.

Q I may have misheard you, but I thought you said these prescriptions believe?

A The number of prescriptions indicates that the physicians preferred Lo Loestrin to these other products.

Q And what is the source data for slide Sims-16?

A This is, again, TRX data from IMS that was produced in this case.

Q And if we could please look at exhibit PTX-179.

Mr. Sims, do you recognize this?

A Yes. This is a schedule that I prepared. It's in my

report.

That indicates by month after launch the number of prescriptions and the total market and, therefore, the market share represented by those prescriptions for each of these products over the first -- I think I actually go through 27 months, but the schedule -- the exhibit only had 24 months.

MR. BLOCK: Your Honor, I offer plaintiff's exhibit 179.

MR. GREEN: No objection, your Honor.

Q So turning back to the list of topics, slide Sims-17.

I guess before we talk about whether the patented features have driven Lo Loestrin's performance, can you just briefly summarize, Mr. Sims, your findings about Lo Loestrin's performance in the market?

A Yes. I mean, I believe the performance was very strong. Obviously, it had very significant and steadily increasing prescriptions. It had significant and increasing sales, net sales. It was one of the top performers in the market.

The market share that it achieved was significant and, again, increasing based on the increasing number of prescriptions.

It performed well relative to other new products that were introduced in the market at about the same time. Not only its market share was strong relative to them as well as relative to all the other products and so overall, I consider

this to be a commercial success.
Q So then how do you go about assessing whether the patented features of Lo Loestrin are what is driving the commercial success performance that you observed?
A Okay. Well, what I've done, what we do is I look at, first of all, the nature of the market and how the product is sold, how the product is purchased.
In particular, who are the decision makers, who's driving the decision maker that are driving those purchases. In this case, we know that's largely physicians who prescribe the product.
Q What is the significance of the role of the physician as decision maker in this market?
A Well, it's significant because physicians are obviously medical professionals and they evaluate their patients to determine what their needs are, what their medical history, what their needs are. They are aware of or they try to be aware of the products that are available to prescribe to their patients and they make decisions based on what they believe is the most effective, the best treatment, medication in this case, oral contraceptive for their particular patient, patients or patient population.
Q And what is the basis for that conclusion?
A Well, it's based on my own experience from working in the pharmaceutical industry and a variety of projects, but also

based on my review of Dr. Kagan's expert report and she indicated, as I would have expected, that physicians make prescribing decisions based on the performance of the drug, the product itself, not other things.

So they prescribe what's best for their patients and if it meets the needs of their patients and they're not influenced by marketing or other things of that nature, even though doctors may give out samples, for example, to patients, they'll do that in order to find out how the patient may react to a product and if it works, then they may prescribe it. If it doesn't work, obviously, they wouldn't prescribe it.

Q You mentioned marketing.

Now, Lo Loestrin is marketed to physicians?

A Lo Loestrin is marketed primarily to physicians. In fact, there was very little consumer advertising or marketing of Lo Loestrin. It was very limited and at the very beginning of the launch of Lo Loestrin.

Q And in your assessment, what is the purpose and impact of the marketing of the product to physicians?

A Well, the purpose of the marketing to physicians, certainly in the case of Warner Chilcott and Lo Loestrin, is to educate physicians, make them aware of the nature of the regimen, what the regimen is, what the benefits are, how it was -- the studies that were done to, the clinical studies that were done to basically get the product approved, showed

them what the benefits are and show what patients might benefit from using that particular regimen.

So it's informational, it's physician education as opposed to image advertising.

Q And could you give us an example of the physicians' education, the types of physician education marketing that Warner Chilcott did?

A Yes. Well, for example, in one of their brand plans, they had a document that was used by sales force when they detailed the product.

Q Can I stop you there?

Can we have slide Sims-18?

A It's hard to read.

Q Yes. There's some glare on the screen so it might be better in your book.

A What was the exhibit number?

Q PTX-209.

A Okay.

Yes. So this is an example of visual aid that was used by the sales force when they were detailing the product to physicians. What it shows is that what they're doing is they're educating the physicians about the regimen, what the regimen is, half the estrogen and how it works. They're talking about the performance, the protection that it has, it's been proven to be effective.

They're also talking about the fact that it has half the estrogen and they're talking about the fact that when it says all the confidence, you can't read it there, but they're talking about the clinical studies that were performed, clinically proven and studied in a certain population of women so physicians can see how it's performed and what it is and use that when they're making decisions about prescribing oral contraceptives for their patients.

Q Just going back to the previous slide, Sims -- I lost track of the numbers. Seventeen was the previous?

A Yes.

Q And more generally in terms of marketing, Mr. Sims, did you consider the amount of money that Warner Chilcott spent in promoting Lo Loestrin as part of your analysis?

A Yes, I did.

Q And what did you find?

A Well, I found, as I would have expected, that at the very beginning when it was launched, there was a fairly significant marketing spent, but I also found was that most of the market spent, the majority of it was for sales force and for physician field education.

So as I said, the sales force is predominantly or primarily educating, communicating the benefits, the existence of and the benefits of the product.

So most of that marketing is really physician

education, it's communicating the benefits of the product, it's communicating what the product is, what the regimen is, how it works so that the physician will be aware of it.

Because for any product, if it's not a commodity product, a certain amount of marketing is required to make the consumers aware that the product exists. If they don't know it exists, then they can't buy it.

Similarly, if a doctor doesn't know a product exists, a drug exists or if they don't know what it does or how it works or where it's effective, they wouldn't be able to prescribe it for their patients.

So in order to communicate the regimen, communicate the benefits of the product to physicians, that requires detailing, sending a sales force out, having focus groups and so forth to talk to the doctors about the product itself. That's where most of the money was spent by Warner Chilcott.

Q And do other companies in the oral contraceptive marketplace expend resources detailing and educating physicians?

A Yes, everyone does. You have to do it, otherwise the doctors wouldn't know about the product.

Q The last bullet --

THE COURT: Excuse me.

Along those lines, have you reviewed any data to indicate whether or not Warner Chilcott's expenses in

marketing are comparable to the expenses of other producers?

THE WITNESS: Well, again, the only data available for other producers is through IMS, which they gather -- they don't gather directly from the source. So I have the information directly from Warner Chilcott as to what they spend and to where they spend it. I don't have that same information from the other manufacturers.

I do have some IMS data that indicates, to the best of their ability, where they can gather data where they spent money and I did find that -- I don't recall specifically the mix, although I have it in my report, where they spent money direct to consumer advertising and so forth.

But clearly, other competitors have large sales forces, Bayer is one of the main competitors, they have large sale forces. They spend a lot of money on detailing. Others actually spent more money on direct to consumer advertising than Warner Chilcott did.

But in total, you know, again this was a new product. It was just launched so at the very beginning Warner Chilcott spent quite a bit, but over the time period relative to these other products, it really didn't spend more. In fact, it spent less on a per prescription and per dollar sales basis than those other branded products did.

THE COURT: That leads to my next question.

What is the measure by which you would determine that

Warner Chilcott spent a lot or about right or a little on marketing, detailing, as you use the phrase?

THE WITNESS: Obviously, if the amount that they spent substantially exceeds the revenues that they're generating, then that would certainly be an indicator of that and that's not the case.

Obviously the first month it was because they had very few sales in the first month and the spend is decreasing over time. It's also consistent with what they spent on other products in the past.

So, for example, their Loestrin 24 product, the spend for Lo Loestrin is consistent with that.

THE COURT: Thank you.

Q And, Mr. Sims, in your experience in the marketplace, is there -- do the sales drive the marketing budget or does the marketing budget drive the sales?

A The sales drive the marketing budget, although again, at the very beginning when a product is launched, obviously they make an assessment as to what they think the sales will be and they launch the product and spend marketing dollars at that point before the sales are made.

Once the product is in the market and sales are being made, typically the pharmaceutical companies will set their marketing budgets based on the level of sales as a percent of sales.

Q If a product is not performing well in the market, in your experience, does throwing or expending a whole additional amount of resources promoting it, turn the product around?
A No, because as Dr. Kagan indicated, physicians don't prescribe products based on marketing. They prescribe products based on performance.

It doesn't matter how much you market a product, if it doesn't work, if it doesn't perform, prescriptions won't be written, doctors won't prescribe.
Q How does pricing impact your analysis in this case?
A Well --
Q Let me ask first, why do you also look at pricing?
A Well, we look at pricing to see whether or not the sales were as a result of the product being sold at a substantially lower price than other competing products in the market. If that's the case, and in a case like this, we're talking about patent validity, if the patent isn't what allowed you to sell it for a lower price, than the inference could be that it was the price that was driving the sale as opposed to the benefits of the patent.

So one would want to confirm that these sales aren't being driven because the product is being sold at a very low price.
Q And what did you find with respect to the pricing of Lo Loestrin?

A Well, I found exactly the opposite was true. In fact, the Lo Loestrin is priced, both at wholesale and at the pharmacy, substantially higher than most products in the market because most of the products are generic.

Even as it relates to other branded products, Lo Loestrin is priced consistent with those other branded products, both in terms of wholesale pricing and in terms of where they fall out in the formulary and the co-pays that would be required at the pharmacy.

Q And what is the significance of that finding with respect to whether Lo Loestrin's patented features are the reason for its performance?

A Well, the conclusion is that it can't be price that's driving the sales because the price is no lower, in fact, higher than most of the other products in the market.

Q Mr. Sims, before we wrap up your findings with respect to Lo Loestrin, I understand that you were also asked in this case to examine the IMS data for market share for certain types of products from 1995 through 2005 time frame?

A I was.

Q Okay.

And can we please have PTX-188?

So this is prior to the launch of Lo Loestrin?

A This is prior to the launch of Lo Loestrin, correct.

Q And am I correct that you were asked to examine the

number of total prescriptions for certain types of products in the market from 1995 through 2005?
A Yes. There were a number of products that were identified to me and I was asked to determine the number of prescriptions for those products in total and what those were relative to the entire number of prescriptions in the market.
Q Does plaintiff's exhibit 188 contain the results of that analysis?
A Yes, it does.
Q On the subsequent pages of plaintiff's exhibit 188, does it list the products that you're including in what's referred in the summary as norethindrone acetate market share?
A Yes. There are literally two pages of products that were included in this.
Q What is your understanding of the common feature of the products that are included under the broad heading "Norethindrone Acetate Market Share"?
A My understanding is somewhat limited, but my understanding it has something to do with the fact it's a first-generation progestin.
Q Do you understand that those products include ones that had norethindrone instead of norethindrone acetate?
A Some of them did, yes.
Q And in terms of which products to include, is that something you were --

A I was told which ones to include and they're listed on the next two pages.

MR. BLOCK: I offer plaintiff's exhibit 188.

THE COURT: Any objection?

MR. GREEN: No objection, your Honor.

Q Then if we can please have slide Sims-19?

Mr. Sims, if you could please just summarize for the Court what you found with respect to your analysis of the commercial success of Lo Loestrin?

A Sure. Again, I concluded that it was a commercial success. There were significant and steadily increasing prescriptions and sales revenues over the first two years, 27 months of sales in the marketplace.

Over three million prescriptions since launch, over $250 million in net sales and another 59 million in the second quarter of 2013; significant growth in their market share, one of the top selling individual products in the market, greater market share than other competitors that were introduced at about the same time and based on all of that, I concluded that the product is a commercial success and, more importantly, my conclusion is that it was not -- that success was not driven because other factors, such as marketing and pricing, as I've described earlier in my testimony.

The way this market works and the way the prescriptions are written, it was not marketing and it was not pricing that

was responsible for that success.

MR. BLOCK: Your Honor, I would like to offer, include in the record, as a demonstrative exhibit, slide Sims one through 19.

MR. GREEN: No objection.

MR. BLOCK: Thank you.

I think Mr. Green has some questions for you.

THE COURT: Why don't we take a short break?

THE CLERK: All rise.

(Recess.)

THE CLERK: All rise.

R A Y M O N D S I M S, previously sworn, resumes the stand.

THE COURT: Thanks, have a seat.

Mr. Green.

CROSS-EXAMINATION BY MR. GREEN:

Q Good morning, Mr. Sims.

A Good morning.

Q When you were discussing pricing for Lo Loestrin, I don't believe that you mentioned the comparative price between Lo Loestrin and Loestrin 24 is correct, is it not, that they're priced exactly the same at the wholesale level?

A That's correct.

Q And in your testimony, you indicated, I believe, that the decision maker, in your view, is the physician as opposed to

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 11-5048 and 12-2928

WARNER CHILCOTT CO., LLC,

Plaintiff,

-vs-

LUPIN LTD. and LUPIN PHARMACEUTICALS, INC.,

Defendants.

WARNER CHILCOTT CO., LLC,

Plaintiff,

-vs-

WATSON LABORATORIES, INC.,

Defendant.

TRANSCRIPT OF PROCEEDINGS

TRIAL

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Trenton, New Jersey
October 10, 2013

B E F O R E:

THE HONORABLE JOEL A. PISANO
UNITED STATES DISTRICT COURT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

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October 10, 2013.

THE CLERK: All rise.

THE COURT: Good morning.

Have a seat.

Are we ready to go, Mr. Conde?

MR. CONDE: Your Honor, plaintiffs call Dr. Ronald Thisted.

R O N A L D T H I S T E D, sworn.

THE COURT: Good morning, sir.

THE WITNESS: Good morning.

DIRECT EXAMINATION BY MR. CONDE:

Q Good morning, Dr. Thisted.

Could you please turn to plaintiff's exhibit 129 in your exhibit book?

A Yes.

Q And what is plaintiff's exhibit 129?

A Exhibit 129 is my curriculum vitae as of February of this year.

MR. CONDE: We offer plaintiff's exhibit 129.

MR. GREEN: No objection, your Honor.

Q Can we please put up a summary of your CV as Thisted slide one?

Dr. Thisted, we'd like to talk a little bit about your background and educational experience.

Could you please tell us about your educational

background?
A Yes. I have a bachelor's degree in mathematics from Pomona College and a master's degree and Ph.D. degree, both in statistics from Stanford University in 1977.
Q Can you please tell us about the academic positions that you held since you have been at the University of Chicago?
A Yes, since 1976, after I got my Ph.D., I joined the faculty at the University of Chicago, initially in the Department of Statistics.

In the middle 1980s, I joined the Department of Anesthesia and Critical Care in addition to statistics and medical school and then when the Department of Health Studies was founded in the middle 1990s, I joined that department as well.

From 1999 until the end of 2012, I was chairman of the Department of Health Studies which comprises the disciplines of biostatistics, epidemiology and health services research.
Q Dr. Thisted, are you currently teaching courses?
A Yes. I teach courses to undergraduates, graduate students, medical students and clinical fellows in the areas of statistical design and statistical methods.
Q Dr. Thisted, have you published any journal articles in the field of biostatistics?
A Yes. I've published over 100 articles that have appeared in the peer-reviewed literature in both statistics and

clinical literature.
Q And have you published any books or book chapters?
A Yes, I've been the author or co-author of two books and over 25 book chapters, reviews and other publications.
Q Now, Dr. Thisted, have you ever been asked to serve on an editorial board for a scientific journal?
A I've served on several editorial boards, including the Journal of the American Statistical Association and for several years I was editor of the Current Index to Statistics, which is an index to the worldwide literature in statistics and biostatistics.
Q Can you please explain the significance of serving on an editorial board for those scientific journals?
A Editorial board members are typically selected based on the breadth of their scientific background and experience and they play a key role in the process of peer review for scientific publications.
Q Dr. Thisted, have you won any awards or honors?
A Yes. I've have been elected fellow of the American Statistical Association and elected fellow of the American Association For the Advancement of Science, both for my scientific contributions.
Q Very good.
Now, Dr. Thisted, have you consulted in the pharmaceutical industry?

A I have. Since the late 1970s, I have consulted regularly with pharmaceutical companies and manufacturers of medical devices.

With respect to the design and analysis of clinical trials, primarily intended for support of regulatory approval of new drugs or devices and in that context, I've also participated with those sponsors in conversations with the U.S. Food and Drug Administration about how studies should be carried out and analyzed.

Q Now, Dr. Thisted, have you done any work in the industry specifically relating to oral contraceptives?

A I haven't done any work related specifically to oral contraceptives. However, the principles of experimental design and statistical analysis apply broadly and I have been fortunate to work in many areas of medicine, including cardiology, psychiatry, dermatology and nephrology, neurology and the principles and methods are the same across those areas.

MR. CONDE: Your Honor, plaintiffs offer Dr. Thisted as an expert in statistical methods used in the fields of medicine, biology and pharmaceutical science.

MR. GREEN: No objection, your Honor.

THE COURT: All right.

Let me get that. That was a mouthful.

Okay.

Q Now, Dr. Thisted, we know you have been asked to perform two tasks.

Can you generally explain to the Court what two tasks you have been asked to look at for this litigation?

A Yes. I was asked first to calculate the number of distinct regimens that were disclosed in each of several patents in the prior art, and I was also asked to compare the pregnancy rates of Lo Loestrin, Loestrin 24 to determine if the differences between those pregnancy rates were statistically significant.

Q So let's look at the first of those two questions.

Now, Dr. Thisted, can you tell us what specifically you were asked to do with regard to the potential regimens in the prior art?

A Yes. Each of the contraceptive regimens in the prior art patents represent a combination of features of components and I was asked to calculate, based on what was disclosed in the patent, how many distinct combinations there could be for those features.

Q Can we please go to Thisted slide two?

Dr. Thisted, can you explain what is involved in calculating the number of possible regimens disclosed in the prior art using Thisted slide two?

A Yes. This simply indicates the specific features that could be combined into a particular regimen. Specifically,

each of the patents incorporated an estrogen, one or more estrogens and those, the particular estrogens needed to be enumerated as well as the dosages that could be -- that each of those estrogens could be incorporated into a regimen.

Similarly, patents identified multiple progestins and for each of those progestins, a specific dosage range that was disclosed by that patent. The amount of time during the cycle of treatment that would be hormone free, in which neither progestin nor estrogen would be administered, and then the order in which the components would be administered to the patient.

Q Please go to Thisted slide three.

Now, Dr. Thisted, can you please explain how you used this information to determine the number of potential regimens in the prior art references?

A Yes. This shows, in general terms, a calculation that needed to be carried out. Essentially, one has to select a progestin dose, one or more estrogen doses and a way in which those are combined temporally in time, and so for each of those, I did the calculation based upon, for instance, for the progestin doses, the number of doses possible as indicated by an analysis of the prior art patent carried out by plaintiff's medical expert, Dr. Darney and provided to me.

Similarly, for the estrogen doses and for the phase combinations, the calculations that I did were based upon the

number of possibilities for each of those features that Dr. Darney identified from the patent.

Q So let's look at the assumptions that were provided to you by Dr. Darney.

Can you please go to plaintiff's exhibit 151?

And, Dr. Thisted, can you please tell the Court what is plaintiff's exhibit 151.

A Plaintiff's exhibit 151 contains the specifics of the analysis of each of the patents provided to me by Dr. Darney.

MR. CONDE: Your Honor, we offer in evidence plaintiff's exhibit 151.

MR. GREEN: No objection, your Honor.

Q Dr. Thisted, let's look at page one of plaintiff's exhibit 151 and I think it's entitled "The '940 Patent."

Do you see that at the top there?

A Yes.

Q Okay.

Below that, there's a series of boxes. Let's just walk through those boxes and explain what type of information was provided to you by Dr. Darney.

Can we start with the first box that says "Progestins"?

A Yes. This box indicates that Dr. Darney identified eight different progestins that were disclosed by the '940 patent and for each of them, it indicates the range of doses for that progestin that were identified as well.

Q And then below that box are two boxes for the estrogen. Mr. Brooks, can you pull up the next two boxes which we have the title "Estrogen First Component" and "Estrogen Second Component".

Dr. Thisted, what's being provided in those two boxes?

A In the '940 patent, estrogens are applied in two different times during the cycle. During the first component estrogens are combined with progestins. In the second component estrogens are administered alone.

In each of those two components, an estrogen has to be identified together with the dose.

For the first component, Dr. Darney indicated to me that there were three distinct estrogens that the patent disclosed, together with the ranges of doses for each of them that could be used during the first component.

The second block indicates that when estrogens were used in the second component by themselves, that, again, there were the same three estrogens identified with somewhat different dosage ranges, when those estrogens were used in the second component by themselves.

Q Okay. Very good.

Mr. Brooks, can we go to the next box in the list of assumptions or analysis provided to Dr. Thisted by Dr. Darney which is entitled "Phases".

What is being indicated in that box, Dr. Thisted?

A This box indicates the information about both hormone-free interval as well as the order of administration that is disclosed in the '940 patent.

Specifically, the first component in which there's a combination of estrogen and progestin, that component has to last either 23 or 24 days, followed then by either days in which no pills are taken or placebo pills are taken for one or two days, and then a final component with estrogen alone for two, three or four days, subject to the restriction that the total number of days must be at least 28.

Q Very good.

Let's go to what I think is the last box which is entitled -- I'm sorry. Let's go to the next box which is the second to last box which is "Increments For Ranges".

Dr. Thisted, what's provided in that box of the exhibit?

A For each of the progestins and estrogens, a dosage range is specified in the patent and they're an infinite number of specific doses within that range.

The question is, what would the -- how many -- for any given range effectively how many different doses are disclosed and Dr. Darney's analysis of the patents indicates that when the ranges incorporate dosages under one milligram, that increments of five micrograms are appropriate, and for ranges that exceed a milligram, a broader increment of .1 milligram

is appropriate, together with a range of steps for ethinyl estradiol of one microgram.

Q So just so we're clear, can we maybe have you walk through a quick example of this?

Could you, Mr. Brooks, pull up Gestodene from the progestins from number one?

Dr. Thisted, can you just apply the Gestodene range for this increment for ranges that Dr. Darney provided you?

A Surely.

The Gestodene range specified here is 0.05 to 0.075 milligrams, which is 50 to 75 micrograms. All of the doses in that range are less than one full milligram and so I counted doses in increments of five micrograms, started with 50, 55, 60, 65, 70 and 75. That's a total of six doses that I counted as possibilities for this feature of the '940 patent.

Q Now, let's go to the last box on page one of PTX-151, which is "Other Assumptions".

What's indicated in this box, Dr. Thisted?

A Each of the patents is somewhat different and has some unique characteristics. And in this box, Dr. Darney identified those characteristics that would affect the calculation of the number of distinct regimens.

Q Okay.

Now --

THE COURT: Excuse me.

You said each patent has different dosages.

Did you analyze -- did you conduct your analysis utilizing the patents that Dr. Darney considered?

THE WITNESS: Yes, that is correct.

THE COURT: Do you know how many patents that was?

THE WITNESS: I looked at -- Dr. Darney provided me with information about six patents.

THE COURT: Okay.

Q And with regard to the other five patents, are the assumptions that Dr. Darney provided you also in plaintiff's exhibit 151?

A Yes.

Q And so we know what assumptions Dr. Darney provided you. Let's take a look about how you actually calculated the number of potential regimens for the '940 patent.

Can we go to slide four, please?

What is slide four, Dr. Thisted?

A Slide four shows the details of my calculations based on Dr. Darney's analysis of the ingredients for the number of distinct possibilities disclosed by the '940 patent.

Q Okay.

There's a lot of information on this slide so let's sort of break it down. Let's start with the top box, Mr. Brooks, entitled "Progestins".

Dr. Thisted, can you show the Court how you used the

information from Dr. Darney's analysis to calculate the total number of progestins as reflected on Thisted slide four?

A Yes. The first four columns are tables directly from Dr. Darney's analysis. We have, in the first column, the eight progestins that were identified.

In the next two columns, we have for each of them, the lower end and the upper end of the dosage range, together with the appropriate increment for stepping through them.

And then in the final column, the number of possible doses indicated for each of the progestins.

So, for instance, for the Gestodene example, the number of possible doses is the six that we stepped through a moment ago.

In total for those eight progestins, there are 194 progestin dose combinations.

Q Very good.

Now, let's go to, Mr. Brooks, the next two boxes on Thisted slide four which relate to the estrogen doses.

Dr. Thisted, what's -- we see two headings, "Estrogen Combination" and "Estrogen Alone".

Could you please explain to the Court what's being depicted in this part of Thisted slide four?

A Yes. As I indicated before, in going through Dr. Darney's analysis, the '940 patent envisions estrogen being treated -- estrogen being administered both in combination

during the first 23 or 24 days, and then separately alone in the last two, three or four days of the specific regimen.

And so the first half of this calculation calculates the number of estrogen dose possibilities for the estrogen as used in the first component.

The second block does the same calculation for the estrogens in the second component.

One of those other assumptions for the '940 patent is that whatever estrogen was selected to use in the first component would not change, the same estrogen would also be used when the estrogen was administered alone. And so with that information, I needed to calculate the number of possibilities for estrogen doses in the first stage combined with the second stage.

So to do that, for instance, if we look at the ethinyl estradiol line in the combination phase, there were a possible 11 doses and then in the estrogen-alone phase, because the dosage range allowed in that phase was actually broader, there were 39 possible doses that could be selected for use in the second phase.

So the total number of estrogen doses for ethinyl estradiol could be selected would be any of the 11 first-phase doses times any of the 39 second-phase doses, which produces a total of 429 possibilities for the ethinyl estradiol and that's shown over on the tab on the right in blue, that shows

that calculation specifically for that estrogen.

I did the similar calculation for the other two estrogens disclosed in the '940 patent and concluded that there were 3,991 distinct possible selections that one could make among the disclosed estrogen doses.

Q Very good.

Let's go to the last box on this slide, which is entitled "Phase Combinations".

Dr. Thisted, could you please explain what you're calculating for the phase combination as shown on Thisted slide four?

A Yes.

The patent disclosed an order of administration, together with the number of days for each of those components that would be permitted. And this shows the number -- this shows the individual choices that could be made that are consistent with the constraints in the patent. Specifically, 23 or 24 days for the combination phase, one or two for the placebo phase, two, three or four for the estrogen-alone phase, but with the caveat that they have to add up to at least 28 days.

These are the eight phase combinations that satisfy that requirement. So there are eight possible ways.

Q Dr. Thisted, with regard to the combination part of this diagram, did any of Dr. Darney's assumptions affect the number

of potential combinations for the combination phase?
A Yes. In that other assumption box for the '940 patent, it indicates that the first composition, the combination phase, could comprise multiple stages. What that means is that the doses, say, of the estrogen could actually change into different parts of that 24-day period.

So for eight days, the dose might be one level, change at another -- for the next eight days and change for the last eight days.

If I were to take into account all the possible ways in which doses can change over the course of 24 days, the calculation would be astronomical.

What I did in my calculation was to simply calculate as sort of a lower bound, a conservative calculation of the number of possibilities that just assumed that there were no changes in doses over that first combination phase.
Q Now, let's look at the very bottom of your slide, which is the actual multiplication of the various progestin dosages, estrogen doses and phase combination.

Dr. Thisted, what was the total possible combinations that you derived based on Dr. Darney's assumptions?
A The panel at the bottom shows the application of the general formula that I discussed earlier and indicates that there are something over six million distinct regimens that are disclosed by the '940 patent.

Q Could we please go to Thisted slide five?

I'm not going to belabor this, but this is the same type of calculation that you did for the '940 patent, but instead were using Dr. Darney's analysis to do the calculation for the '490 patent.

A That's correct.

Q And then let's go to the next slide, Thisted slide six and, again, this is the same type of calculation, but this time you're applying Dr. Darney's analysis to the '394 patent?

A That is correct.

Q Have you provided a summary page showing the number of possible regimens for those three patents?

A I have.

Q Can we go to Thisted slide seven, please?

What is depicted on Thisted slide seven?

A This summarizes the results from the three calculations. Specifically that the '940 patent discloses at least six million possibilities; the '490 patent discloses at least 16 million distinct regimens; and the '394 patent discloses at least half a million distinct regimens.

Q Now, I see there's a source document on this slide. Dr. Thisted, plaintiff's exhibit 152.

Can you please turn to that?

A Yes.

Q What is plaintiff's exhibit 152, Dr. Thisted?

A Plaintiff's exhibit 152 contains the calculations that I carried out for the six patents that Dr. Darney analyzed and this is from my expert report.

MR. CONDE: Plaintiffs offer into evidence plaintiff's exhibit 152.

MR. GREEN: No objection, your Honor.

Q Okay.

So now we're going to shift gears to the second question that you were asked to analyze.

Dr. Thisted, could you please explain what question you were asked to analyze with regard to the Pearl Indices of the Loestrin 24 --

THE COURT: Before you get to question two, may I -- forgive me. Mr. Green, if I'm intruding on expected cross, let me know and I'll be quiet.

Have you looked at the six patents in the prior art that Dr. Darney referred to?

THE WITNESS: Yes, I have.

THE COURT: Are you aware of the fact, at least I'm looking at the '940, that although there are eight separate progestin compounds that are set forth and three separate estrogen compounds that are set forth, nevertheless, the '940 patent at least contains statements that there are preferred embodiments, which limit the use to ethinyl estradiol in particular amounts and, I lost the progestin.

MR. CONDE: I think it's Gestodene.

THE COURT: Gestodene and something else. Instead of having eight progestins and three estrogens, there are only one and -- there are only three compounds that are preferred embodiments.

If a person of skill in the art were to limit consideration to what the preferred embodiments are, what would that do to your calculations?

Is that a decent question?

MR. GREEN: It is, your Honor.

THE COURT: Am I intruding on you?

MR. GREEN: Not at all.

THE COURT: How am I doing?

MR. GREEN: B plus, your Honor.

THE COURT: Better than I usually get.

Do you follow me?

THE WITNESS: I do.

THE COURT: In other words, instead of doing the multiplications using eight and three, if you just did the multiplications using two and one, what would you get?

THE WITNESS: I haven't actually carried out the calculation for the preferred embodiments that you indicated. You would get a smaller number.

THE COURT: Of course, you would.

Anyway, Dr. Darney didn't suggest that you do that?

THE WITNESS: That's correct.
THE COURT: Okay.
Q So, Dr. Thisted, let's go to the second question that you were asked to analyze.
THE COURT: Excuse me.
I want to just establish the ground rules. The argument is going to be that although Dr. Thisted does his calculations and comes up with these astronomical appearing figures, the argument is going to be that in reality, a person of skill in the art would look at what the preferred substances are in the embodiments and if you did that analysis, you'd get a much lower number.
MR. CONDE: But then you wouldn't have norethindrone acetate, which is the only claimed progestin.
THE COURT: Believe me, I'm not drawing any conclusions. I'm just trying to understand the issue.
MR. CONDE: Right.
THE COURT: I think it's fair for Dr. Thisted to understand the issue, which I'm sure he does.
Q So, Dr. Thisted, what question were you asked to analyze with regard to the Pearl Indices of the Loestrin 24 and the Lo Loestrin clinical trials?
A I was asked to examine the Pearl Indices from the two clinical trials, to determine whether the difference -- the difference between the two drugs with respect to the Pearl

Index was statistically significant. That is to say, whether there was evidence of a difference.

Q Dr. Thisted, can you explain why you conducted a statistical comparison of the trial data from the two regimens?

A Yes. Lo Loestrin and Loestrin 24 are different formulations. Lo Loestrin has half the ethinyl estradiol as Loestrin 24 and if it's the case lowering the ethinyl estradiol reduces the contraceptive efficacy, one would expect to see a substantial increase in the pregnancy rates with the lower ethinyl estradiol. So the question is, is there statistical evidence for that.

Q Dr. Thisted, before we go into your analysis, could you explain what a Pearl Index is?

A Yes. The Pearl Index is a measure of the effectiveness of a contraceptive regimen. Probably more accurately, it's an expression of the failure rate of the contraceptive regimen and it is the expected number of unwanted pregnancies that one would see in 100 women treated for a year with a specific regimen.

Q So, Dr. Thisted, can we go to Thisted slide eight, please?

Could you please, in general, explain the steps that you took to conduct your analysis?

A Yes. In order to compare the results from the two

studies, I first had to make certain that it was appropriate to do the comparison, that the clinical studies were sufficiently similar to support scientifically a comparison of the results.

The second step was to collect the clinical study results from the two studies based on FDA documents and documents submitted to the FDA, and then finally to carry out the statistical comparison between the two Pearl Indexes to determine whether the difference was statistically significant.

Q Okay. Let's talk about the steps that you undertook.

The first one relates to examining the clinical study characteristics.

What clinical, in general, what clinical study characteristics did you look at?

A I looked at the general, the overall way in which the studies were designed. Specifically, I looked at the inclusion and exclusion criteria for participants in the study to ensure that the patients studied were similar, and I also looked at the demographic characteristics of the patients in the two studies. Again, to ensure that they were studying the same kinds of patients.

Q Can we please turn to plaintiff's exhibit 148?

Dr. Thisted, what is plaintiff's exhibit 148?

A Plaintiff's exhibit 148 is a document that I prepared

that extracts information from the clinical study reports of the Loestrin 24 study and the Lo Loestrin study that show the characteristics of the patients who participated in the study.

Characteristics such as age, height, weight, ethnicity and so forth to determine whether the patients studied were similar.

Q And, Dr. Thisted, what did you conclude with regard to the comparison of the patient demographics between the Loestrin 24 clinical study and the Lo Loestrin clinical study?

A My conclusion was that the characteristics were very similar between the two studies. For instance, the average age was 28.9 years in the Loestrin 24 study and 28.6 years in the Lo Loestrin study. About the same fraction of individuals, about 18 percent was older than 35 in both studies.

The ethnicity of subjects was very similar between the two studies; height and weight were very similar.

The only notable difference in the demographics is that the Lo Loestrin study had a somewhat higher fraction of individuals who were using oral contraceptives for the first time.

Q What impact, if any, would the fact that the new user status was higher with the Lo Loestrin study compared to the Lo 24, Loestrin 24 study would have on the Pearl Index?

A I inquired of Dr. Darney what impact that might have and

he indicated that it would have negligible impact on the Pearl Index. If anything, the higher fraction of new users in the Lo Loestrin study would tend to inflate the Pearl Index somewhat. There would be a somewhat higher risk of pregnancy in that group of individuals.

Q So what did you conclude with regard to the comparison of the patient demographics of the two studies?

A That they were substantially similar, that they were comparing the same kinds of patients.

Q And you mentioned that you reviewed the clinical study data from the two reports.

Are those at plaintiff's exhibit 230 and plaintiff's exhibit 231 in your binder?

A Yes. 230 and 231 are the clinical study reports for the Loestrin 24 and Lo Loestrin studies respectively.

MR. CONDE: Your Honor, we move into evidence plaintiff's exhibit 148, 230 and 231.

MR. GREEN: No objection, your Honor.

Q Now, Dr. Thisted, let's look at the second comparison you made between the studies regarding the inclusion and exclusion criteria.

Can we please go to plaintiff's exhibit 150?

What is being shown on plaintiff's exhibit 150, Dr. Thisted?

A This is an exhibit that I had constructed that extracts

from the clinical study reports the details of inclusion criteria for patient participation, as well as exclusion criteria and lists them side-by-side for comparative purposes.

Q So can you please first explain what inclusion criteria are?

A Yes. Inclusion criteria in a clinical study identify the patients who are eligible to participate and describe typically the kinds of patients in whom the drug would be used in practice. And so the inclusion criteria basically identify the kinds of patients who were being studied.

Q And now, can you tell us what the result was of your comparison of the inclusion criteria between the Loestrin 24 and the Lo Loestrin clinical studies?

A With some minor differences in wording, the two are essentially identical.

Q Now, let's go down to the next page, please, Mr. Brooks, and look at the exclusion criteria.

Dr. Thisted, what is being depicted here -- first of all, what is the exclusion criteria, what does that mean?

A Exclusion criteria are factors which would make an individual who would otherwise be eligible inappropriate to participate in the study because it might put them at risk or because the results that they produced would not be readily interpretable.

And so they identify people who are then excluded from

the pool of otherwise potential individuals.
Q And what was the result of your analysis of the exclusion criteria of the Loestrin 24 study compared to the Lo Loestrin clinical study?
A Again, with minor wording differences, they were substantially similar.
MR. CONDE: Your Honor, plaintiffs move into evidence plaintiff's exhibit 151.
MR. GREEN: No objection.
Q Can we please go to slide nine?
Dr. Thisted, what is being depicted on Thisted slide nine?
A This summarizes the results of my assessment of the two study characteristics. Specifically, that the patient demographics and the inclusion, exclusion criteria were substantially similar and that as a result, it made good scientific sense to compare the pregnancy rates from the two clinical trials using statistical methods.
Q Dr. Thisted, what was the next step in your analysis?
A The next step was to assemble the data about pregnancy rates from the two studies.
Q Let's go to this said slide ten, Mr. Brooks.
Dr. Thisted, in general, what is being depicted on Thisted slide ten?
A This summarizes the clinical study results as it relates

to pregnancy from the two studies.

Q Now, I think most of the columns are self-evident, but there's a couple their we probably should provide some definitional context.

On the very left-hand side, there's a column that says "cohort" and underneath that column, it has two acronyms, MITT and PITT.

Can you please explain those, Dr. Thisted?

A MITT and PITT are, essentially, labels that are applied to two different groups of patients who were studied.

The MITT cohort, the modified intent to treat cohort, essentially comprises all of the women who participated in the study.

The PITT cohort, includes only those women who were under age 35 when they started the study, so those are women who are younger than the total population. Essentially, it's looking at everybody and then looking at the younger subset of them.

Q And then I think all of the rest of the rows are self-evident or we talked about Pearl Index.

On the very right-hand side, there's something that says 95 percent CI.

What does CI refer to?

A CI is an abbreviation for confidence interval.

And what's depicted in that column, the 95 percent

confidence interval shows the range of Pearl values that are consistent with the observed data.

So, for instance, with the -- in the first row, Loestrin 24 study, if another study were carried out in 705 women for about 3600 cycles, we may or may not see exactly five pregnancies, even though we're studying the same drug. You might see four, you might see six or you might see three.

That inherent variability from study-to-study is the background against which the statistical analyses are carried out and the 95 percent confidence interval indicates against that background of inherent study-to-study variability how precisely the studies actually estimate the Pearl Index.

So in this case, it indicates that based on the observed Pearl Index of 1.82 in the Loestrin 24 study, those data are consistent with Pearl Indices as small as .6 or as high as 4.2.

Q Now, Dr. Thisted, if we look at the source material for slide ten, I think we've already talked about 230 and 231.

There's also PTX-233.

Can you just turn to your book and tell us what PTX-233 is?

A Yes. PTX-233 is the report of the statistical reviewer at the U.S. Food and Drug Administration in the review of the Lo Loestrin NDA.

Q And did you use information from that document to

generate Thisted slide ten?
A Yes, I did.
MR. CONDE: Your Honor, plaintiffs move into evidence plaintiff's exhibit 233.
MR. GREEN: No objection, your Honor.
Q Okay.
So we're almost -- we're at the third step. We're finally getting to the end here.
Can we please go to Thisted slide 11 and, Dr. Thisted, can you just tell us in general what is being depicted on Thisted slide 11?
A In general, I'm showing the results of the statistical comparisons of pregnancy outcomes between the two studies.
Q Okay.
So before we go into the slide, I notice that you have a source document, which is PTX-146.
Could you please turn to that document in your book and tell us what is PTX-146?
A PTX-146 is a complete catalog of the statistical calculations that I carried out in this case.
Q And so those calculations, the results of which are reflected on Thisted slide 11?
A That is correct.
MR. CONDE: Your Honor, plaintiffs move into evidence PTX-146.

MR. GREEN: No objection, your Honor.

Q So now let's look at Thisted slide 11 and go through some detail about what's being depicted here.

First, let's start on the right side, there's a box that says "Result". In parentheses, it says "p-value."

Dr. Thisted, could you please explain to the Court what is being referred to as a p-value?

A Yes. The result of any statistical test is an index called p-value, which ranges from zero to one and it's an indication of the extent to which differences are -- let me back up.

The way the p-value is used is that p-values that are very small, that are less than 0.05 by convention, very small p-values indicate that there's strong evidence for differences between the two groups being compared and p-values that are larger than 0.05, don't provide strong evidence that there's a difference.

The term "statistically significant" is simply a shorthand for the p-value being less than 0.05. The results that I show here are the results for comparisons based on each of the numbers of statistical tests.

Q Now, we understand what the p-value is, let's look at the statistical calculations that you made. I'm going to break them up into two groups.

The first group are the first three on the left-hand

column that says Chi-square test, Fisher's exact test and Prazone's rates test.

Could you please tell the Court why you conducted those three statistical calculations?

A Yes. Each of these three methods is a standard statistical method for comparing failure rates. They have subtle differences between them, but they're all addressing the same question, is the difference in Pearl Indices statistically large?

The reason that I did all three of them was simply to assure myself of the reliability of the results. Rather than simply calculating one, I wanted to ensure that the other two provided similar results and, in fact, they do. All of these p-values are very similar and substantially larger than 0.05.

Q And the last statistical calculation depicted on Thisted slide 11 is called a "Life Table Analysis."

Can you please explain what is involved in that calculation?

A Yes. I carried out the so-called Life Table Analysis which looks at how pregnancy rates change over time because the two studies, Loestrin 24 and Lo Loestrin, were actually carried out for different periods of time. The duration of the Loestrin 24 study was six cycles, the Lo Loestrin study went on for 13 cycles.

So I wanted to make sure that any results that I had

weren't an artifact of the difference in duration of the studies.

The Life Table Analysis is a method that is appropriate for doing that.

Q What result did you obtain in terms of the p-value for the Life Table Analysis?

A The p-value for the Life Table Analysis was virtually the same as that produced by the other methods.

Q So, Dr. Thisted, what conclusion did you reach based on the statistical calculations that you made comparing the Loestrin 24 clinical study with the Lo Loestrin clinical study?

A If having the amount of ethinyl estradiol substantially increased the pregnancy rate, then one would expect to see evidence of that in the data. The statistical evidence here indicates that there is no statistical evidence to support a substantial increase in pregnancy rates with Lo Loestrin compared to Loestrin 24.

Q And so using the terminology we talked about earlier about statistical significance, how would you characterize the results of your statistical analysis?

A The differences in pregnancy rates between Loestrin 24 and Lo Loestrin do not reach statistical significance.

Q Now, Dr. Thisted, have you had an opportunity to look at the testimony this week from Dr. Barnhart while he was at

trial?
A Yes, I have.
Q And, Mr. Brooks, can we put up trial transcript page 145, lines ten to 11?
Do you see this is from Dr. Barnhart's testimony on Monday, I believe. He says, "So you're left right where you were before, which is Pearl Index of Lo Lo is higher than Pearl Index of Lo," which he's referring to Lo 24.
Dr. Thisted, do you agree with Dr. Barnhart's conclusion about the differences in the Pearl Index of Lo Loestrin and Loestrin 24?
A No, I don't.
Q Why not?
A It's certainly the case that one of the two Pearl Indexes is larger numerically than the other, but the purpose of the statistical analysis is to determine whether there's statistical evidence that one can conclude that the Pearl Index is systematically higher for one treatment than the other.
The result of the statistical analysis is not where we were before. The statistical analysis indicates that there is no strong evidence for a difference in the Pearl Indices between the two treatments.
MR. CONDE: No questions at this time.
THE COURT: Excuse me, one second.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 11-5048 and 12-2928

WARNER CHILCOTT CO., LLC, Plaintiff, -vs- LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants. WARNER CHILCOTT CO., LLC, Plaintiff, -vs- WATSON LABORATORIES, INC., Defendant.	TRANSCRIPT OF PROCEEDINGS TRIAL

Trenton, New Jersey
October 15, 2013

B E F O R E:

THE HONORABLE JOEL A. PISANO
UNITED STATES DISTRICT COURT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

S/Joanne M. Caruso, CSR, CRR
Official Court Reporter
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WITNESS	DIRECT	CROSS	REDIRECT	RECROSS
PHILIP DARNEY				
By Mr. Pappas	600			

October 15, 2013.

THE CLERK: All rise.

THE COURT: Good morning.

Thanks, have a seat, everybody.

I've got binders here.

What's next?

MR. PAPPAS: Your Honor, we gave them to Dana. Those are the binders for the direct of Dr. Darney as well as the slides.

THE COURT: Are we ready to go with Dr. Darney?

MR. PAPPAS: We are.

There's one preliminary matter I think they have.

MR. WEZOWSKI: During the Thisted cross-exam, there was one document --

THE COURT: During the?

MR. WEZOWSKI: Thisted cross-exam, there was one document that you discussed, DTX 239 and we ask to move that into evidence. We discussed it. Thisted exhibit two.

MR. CONDE: What was the document?

No objection.

THE COURT: Okay. Anything else?

Let's get the witness.

MR. PAPPAS: Your Honor, plaintiffs would next call Dr. Philip Darney.

P H I L I P D A R N E Y, sworn.

P H I L I P D A R N E Y, sworn.

THE COURT: Good morning, sir.

THE WITNESS: Good morning.

THE COURT: Have a seat, keep your voice up.

THE WITNESS: Thank you.

DIRECT EXAMINATION BY MR. PAPPAS:

Q Dr. Darney, please state your full name.

A Philip with one L, Darney, D-a-r-n-e-y.

Q What is your profession?

A I'm a professor of obstetrics, gynecology and reproductive sciences, University of California, San Francisco.

Q Mr. Brooks, may I have PTX-130A?

Dr. Darney, can you take a look at the screen either behind you or directly in front of you.

Tell me if this is a copy of your current curriculum vitae?

A Yes, it is.

MR. PAPPAS: I move plaintiff's exhibit 130A into evidence.

MR. GREEN: No objection, your Honor.

THE COURT: Okay.

Q Dr. Darney, have you prepared a slide that summarizes your current and former positions out of your complete curriculum vitae?

A Yes.
Q May I have, Mr. Brooks, slide, Darney slide number two?
A At the top is my current position.
Q Yes, please tell us what your current position is?
A Distinguished professor of obstetrics, gynecology, reproductive sciences University of California, San Francisco and the founding director of the Bixby Center For Global Reproductive Health.
Q Sit close to the mike so that --
A Excuse me.
Q The court reporter can hear you.
A How's that?
Q I think much better.

Now, Dr. Darney, I also note there's an entry there from 2004 to 2007, as the president or founding president of the American Society of Family Planning.

What is that, sir?

A That's an association of scientists, sociologists, physicians, physiologists who conduct research in family planning and contraception, which colleagues and I organized in 2004, and my colleagues elected me the founding president.
Q And are you currently a practicing physician?
A Yes, I am.
Q Where?
A At San Francisco General Hospital, teaching hospital

University of California, San Francisco.
Q And where are you currently licensed to practice medicine?
A In California.
Q Where did you go to medical school?
A I went to medical school at my president institution, UCSF.
Q And where did you do your surgical residency?
A I did an internship in general surgery at the U.S. Public Health Service Hospital in the City of San Francisco.
Q And what did you do after completing that?
A I went to the Center For Disease Control to do my public service time where I was trained and served as an epidemiologist and continue to work at the CDC in Atlanta and around the world for five years.
Q And what did you do after that?
A After that, I completed my clinical training at the Brigham Young Woman's Hospital in Boston.
Q And then did you join the faculty at Harvard Medical School?
A Yes. After completing my residency, I joined the faculty there. I should probably have added that while I was at the CDC, I during the five years, I completed a residency in preventive medicine so I have done that prior to the residency in obstetrics and gynecology.

Q When did you join the faculty at the University of California, San Francisco?
A From Harvard, I went to the Organ Health and Science University in Portland, Oregon where I stayed for two years as and associate professor and then I moved back home to the University of California, San Francisco in 1981.
Q Now, the earlier slide, actually the one that is up on the screen now, Darney number two, there's a reference to the Bixby Center for Global Reproductive Health.

Can you just tell us briefly what that is, sir?

A Yes. An epidemiologist colleague of mine at UCSF and I founded what's now called the Bixby Center in 1999, to conduct research and training in various aspects of family planning and its relationship to sexually-transmitted infections.
Q And, sir, do you also specialize in what is typically called family planning?
A Yes, that's my area of research and writing.
Q Mr. Brooks, may I have Darney slide three, please?

Dr. Darney, can you just briefly describe the work you have done in the family planning area?

A Yes. This is a description of work accomplished at what became the Bixby Center and at the Bixby Center over the past years, we conducted, along with other research, clinical trials, contraceptive, we've studied every contraceptive, every type of contraceptive that has been approved by the FDA

in the past 30 years, including over 20 different oral contraceptive preparations.

I established a fellowship in family planning to produce new researchers in contraception in 1992, and that spread now to 29 major medical schools around the country.

As an example of our work at the Bixby Center, we evaluated the State of California that monitored that program for the past 15 years, one of the world's largest best evaluated family planning programs.

In addition, we provide direct services to patients in San Francisco so I have established several clinics to accomplish that.

Q Now, Dr. Darney, have you, during your career, published articles and books on the subject of contraception?

A Yes, I have.

Q Mr. Brooks, may I have Darney slide four, please?

Is it correct that you've authored over 300 scholarly publications related to contraception and family planning?

A Yes, most of them, not all are related to contraception and family planning. Among those are about 150 peer-reviewed publications.

I and colleagues have also written three books about contraception and my fellows and I have written more than 20 book chapters for other people's textbooks about contraception.

Q I'd like to focus on just a couple of those books.

Mr. Brooks, could you please put up Darney slide five?

Dr. Darney, can you describe the first book that's shown there that was first published in 1992, authored by you and Leon Speroff called A Clinical Guide For Contraception? Just basically tell his Honor what it is and what it covers.

A Yes. Leon Speroff was my boss and close colleague at the University of Oregon where he still is. He and I have written five editions of the referenced textbook called Clinical Guide For Contraception.

Bob Hatcher, a physician I first met when I was in Atlanta, and I have authored and worked with our family planning fellows, two books about contraception. The bottom one is a handbook, smaller than our textbook, a handbook for residents and practitioners, nurse practitioners in family planning and it's in its 11th edition.

The middle one is a conversion of that book for lay people to learn about contraceptives.

Q Doctor, let me just ask you a couple of questions on the first book, the five editions, Clinical Guide to Contraception.

With what popularity has that achieved in the world of contraception?

A I believe it's the most-widely sold, I'd like to think read, textbook around the world on this topic.

Q Has it been translated into languages other than English?
A Yes, Portuguese, Japanese, Russion, Spanish, Serbo-Croatian, for example.
Q Now, I'd like to turn to briefly to research grants and consulting.
Mr. Brooks, could we have on the screen Darney slide six, please?
Have you extracted from your lengthy CV, Doctor, just a few of your consulting assignments or research grants over the years?
A Yes. These are representative of research projects beginning with the first one, looking at oral contraceptives, Syntex Laboratories, trial.
The next one is a trial of Desogestrel and norethindrone, oral contraceptives.
Next is one for Levonorgestrel, oral contraceptive.
Next is one about the use of oral contraception immediately after elective abortion.
These provide examples of more than, as I said, 20 studies of various oral contraceptives over the years.
Q Have you worked with Government agencies as well on issues of contraception during your career?
A Yes, I've worked closely with National Institutes of Health, with the Centers For Disease Control, with USAID, the foreign aid part of the State Department, State of California.

Q Have you consulted continuously from the mid-1980s until today with various companies engaged in oral contraceptive or contraceptive research generally?

A Yes. Beginning in the early 1980s, I've worked with every company that's ever marketed an oral contraceptive and a variety of other contraceptives, with a couple of exceptions.

Q I'd like to turn momentarily to your service to specific professional publications.

Mr. Brooks, can we have on the screen page 7-8 of PTX-130A, the CV?

Can you blow up the first one?

Now, Dr. Darney, the first one is the Obstetrics and Gynecology Journal, correct?

A Yes.

Q What does it mean that you're a peer reviewer, what is that?

A Peer reviewer is an individual with specialized knowledge in a particular field, usually having published in that field, who reviews manuscripts for possible publication in scholarly journals, to decide whether they are worthy of publication or not.

Q I notice you have been in that position from 1985 until the present. Is that correct?

A Yes, that's when I first began reviewing for Obstetrics and Gynecology and I still do it. I was on the editorial

board.
Q As a peer reviewer, does that put you in a position to review articles being written on a current basis, on trends or new developments in contraception?
A Yes, that's where new developments are publicized in the scholarly journals.
Q Now, we've, of course, blown up the International Journal of Gynecology and Obstetrics, but let me pass from that.
The last one we highlighted, 1993 to present, does it list you as a peer reviewer and editorialist for the New England Journal of Medicine?
A Yes, New England Journal publishes once is considered for publication a manuscript about contraception, further aspects of reproductive health, usually contraception. You have a panel of reviewers with experience in that field and I've regularly reviewed for them.
Q Dr. Darney, do you also teach medical students?
A Yes, I'm always with medical students, residents, my own fellows.
Q Mr. Brooks, can you please bring up page two of plaintiff's exhibit 130A? Actually, let's do page 17 of 130A.
Dr. Darney, does that give a brief summary of the various teaching positions that you have held?
A This start of the list of the fellows I've supervised at the beginning of the family planning fellowship I described

and lists their current positions. These are the first four of those fellows who I'm very proud of.

Q And, generally, what are the subjects that you teach?

A Well, to these fellows, they're engaged in contraceptive research with me. I'm teaching them research methods as well as clinical skills to medical students and residents, I teach general obstetrics and gynecology with a focus on contraception.

Q Let's turn briefly to your clinical work.

Do you see patients?

A Yes. Now, about once a week San Francisco General Hospital.

Q On issues relating to contraception and specifically oral contraceptives?

A Yes.

Q For how long have you seen patients?

A Since 1969.

Q How often do you see patients?

A Well, I see patients less now than I did several years ago, but right now once a week, sometimes in the past everyday.

Q Have you seen patients on some basis, either very frequently or at least once a week, throughout your entire 44 years of practice?

A Yes, I have.

Q Do you continue to see patients even today? Well, not today you're in court, but at the present time and prescribe oral contraceptives as appropriate?
A Yes. As I said, now it's about once a week.
Q Let's turn to --
A One day a week, I mean.
Q One day a week.

Let's turn briefly to your service to professional organizations.

Mr. Brooks, can we have Darney slide seven, please?

Dr. Darney, these are just a few from your CV, but can you pick one of them and just explain to his Honor the nature of these professional organizations and whether or not you're paid for your services or you donate your time?
A These are a sample of consultations I've had over the years, first began when I worked at CDC in 1971. I was regularly consulting and I still do that. These are representative ones.

These three happened to be agencies that would be funded by USAID and I would be asked for them -- by them, for example, to travel to Zimbabwe and consult with the Ministry of Health. In this case, it was about the integration of oral contraception and inter-uterine contraception into the private sector which was growing in Zimbabwe at that time. That trip resulted in a long-term relationship with the University of

Zimbabwe which goes on to this day.

UCSF University of Zimbabwe in collaboration for research in sexually-transmitted infections in relationship to contraception.

Q All right, sir.

A This is -- next is an example from work with the Government of Nepal where I spent part of a sabbatical in 1993 and '94, and we continue to have a long-term relationship with our Nepal colleagues. Our fellows and residents go there to work with them. They come to visit us, same with Zimbabwe.

Same with Vietnam. We established a program in Vietnam to reform the medical school curriculum and worked there for five years and have close relationships with colleagues in Vietnam and I believe we're very successful in helping them improve medical education in that country.

We translated one of our textbooks into Vietnamese actually, distributed to all medical students and residents in Vietnam.

Q Dr. Darney, finally, I would just like to talk for a moment about honors or awards of particular note that you have received.

Mr. Brooks, may we have Darney slide eight on the screen?

Sir, I'd like to direct your attention to two of the awards in particular and tell the Court what they -- why

you're selected and what they stand for.

First is in 2011, the Lifetime Achievement Award in contraceptive research and most recently the recipient of the Margaret Sanger Award in 2012.

Let's take the Lifetime Achievement in contraceptive research. Who gave that to you and what does it represent?

A The society that I helped to found, grateful that they recognized me for my contributions to contraceptive research in 2011. That means you have a long history of publication and contribution to the development of contraception.

The next one is an award from Planned Parenthood Federation of America in honor of their founder, Margaret Sanger, who was instrumental in the development of birth control pills, by the way, and that was given to me and Dr. Landy for our founding and implementation of the fellowship and family planning in a training program for residents in contraception, residents in obstetrics and gynecology and family medicine, which is now at 70 medical schools.

I was very pleased to be recognized by PPFA for that work over the years.

Q Are you aware of any other fairly recent winners of the Margaret Sanger Award?

A Yes, very recently during her time as Secretary of State, Hillary Clinton received the award and in years past, because of his support for human rights and family planning, Martin

Luther King received the award, among others.

Q Dr. Darney, do you consider yourself an expert in gynecology, contraception and family planning?

A Yes, I do.

MR. PAPPAS: Your Honor, based on Dr. Darney's extensive CV, which is plaintiff's exhibit 130A, and the questions to which he's responded today, plaintiffs would offer Dr. Philip Darney as an expert in the areas of gynecology, family planning and contraception.

MR. GREEN: No objection, your Honor.

THE COURT: Okay.

MR. PAPPAS: Your Honor, let me just say at the outset where we are going with Dr. Darney just to give your Honor sort of a road map.

First, Dr. Darney will testify about how combination oral contraceptives basically work in the human body, specifically obviously the female, then a brief testimony on the evolution of combination oral contraceptives.

Third, the -- he will review with the Court teachings that we believe demonstrate that in the prior art, there was a strong belief against lowering estrogen below 20 micrograms.

Fourth, he will then testify about if you even attempted to go there, you would have to choose a more potent progestin.

Fifth, he will give his opinion for the basis of his

opinions that the '984 patent is not obvious in light of the prior art.

Six, his opinions as to why he believes that the defendants are engaged in hindsight use of prior art references and finally, he will have very brief testimony on unexpected results.

I thought it might be of some assistance to your Honor in terms of knowing where we're going.

THE COURT: Thank you.

Q Dr. Darney, let's turn now to the claims of the '984 patent.

First of all, sir, when you were retained, what were you asked to do?

A I was asked to determine whether the '984 patent was obvious in light of previous work.

Q And what conclusion did you reach?

A It is not obvious.

Q Now, I think we need to clear up a few preliminaries as we start with your opinion.

Mr. Brooks, can we have Darney slide nine?

Did you assist in the preparation of this slide, Dr. Darney?

A Yes, I did. This is an abbreviation of the claims of the '984 patent.

Q Can you briefly explain what you understand about what's

claimed in claim 1 of the '984 patent?
A Well, as an oral combined contraceptive, it combines progestin and estrogen, specifies what those should be and the ranges of the doses.

And in this case, they're administered for combined preparations is administered for 24 days. I'll make my first attempt to draw on this screen here.

That's the combined part of the preparation. It's followed by two days, two pills, a pill everyday of estrogen alone in the same range as the estrogen is given in the combined preparation of 24 days and then finally, to make up the full 28 days of typical of combined oral contraceptive packaging, placebo. That is a pill with nothing in it is given.
Q All right.

Now, can we have, Mr. Brooks, Darney slide ten, which summarizes claim 6 and, again, did you help us in preparing this slide, Dr. Darney?
A I did.
Q Please tell us how it helps your understanding.
A It lists the limitations of the previous claim which specifies that rather than norethindrone or norethindrone acetate, both first-generation progestins, of the progestin uses norethindrone acetate.

The fourth claim specifies that it's given at a dose of

one milligram per tablet in the combined portion of the regimen where it's used and finally, six specifies that the amount of estrogen in both the combination first 24 days and the following two days of unopposed estrogen, that is estrogen alone, is the same, the dose is the same in those 26 tablets.

Q Dr. Darney, are the opinions you're going to give today applied to all nine claims of the '984 patent?

A Yes.

Q Okay.

Now, Dr. Darney, before we go further, when you first heard about the product Lo Loestrin FE, what was your reaction?

A I should preface by saying that I did not conduct a clinical trial on Lo Lo, abbreviated by calling it Lo Lo. My first acquaintance with this was when it was marketed.

I was surprised that such a pill, that is with the doses we just described, would be approved by the FDA as an effective contraceptive. I simply thought that the doses and the choice of progestin in the administration scheme, that it was a surprise that they were effective.

Q Did your views change after Lo Loestrin FE began to be marketed?

A Well, if it's marketed, that means the FDA approved it, so I thought, well, that regimen must have actually worked.

Q Do you have an opinion today, Dr. Darney, after Lo

Loestrin FE has been on the market for about two years, whether it has been generally accepted by the medical community?

A Well, I know that it's prescribed, yes. I don't know the sales figures right now.

Q Are any of your colleagues still skeptical today whether it will work?

A Yes, yes, they are.

Q Why is that?

A Despite FDA approval, they think it's too low a dose, that it's -- they need reassurance about its efficacy and in particular, they need reassurance about what its -- the bleeding it will cause for patients.

The FDA, of course, approval means that it's effective and safe, doesn't necessarily mean that it has what we call an acceptable bleeding pattern. So there's still skepticism about a pill with doses that low and a progestin of that potency.

Q All right, sir.

Did you assist in preparing a summary slide of the reasons you believe that a person of ordinary skill in the art in April, 2005, would not have found claims of the '984 patent obvious?

A Yes, I did.

Q Mr. Brooks, can we have Darney slide 11, please?

Can you, Dr. Darney, briefly go through each of those opinions and let me just say we will get to them in much greater detail later, but I'd like you to at least outline the opinions that you have as to why the '984 claims were not obvious in light of the prior art.

A Well, the first three are the reasons, skepticism I just described and that is that it wasn't believed, still not completely accepted, that you could lower the estrogen dose below 20 micrograms and have an effective pill with acceptable side effects, particularly bleeding.

If you're going to try to do that, I and I believe persons of ordinary skill in the art, would have thought you'd certainly have to use a second- or third-generation progestin, not a first-generation progestin.

In addition, there was no information that shortening the hormone-free interval, that means below the traditional and still typical 21-7 day pattern, three weeks on, one week off, three weeks on, one week off, would make it possible to lower the estrogen dose below 20 micrograms based on experience we'd had with that dose in the past, and certainly no evidence that giving the estrogen alone that we described previously before the placebos was going to compensate for that dramatic change.

Then to go on from the regimen itself, I think the '984 patent isn't obvious because its obviousness is predicated on

hindsight use. That is, knowing what the preparation resulting from '984 actually was and finding the components in the prior art, components that would certainly not have been obvious prior to the actual production of something from the '984 patent, the Lo Lo product.

Then I think something I mentioned already, the skepticism about the possibility that such a preparation could be effective. Certainly skepticism that I, myself, held and, therefore, the unexpected efficacy that was demonstrated relative to other more potent contraceptive regimens, if I can use that term. I think those demonstrate that it was certainly not obvious.

Those are the five points.

Q We will return to those very soon, Dr. Darney, and allow you to testify in greater detail about your reasons in support of each of those opinions.

Before we get there, though, do you have an understanding of the legal standard in a patent case for obviousness?

A Yes, I have an understanding of that based on what's been shared with me.

Q And did you receive that understanding or explanation of obviousness from counsel?

A I did.

Q Mr. Brooks, may we have Darney slide 12?

I don't think that it's necessary for you to read it, Dr. Darney, but except to review it and tell his Honor if this is the standard for obviousness that was explained to you, which you have applied in the opinions you have given this Court and will explain in subsequent testimony?

A Yes, it's the standard I used.

Q Now, there's a reference in the standard to one of skill in the art or, specifically, level of ordinary skill in the art.

Do you see that, sir?

A Yes.

Q Okay.

Have you prepared a slide that you believe one of ordinary skill in the art would be in the subject matter of this patent as of April, 2005?

A Yes, I'm familiar with the term and the next slide will show my definition.

Q Mr. Brooks, can we have Darney slide 13, please?

Please explain to his Honor what your basis or your definition is of the person of ordinary skill in the art?

A I believe it's a person, physician who's had several years of experience prescribing oral contraceptives, or person with an advanced terminal degree in physiology, pharmacology or pharmaceutical science who studied oral contraception specifically for several years.

I don't think such a person would necessarily have experience in actually developing oral contraceptives.

Q So is that point one with which you differ with Dr. Barnhart's definition of one of ordinary skill in the art?

A Yes, I've read Dr. Barnhart's definition and that's a point of difference.

Q Even if the Court were to accept Dr. Barnhart's definition, would that have any affect on the opinions you will give today?

A No.

Q By the way, before we pass from that, have you consulted with pharmaceutical companies engaged in the development of oral contraceptives?

A Yes. As I said, I've consulted, both consulted and conducted trials with most of the pharmaceutical companies developing oral contraceptives since 1982.

Q Dr. Darney --

MR. PAPPAS: Your Honor, as I now indicated, I'd like to turn Dr. Darney to brief explanation of how these combination oral contraceptives work from an anatomical point of view.

THE COURT: May I ask a question?

MR. PAPPAS: Sure.

THE COURT: Off topic perhaps, but have you previously been qualified as an expert witness in cases?

THE WITNESS: Yes.
THE COURT: How many times?
THE WITNESS: Well, I've served as an expert occasionally in medical liability cases, I've served as an expert in product liability cases and I've served as an expert in patent issues in two previous occasions. So I've testified more frequently in liability, a few times in product liability, a few times and in patent cases, I believe this would be the third time.
THE COURT: Did either of the other two cases that you testified in, patent cases, did either of those two cases involve the issue of obviousness?
THE WITNESS: Yes, both of them did.
THE COURT: Okay.
Thank you.
Q And the questions you've just answered for his Honor, is that the number of times, does that pretty much capture during your 40-year career as a physician?
A Yes. It's not something I spend a lot of time doing.
Q Okay.
So let's turn then to how these combination oral contraceptives work.
Have you assisted us by preparing a few slides that you believe will aid in your explanation of how they work?
A Yes.

Q May we have, Mr. Brooks, Darney slide 14?
A This is a simplified description of the normal female menstrual cycle. Probably be best to start at the bottom and work up.
Q Let's take it one step at a time, all right, Dr. Darney? Please identify what you're describing on Darney slide 14. All right.
A Yes. I'll start by noting that the normal female menstrual cycle is about four weeks. We already talked about how most birth control pills are also four weeks to roughly duplicate that cycle. Obviously in an individual women, it varies in length.

During the cycle, the menses denudes the lining of the uterus and that blood flows off as a menstrual period, which is described here as lasting roughly three to five days in a normal cycle.

In a normal cycle, there is no bleeding. As the lining of the uterus, the endometrium builds up in the first portion of the cycle, primarily under the influence of endogenous estradiol depicted here, that causes a proliferation. This is called a proliferative portion of the menstrual cycle, and that's preparing the lining of the uterus for implantation of the egg. We'll work our way up to the egg in a moment.

Under the influence of progesterone, the second hormone secreted by the ovary, and we'll describe that in a moment,

progesterone rises, the endometrium, the lining of the uterus, becomes more glandular. This is called the secretory phase, so that it provides a kind of a place for the egg, if it's fertilized, to land and be nourished and grow.

Fertilization doesn't occur in most menstrual cycles, it doesn't, then the progesterone is no longer produced by the corpus luteum. We'll describe in a moment where that came from. Progesterone levels decline steeply and falling progesterone levels cause shedding of the endometrium and menstrual flow ensues.

That's got us through what happens to the endometrium over the course of the roughly four-week cycle that birth control pills duplicate.

Q So, Doctor, can you comment going up the slide?

First of all, let me be clear, the estradiol and progesterone that's shown there, is that endogenous meaning in the woman naturally produced?

A It's being produced, both are being produced in many places in the body, but primarily we'll focus on their production in the ovary.

Q Okay.

Doctor, before we get there, I want to be clear on one thing.

Before we introduce the concept of an oral contraceptive with synthetic progestin and estrogen, does a

woman's body normally produce endogenous progestin and estrogen in her body?

A Yes. And it was observed, I think it would be earlier, in the early 19th century, that animals, creatures who were pregnant, including women, didn't get pregnant again and curiosity about that, how that could happen.

And anatomists discovered that in the ovary, if they looked at the ovaries in pregnant animals, they would see in pregnant animals, a large ovary and in animals that weren't pregnant, a much smaller one. They surmised there must be something happening in the ovary then that prevented pregnancy.

Haverlandt, an Austrian physiologist, made the leap conclusion from those anatomical observations, perhaps it would be possible to develop a contraceptive based on, without knowing what the ovary was doing in a biologic sense, he hadn't identified progesterone, but using substances from the ovary, which must be keeping animals from keeping pregnant. So he collected material from pregnant ovaries in pigs and injected it into mice in the mid '30s, and the mice didn't get pregnant.

So he had the idea then of developing a contraceptive based on that from what turned out to be progesterone. World War II came, he died of a heart attack prior to that and nothing came of the idea until the 1950s, but the problem in

developing a contraceptive -- tell me if this is more detail than you want about this, but it's a fascinating story, the problem was that in order to get one milligram of progesterone, which is a weak progestin, you had to take -- you had to take the progesterone out of 2500 pregnant pigs' ovaries. So it was extremely expensive and, as you can imagine, extremely laborious.

A pill couldn't develop until there was a way to more efficiently make progesterone, which could be used for other purposes to make other kinds of steroids. It was important in that way, too, not just for contraception. So biologists embarked on an effort in the early 1950s, after the war in the United States, actually. Russell Marker, to discover a way to make a lot of progesterone relatively cheaper and that was accomplished.

We'll be talking later on about the generations of synthetic progestins or progestogens. That is they're derived from this original substance that they were able to make from plants that were high in something that could be easily converted or cheaply converted to progesterone. This was accomplished and it was possible to make birth control pills from that kind of work in the mid 1950s, and as we'll hear later, birth control pills were available by the early 1960s.

That's where the idea came from. We could, if we want to, talk about how estrogen got into it later on, but it comes

from the observation that animals already pregnant don't get pregnant again, must be due to something. It's that progesterone that's made in the ovary by this corpus luteum.

This corpus luteum gets us back to our original chart, comes -- develops from the production of the egg by the ovary. The ovaries making many follicles. It's selected, a particular follicle is selected by follicle stimulating hormone to grow. It reaches a big enough size that it releases an egg. The egg leaves. When it comes out, leaves a scar called corpus luteum yellow body and that produces progesterone, which maintains the pregnancy.

If the egg isn't fertilized, a signal is sent to the corpus luteum, no need to continue to make progesterone, progesterone levels fall and the endometrial lining sheds off, menses ensues and the cycle begins all over again.

And what birth control pills do is alter this cycle in a simple way to say, body, you're still pregnant, don't release another egg.

Q All right, Doctor.

Before we leave this slide --

A And just to close up, all that is mediated by the hypothalamus and the pituitary through a negative feedback mechanism which I won't describe.

Q But the brain is involved?

A Yes, primary action of giving that -- giving Haverlandt's

progesterone is a central action. There are other actions, but he didn't know that, but that's how it was subsequently discovered to work.

Q All right.

Doctor, now that we've covered how the female menstrual cycle typically works, have you prepared a slide then to help explain how combined oral contraceptives work to interfere with the normal cycle?

Have you prepared such a slide?

A Yes, I have. And I hope I laid some groundwork for what will now be, as this was a simplification of menstrual cycle, simplification of the way oral contraceptives work.

Q All right.

Mr. Brooks, can we have Darney slide 15, please?

Now, Dr. Darney, let's, first of all, I'd like you to explain the systemic effects of a contraceptive first before we get to the local effects, okay. I'd like to take them separately; systemic effect and local effect.

A Systemic effect, green on my chart here, and remember that I started telling this story by saying that it was a progesterone mostly that Haverlandt collected.

It turned out that estrogen is an important component of the combined oral contraceptive. Estrogen increases efficacy, increases the utility of, for example, improves bleeding pattern. It makes the pattern like that of a normal

menstrual period. It turned out that progesterone by itself didn't do that.

So we've talked about combined oral contraceptive pills containing both estrogen and progestin. Both of those have central actions to suppress ovulation. The estrogen works more on the follicle stimulating hormone.

THE COURT: Excuse me.

You're going to be educating a group of Italian police officers in a few minutes, Doctor.

Go ahead.

Q Dr. Darney, before you go further, I want to make sure the record is clear.

In the prior slide, 14, you were describing natural progestin and estrogen that's in the woman's body.

Now, that we're talking about combined oral contraceptives on Darney 15, you've labeled it estrogen and progestin.

Is this the natural or are we now introducing into the woman's body the synthetic estrogen and progestin?

A That's a good point. Sorry I skipped over that.

I talked about the need to make more potent progestins that were cheaper than progesterone. We're talking about what came out of Russel Markers, Carl Djerassi's effort and now they're available, at least 20 synthetic progestins, and I talked about the generations of their creation from wheat

progestins in generation one to progestins with varying degrees of selectivity, we call it over time.

So we're talking about those synthetic progestins as a class.

Q Can you just comment on this chart in terms of what the estrogen and progestins do in terms of systemic brain effects and then local effects?

A Yes. The estrogens, the varieties are smaller but they're also now synthetic. They're not natural estrogen although we're later on address the use of natural estrogens that are like the estrogens the ovary itself makes. There are some advantages of doing it that way.

So the estrogen and progestin together act on the hypothalamus first and on the pituitary. The estrogen primarily inhibits the hormone, follicle stimulating hormone that causes the ovary to grow eggs and selects one egg to get big enough to produce an egg.

The progestin also has central actions to aid in inhibiting ovulation and progestins vary in their capacity to do that. That's the selectivity I mentioned.

Primarily, the progestin inhibits luteinizing hormone and luteinizing hormone, you remember from my previous diagram, is the trigger that lets the egg come out of the follicle, the big follicle, the follicle stimulating hormone as stimulated the ovary to produce.

Those are the principle central actions and those are, as you'd expect, dose related and there are other central nervous system actions of estrogens and progestins on the other parts of the brain.

Q Okay.

Before we leave this slide, I would like you to make clear for us the three ways in which an oral contraceptive works, either alone or in combination, to prevent pregnancy, just the three basic ways, sir.

A Well, primary way is to inhibit ovulation, but in addition, this responsibility is the progestin. Those are local effects and by local, we mean that the ingested progestin is circulating in the blood, but it effects the reproductive organ specifically, where the greatest concentration of receptors for progestin and estrogen are. That is the reproductive organs, the uterus, the cervix and the ovaries themselves and the tubes are sensitive to estrogen and progestin.

The contraceptive actions primarily are progestin, in addition to inhibiting the luteinizing hormone trigger and preventing ovulation are to make the cervical mucous thick and viscous so that sperm can't get through the cervix, can't go up the tube and meet the egg and fertilize it.

In addition, the progestin, as I described earlier, has a different effect, an opposite effect on the endometrium.

The estrogen causes the endometrium to grow while the progestin causes it to become granular and if progestin is withdrawn, to shed off and that's an important property of the birth control pills, withdrawal of the progestin to establish regular menstrual bleeding.

It turned out that estrogen is an essential component in establishing that regular menstrual bleeding. So Haverlandt and others were wrong, it turned out, about the possibility of using progesterone or progestin by itself to have an effective and acceptable in terms of bleeding, oral contraceptive. We have these three effects.

Q So, in other words, three ways; the combination can either inhibit ovulation or thicken the cervical mucous so that the sperm and the egg can't meet or thin the endometrial lining so the egg and the sperm do meet, there wouldn't be enough blood to nourish the egg, three ways, right?

A Those are the primary three ways listed in order of probability of keeping a woman from becoming pregnant and inhibition of ovulation, obviously, is a long way ahead of the others for the combined oral contraceptive approach.

Estrogen and progestins have effects throughout the body. Estrogen and progestin receptors throughout the body and cortex of the brain, the liver, very important effects in the liver where they're metabolized. We focused here on the effects on the hypothalamus, pituitary and the uterus.

Q All right.

Now, I'd like to turn, as our final sort of slide about how these work, to a slide you helped us prepare. If I can have that, Mr. Brooks, Darney slide 16.

Now, I'd like to you to explain briefly, Doctor, what is meant by synergistic and antagonistic relationships between these two synthetic steroids that have now been introduced into the woman's body. I'd just like you to explain briefly to the Court how they work synergistically, but also how they work antagonistically so we understand just the challenges that face people who are designing oral contraceptives.

A Haverlandt, as I said, thought if you just sucked whatever was in the corpus luteum of a pregnant pig out, and injected in the mouse, the mouse wouldn't get pregnant and that's what you needed. Obviously, wasn't looking at other important qualities of combined oral contraceptives in women and it turned out that combining estrogen with the progestin resulted in a more effective contraceptive because together, they have effects that I described on the brain. Estrogen mostly on follicle stimulating, production of follicle stimulating hormone. Progestin mostly on the production of the trigger to release the egg, luteinizing hormone, but they have interactions.

Those interactions are synergistic. That is they enhance one another in the central nervous system and make the

contraceptive, the oral contraceptive more effective.

In addition, particularly important for the estrogen performance of oral contraceptives are the local effects. We've talked about the progestin making the cervical mucous viscous and thinning the endometrial lining. The effect of that thinning that glandularization is going to make the endometrium able to receive the egg is to cause irregular bleeding.

So the addition of estrogen to combined oral contraceptives, first observation during the first clinical trials was that estrogen, which by accident, happened to be in one of the lots, the first contraceptive trial and they noticed very different performance of those two contraceptives.

Gregory Pincus, the father of the birth control pill, at least the clinical aspects of it, success has many fathers and mothers, of course.

They asked themselves, what's different about these two lots? They observed that there was an estrogen contaminant in these pills that were supposed to be a progestin alone. The manufacturing process in the '50s was much more crude and relied on this natural substance. The principle effect they observed was not more efficacy. That came out later.

The principle effect they observed was regular bleeding. The women who were having regular bleeding were

more satisfied with the pill, were willing to continue to use it and continue participating in this famous initial trial carried out in Puerto Rico that led to the birth of the pill.

I should say Margaret Sanger arranged the funding for this trial. She was the founder of the Planned Parenthood Federation of America.

So it was observed that the estrogen had an opposite effect of the progestin. That is, that it stabilized endometrium, made the endometrium stay where it was, the lining of the uterus so there was erratic shedding between those two menstrual periods.

The goal of the producers then and the goal of those who make birth control pills in this 28-day pattern, ever since, is to achieve synergistic relationship between estrogen/progestin for efficacy and the antagonistic relationship between estrogen and progestin to make an acceptable birth control pill.

Q Dr. Darney, would it be fair to say that understanding that relationship and then designing an oral contraceptive is a complex task?

A Yes.

Q Okay.

A And we, over the years, have learned a lot about that complexities and dealing with them, that task.

Q Is it still a challenge even today?

A Yes.
Q Now, let's turn to the next topic, your Honor.
A You could say it's an increasing challenge because pills have become better and better, first generation, second generation, third generation and the better they are, the more of a challenge there is to make them better.
Q Okay.
I'd like to turn now --
THE COURT: Along those lines, what makes -- once the concept, once the technology had become understood, what makes a birth control pill better than another one?
THE WITNESS: Better efficacy, but principally fewer side effects. Both the side effects that are a threat to health and life and the side effects that keep women from using the pill successfully, too much bleeding would be an example. Irregular bleeding, headaches, not having a period when you expect to have one, nausea.
So mitigating those side effects, and the first side effect that was recognized, it was thought based on Haverlandt's work, that you had to use a lot of the progestin to suppress ovulation. Turned out, you didn't need as much as they thought.
So the first pill had a lot of progestin. If you had a lot of progestin, then you have to counteract the adverse effects on the endometrium with a lot of estrogen. Then

within ten years of the marketing of the first pills, and we're going to get to that first pill, aren't we?

Q Yes.

THE COURT: I have a feeling we're going to get to all of them.

MR. PAPPAS: Not all of them, just the high points.

A It's not going to get any simpler. The first -- they put a lot --

THE COURT: Let me get out of this. If this is interfering with your logical presentation, feel free to object to my question.

MR. PAPPAS: No, not at all, your Honor. I think it will hasten, but your Honor's question was right on point, which was, does the complexity still exist to this day and I think he was explaining that.

We will cover it more, but particularly in the next segment, Judge, when we turn now -- that's how the women's body works, that's what happens when you give her synthetic steroids. How does this affect people who actually then try to design combination oral contraceptives?

We thought it was important to understand at some level the complexity of what's going on in her body so the realization is that it's not a simple task.

Q So let's turn then to, Doctor, to the design or the creation of a combination oral contraceptive with this basic

knowledge, all right?

Let me ask you if you -- what are the three basic considerations that one has to take into account in designing a combination oral contraceptive?

Let me ask Mr. Brooks to bring up slide 17, which I think you designed to help us with this. Is this correct?

A Yes.

Q First of all, what I'd like you to do is identify, Dr. Darney, first what each of those terms are, efficacy, tolerability and safety that are all part of a pill and then tell his Honor why they're all interlocked like a puzzle and depend on one another.

Can you do that, please?

A I think that's the story I was starting here. You liken the development of the pill and it's refinement to a Model T and BMW. First it was relatively easy to improve, simple measures, but the product is now sophisticated enough that it's more complicated to make additional improvements, but they're being made and we know a lot more, obviously.

Oral contraceptive pill is the most studied drug there is, tens of thousands of papers written about it. It's more studied than insulin. Why is that? Because a key issue, when you give a drug to people who are otherwise healthy, is the safety of the pill. It's easy relatively in an epidemiologic sense, to observe effects on the safety when otherwise

completely healthy people, young women are using a product. That was the case of the birth control pill.

Of course, safety is the key consideration. Efficacy, no one would use something that doesn't work to do what it's supposed to do. Those are intertwined with what I talked about the bleeding as an example of tolerability side effects.

The third consideration is whether somebody can -- the pill is safe, it works, but can you actually use it? Does it cause so much irregular bleeding, does it cause so much nausea that a significant proportion of people would simply say it's not worth it, I can't take this.

Those effects may not be manifested in the person actually saying I won't take it, I can't stand it, it may be more subtle than that. That is, well, I'm going to skip a pill or two and maybe the nausea will go away. We all have that when we're taking an antibiotic and it makes us feel sick, I'll stop, feel better and start it again. That may or may not work on an antibiotic, but it certainly doesn't work with a birth control pill because depending on the pill, you have to take it everyday for those 28 days to be effective.

Working on developing pills you can just take when you need them, but we're a long way from that.

Q Dr. Darney, could you -- have you -- I noticed you've drawn the drawing as a puzzle fitting together.

My question is this: Can you just change one aspect of

the combination oral contraceptive, such as efficacy, without considering what effect it will have on tolerability or safety?

A No. A good example of that would be for me to resume my story about what happened with the first pill.

Clinical trials in Puerto Rico, they developed a pill that had a lot of progesterone because they believed that's necessary in order to make it tolerable, controlled the bleeding, they added a lot of estrogen.

Then the pill was marketed, this pill with a lot of estrogen and a lot of progestin in it. You can't usually, unless something is obviously unsafe, in a trial, in a clinical trial, is not going to be big enough to show relatively rare effects that can be severe. So epidemiologists, actually Professor Sir Richard Doll, who discovered the association between lung cancer and smoking, looked at data from Britain and saw that otherwise healthy young women were getting deep vein thrombosis and dying of pulmonary embolists, a kind of epidemic when the pill was marketed.

He wondered, as he did about smoking and lung cancer, what could be causing this? These women were taking birth control pills. Now, it was affecting so few women that it could never have been detected in the initial trial, but it was detected in a population, a large population taking pills.

So changes had to be made in the pill to -- and that was attributed later on by looking at different kinds of pills with different doses of estrogen. That serious side effect, the main concern still with the safety of birth control pills, although it's an increasingly rare event obviously, was this side effect and it was related to estrogen dose.

That started what we'll talk about later was an effort to reduce the estrogen dose in pills to make them safer.

But as the estrogen dose went down, tolerability was made worse. That is, there was more bleeding, questions about efficacy, and that's the story we'll get into.

THE COURT: In the first iteration, what were the dosages of the progesterone and estrogen?

THE WITNESS: The pills Richard Doll and Martin Vessey discovered to be causing DVTs had five times the estrogen that's in the standard pill today.

Q Can you give the approximate micrograms of that? What was the high dose that was causing the problem?

A We have the Enovid pill on here, don't we?

Q Yes, can you just give us the number?

A It was about 1.5, like that. The Enovid is no longer used, of course.

Q Mr. Brooks, can we have Darney slide 20?

Is this the pill you were referring to, to respond to his Honor's questions?

A Yes.
Q How much of estrogen was used?
A 150 micrograms and the standard pills, the most commonly prescribed pills today are 30 to 35, about five times.
THE COURT: Okay. That answers my question.
Q Dr. Darney, now, let's move to what a person of ordinary skill would have to consider in terms of their choices to make a contra -- combination oral contraceptive.
With that, Mr. Brooks, can we have Darney slide 18, please?
Now, what I'd like you to do here, Dr. Darney, is just briefly explain what each of those areas are in terms of consideration. We'll explore them in some detail later.
A We already talked about estrogen dose. You can adjust that.
Q Okay.
A That was adjusted early on and gave an opportunity to look at DVT and bleeding, for example.
And I mentioned earlier that there are four types of estrogen, others could be used but have been used in birth control pills. So estrogen type is important.
Q Okay.
What else do you have to consider?
A Then we've talked about progestin type. Remember, we started with progesterone, you couldn't -- you had to produce

synthetic progestins and over 20 progestin types have been produced. They're not all currently used in oral contraceptives.

Then the dose of that progestin. Remember, there has to be a balance and there's debate about what the balance should be. We can list that as another factor between estrogen and progestin because of this synergistic and antagonistic relationship. So progestin dose and the relationship between estrogen dose, progestin dose, estrogen and progestin type is important. That's all tied in together.

And then I mentioned that the first pill, and most pills prescribed today, use the 28-day cycle typical of the normal menstrual cycle. That meant that the first pills and most of the pills used today are 21-7, 21-7. Depending on other factors, estrogen, progestin, dose and type, you can vary that interval without any hormone.

Standard, most pills are still seven days, but it can be adjusted and there are arguments for and against adjusting that hormone-free interval, and what you put in hormone-free interval. If you put in more combined pills, do you put in estrogen, do you put in progestin in that seven days traditionally that have been free of hormone? That is, take a placebo pill usually so you don't forget to start the pill again.

Then finally, the order, administration of the pills,

the combined pills in relation to the progestin, the estrogen pills in relation to the hormone-free interval. How do you order that administration? That's become -- it's an example of the increasing complexity and the factors that affect that complexity in the current development of oral contraceptive pills.

So we quickly covered all of them.

Q Thank you.

MR. PAPPAS: Your Honor, I noticed we have been going about an hour and a half.

THE COURT: Anybody need a break? Let's take a few minutes.

(Recess.)

THE CLERK: All rise.

THE COURT: Thank you.

P H I L I P D A R N E Y, previously sworn, resumes the stand.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Dr. Darney, I want to turn now to a slightly different topic that has to do with the different progestins that were available in April, 2005. I want to elicit testimony from you about progestin potency and half life --

THE COURT: Are we going to focus on the 2005 period?

MR. PAPPAS: Yes, your Honor, in terms of progestin.

THE COURT: Good. I don't want to overstate the

obvious, but Dr. Barnhart's testimony was that we shouldn't look at this as though we're in 1965 or 1975, we should look at this as though we're in 2005, and we're aware of all of the above, right? That's what he said, Mr. Green?

MR. GREEN: Indeed, your Honor, that's correct.

MR. PAPPAS: Your Honor, that is certainly true what I'm going to cover now. Then there is something that has to do with understanding the gradual lowering of estrogen, but that will, again, be brought up to the current time.

THE COURT: Okay.

Q Mr. Brooks, can I have Darney slide 19, please?

Now, in terms, Dr. Darney, of the design or creation of an oral contraceptive, you gave the Judge the six things that you must consider. I want to focus on progestins now.

You prepared a slide listing some of the progestins available to a skilled artisan in April, 2005.

A Yes.

Q And is that shown on slide 19?

A It is. We discussed progestin types and this is an abbreviated list that discusses generation of progestin development. This is an abbreviated list of progestins used in birth control pills from the earliest first generation following the observation that synthetic progestins could be made to second generation to third and we have fourth-generation progestins also available.

These are selected typical progestins.
Q All right.
I want -- I take it you described them in terms of whether they're first, second or third generation. Is that correct?
A Right.
Q Okay.
Just very briefly, can you tell us what is meant by generation and the number given to them?
A It refers to time when they were developed. Remember, we went back to the 1950s, 1960s. It refers to molecules from which they were derived. All of them, of course, are related to progesterone, but they have different molecular derivations. That determines the generation as well, as they became more modern, so to say.
The second column --
Q We'll get to the second column in a minute.
All I want to establish right now is in terms of generation, does first generation mean the oldest progestin going back in time?
A Yes, to the 1960s.
Q And second generation, Norgestimate, Levonorgestrel are newer progestins, they came after norethindrone and norethindrone acetate, correct?
A Yes. And sometimes they are simply called old, new,

newer.
Q Okay.
And then Desogestrel and Gestodene are examples of third-generation progestins that came after Levonorgestrel, correct?
A Yes, they're actually derivatives of Levonorgestrel.
Q And now, I do want to explore both potency and half life, but let's start with potency first.
What does it mean to be a more or less potent generation progestin?
Do you understand my question? We want to focus on potency.
A I do.
Q What does that mean, when oral contraceptive specialists talk about the potency of a progestin, what are they measuring or referring to?
A Remember, it took 2500 sows over each to get a milligram of progesterone and progesterone is a weak progestin. So the effort was to develop more potent progestins and the earlier ones are weakest in the sense that they bind to progesterone receptors. Obviously, that wasn't known in 1950. They bind to progesterone receptors with less strength, less affinity we call it.
So in a general way, potency means the strength with which the compound binds to its cellular receptor.

Q Take it then to a second-generation progestin, which is often referred to as more potent.

What does it mean then to say that Levonorgestrel and Norgestimate are more potent than norethindrone and norethindrone acetate, what does that mean?

A They bind with greater strength and affinity to their receptors.

Q Okay.

What does it mean then in terms of binding affinity with a third-generation progestin, such as Gestodene or Desogestrel?

A They have a strongest affinity. Remember, though, that there are progestin receptors that I said throughout the body in varying concentrations. The greatest concentration in the uterus and cervix, but in the liver, progestins also bind.

So important also in creating these progestins was the, I mentioned this word earlier, selectivity. That is, do they bind with greater affinity to progesterone receptors in the liver or in the endometrium, do they bind in addition to androgen receptors? That depends on their molecular derivation. That's also a factor in this potency.

This is simple ranking of potency, but it's more complex than that.

THE COURT: Hold it.

Q Let me have, if I can, direct your attention, Dr. Darney,

to plaintiff's trial exhibit 87.

Can we put that up on the screen?

It's an article by Frank Stanczyk entitled Pharmacokinetics and Potency of Progestins Used For Hormone Replacement Therapy and Contraception.

Do you know the date of that, Doctor?

A 2002.

I know this article.

Q Therefore, it was prior art in this case?

A Yes.

Q What's this article generally about?

A It's Frank Stanczyk's description of his work. He's a leading scientist in steroid biochemist at USC. His work and other's work describing pharmacokinetics and potency of progestins.

Q All right.

Let me direct your attention to page 222 -- first of all, before I actually have you read part of this article, very short part --

MR. PAPPAS: I offer plaintiff's exhibit 87 into evidence.

THE COURT: Any objection?

MR. GREEN: No.

Q Can we have, Mr. Brooks, page 222 and, Doctor, you have highlighted the following language: "Among the latter group

of progestins, progesterone is less potent than Dydrogesterone, which in turn is less potent than medroxyprogesterone acetate in the 17 ethinylated 19-Nortestosterone group, Gestodene, Levonorgestrel and Desogestrel are more potent than Norgestimate, whereas norethindrone and its pro drugs, norethindrone acetate, are considerably less potent."

Do you see that, sir?

A Yes.

Q What is Dr. Stanczyk saying in 2002, in that article?

A He's describing the progestogenic potency of some of progestins commonly used in therapy, either for contraception or in hormone therapy, primarily in the menopause, but in other situations, too; endometriosis, for example.

Q As of 2005, was it still well understood by skilled artisans that Gestodene, Levonorgestrel and Desogestrel were more potent than Norgestimate as well as more potent than norethindrone?

A Yes, that would have been common knowledge.

Q Okay.

Now, would a skilled artisan recognize, in 2005, that a more potent progestin would also have had advantages for contraceptive efficacy?

A Yes.

Q And what would those be? In other words, what would the

advantages be of the more potent progestins with respect to contraceptive efficacy?

A Not that I described. They bind with greater avidity their receptors and have a greater effect of depending on their selectivity.

For example, Desogestrel is especially effective in restricting follicular development. Each have special characteristics, but the theme here is that they bind, some bind with greater avidity than others.

Q Is a more potent progestin better or worse at suppressing ovarian activity?

A Better.

Q What affect will the more potent progestin have on the cervical mucous viscous?

A Well, there it's especially important, depending on the progestin. A more potent progestin will make the cervical mucous viscous than a weaker one.

Q And what affect, if any, will a more potent progestin have on preventing the sperm from being able to go up the tube, meet the egg and become fertilized?

A The more viscous and scant the cervical mucous, the more potent the progestin, the less likely the sperm will be to penetrate it.

And some contraceptives, I might add, work primarily on that mechanism, not combined oral contraceptives.

Q And what affect would a more potent progestin have on the endometrium in terms of more or less bleeding?
A More potent progestin will result in less bleeding.
Q Now, let's move, if we can, to another topic, if we can. Mr. Brooks, can you put Darney slide 19 up again?

Dr. Darney, the other category in which you ranked the strength of the progestin choice was something called half life.

Do you see that?
A Yes. That's the pharmacokinetics part of Stanczyk's paper.
Q Okay.

Now, let's get a definition first.

What is meant by half life of a progestin?
A The time after reaching peak concentration that the concentration falls to one-half of its original concentration.
Q And why do we care about half life?
A Well, that's a key factor in any drug because the shorter the half life, the less the time you have a serum concentration adequate to do its job, whether that's killing bacteria, if it's an antibiotic; that you have to take four times a day because it has a short half life, or whether it's a birth control pill. The efficacy is, in part, determined by half life.
Q So, in other words, the longer the half life, the longer

the progestins in the woman's body to be contraceptively effective. Is that about it?

A Yes.

Q Now, by referring to Darney slide 19, can you approximate the difference or do you know the difference between the half life of norethindrone acetate, one of the weakest progestins, as opposed to, for instance, the second and third generations in terms of their half life, how long they're in the woman's blood?

A Yes. The first-generation progestins are more rapidly degraded. Their half life is about eight hours.

The third-generation progestins are more slowly degraded. By that I mean metabolized in the liver because of their molecular structure and Gestodene has about 14 hours half life.

Q All right.

Now, Dr. Darney, have you had an opportunity to review the trial testimony of Dr. Barnhart that was given last Monday and Tuesday in this courtroom?

A Yes, I have.

Q Let me -- I want to show you some of his testimony that you reviewed.

Mr. Brooks, can we pull up the trial transcript, day one, lines one -- page 118, lines ten through 119, line six?

I want to go at this in three parts, Dr. Darney, and

ask you questions about each one.

THE COURT: What page?

MR. PAPPAS: 118, your Honor.

THE COURT: Okay.

MR. PAPPAS: Line 10 through 119, line six.

Q Now, let's start, Mr. Brooks, can you highlight on the screen lines -- page 118, line 10 through the first answer?

Do you see that, Mr. Brooks?

The question was asked by counsel for Lupin to Dr. Barnhart, "Now, do you understand, Dr. Darney argues the prior art taught away from using low doses of ethinyl estradiol in combination with norethindrone acetate because the art expressed a preference with newer progestins that were more potent and had longer half life?"

Dr. Barnhart's answer, "Again, the description of potency and half life is a red herring."

Do you agree with Dr. Barnhart that considerations of potency of the progestin and half life is a red herring?

A No, I do not.

Q By the way, do you understand the general vernacular or colloquial use of the term "red herring"?

A Yes, I think in a general way I do.

Q Do you understand what Dr. Barnhart was saying when he called potency and half life of a progestin a red herring in this case?

A Yes.
Q How did you interpret that?
A Well, it's not the term I would have used in a similar situation, but I think what he's saying is that it's not important. You're going down, looking at the wrong -- it's mis -- wrong thing.
Q Do you agree with that testimony?
A No.
Q Okay.
Will you tell his Honor why potency and half life are important factors and were important factors in April, 2005, to a skilled artisan considering what to do in designing an oral contraceptive?
Go ahead.
A There are a number of reasons. I'll start with one, with half life, for example.
As I said, short half life means that you have to need to take a drug more often. Taking antibiotics four times a day is less convenient and less likely to occur on time than if you needed to take the antibiotic just once a day, or if you can have a long-acting antibiotic, azithromycin, for example, which you just have one injection. It works.
Compliance, that is taking the drug correctly, so it can achieve its end, then becomes much easier.
The same is true with birth control pills. The longer

half life means that it's not as important to take the pill exactly on time everyday. The pill is more forgiving.

You could be several hours late because you'll still have an adequate concentration to inhibit ovulation or to keep the cervical mucous viscous. That's a fact, cervical mucous is exquisitely sensitive to changes in progestin concentration and returns to its normal state very quickly. So the longer half life keeps it where you want it from the point of view of contraception for a longer time.

So that's just one example about why half life is not a red herring. That's why progestins have evolved over the years, since 1960, first, second, third generation long-acting progestins. You've seen that happen with other drugs, moving toward extended release, longer half life.

Q Doctor, now, sticking with half life for a moment, can you tell us what effect progestins with longer half lives, such as the second and third generations, tend to have with respect to cycle control?

In other words, do the longer half life help control bleeding or does it make it worse?

A It helps control it. Remember our initial description of the way the menstrual cycle works. Progesterone withdrawal, that is when no fertilization occurs, the corpus luteum stops making progesterone, the endometrium promptly sheds off giving regular menses that women expect if they're healthy and

normally functioning.

We want to achieve the same thing with combined oral contraceptives. A longer half life means that the endometrium remains in place, if you fill, to take the pill exactly on time. With a short half life progestin, if, during those 21, 24 days of pill taking, you fail to take it on time or miss a pill, the endometrium perceives that as progestin withdrawal and begins to bleed.

Longer half life means the endometrium won't have that perception and won't shed off erratical and we talked about the importance of regular bleeding, no intermenstrual bleeding to a women's capacity to continue taking combined oral contraceptives.

Q And, Doctor, do the second and third generation of progestins, such as Levonorgestrel, Norgestimate, Gestodene and Desogestrel have longer half lives than norethindrone acetate?

A They do. I mentioned roughly eight versus 14. For example, they were designed, developed to have longer half life.

Q All right.

And is norethindrone acetate's shorter half life one of the reasons it has been associated with poor cycle control?

A Yes.

Q Now, I want to direct your attention to another part of

Dr. Barnhart's testimony.

If you can scroll down, Mr. Brooks, to the paragraph that refers -- starts with "It's true."

MR. PAPPAS: Your Honor, this is continuing on page 118.

Mr. Brooks, can you give me the line number?

MR. BROOKS: Twenty-two.

MR. PAPPAS: To 119, three.

Q This is in follow-up, Dr. Darney, to Dr. Barnhart's testimony that potency and half life was a red herring.

You see where he testified in a response to a question about why he said that, he said "It's true, some progestins are more important than others, but that's taken into account in the dosing. If one potency, you need only -- you only need one milligram, that's a potent one. If you need five milligrams of another one, you need five milligrams, but at the end of the day, they're equally potent on the progestin receptors and they cause effective concentration. That's why the Gestodene dose, for example, is lower than the norethindrone dose, but they're equally ultimately potent according to the body."

Do you see that, sir?

MR. GREEN: Your Honor, if I can object on one issue? We believe there's a transcription error where the word is "important".

THE COURT: I think it should be potent. I agree, it seems to be out of context. Line 22, correct?

MR. GREEN: Yes, thank you, Judge.

THE COURT: You see that, Mr. Pappas?

MR. PAPPAS: Yes, your Honor.

Q Are more potent than others?

A Yes, I agree.

Q Thank you.

My copy still had "important", but I'll adjust it.

Do you see that correction there, Dr. Darney?

A I do, yes. I agree with it.

Q Do you agree with that testimony of Dr. Barnhart?

A No, I agree with the correction, but I don't agree with the statement.

Q What is he saying there about the potencies of progestin and being controlled by dose?

A He's saying that you can simply increase the dose enough to make up for the lack of potency, and I believe the short half life of the first early progestins and, therefore, make them equal to the third-generation progestins and here he's addressing efficacy rather than bleeding.

Q Is that true?

A No, that's not true.

An analogy would be a less potent antibiotic or antibiotic with a short half life and you decide that well,

I'll just -- I'm worried I can't remember to take it four times a day, so I'll just take them all at once. Taking a big dose like that, remember, I described -- talked about the fact that there are progestin receptors throughout the body, liver and so on. If you took all of your antibiotics at once, you'll notice that that drug, all of that increase in dose has adverse effects. In the case of an antibiotic, it might be nausea. In the case of a progestin, it's going to affect the liver adversely because the dose is so high.

That's why doses aren't simply adjust, of any drug, aren't simply adjusted upward to account for other characteristics of the drug.

Q Taking Dr. Barnhart's testimony then to its conclusion, in other words, if I want to ask you this, hypothetically, you would want to give a woman more of a drug containing norethindrone acetate to try to make it act like one of the potent progestins like Desogestrel, are you with me?

A Yes.

Q Could you simply, in your view, medically sound just dose the woman up?

In other words, instead of giving her one milligram of norethindrone acetate, you gave her four to try to equal the potency of Desogestrel, could you do that, would that be a wise medical practice?

A No. As I was describing, you would risk unexpected side

effects.
Q Such as?
A Intolerability at least and perhaps safety.
Q Now, Dr. Darney, Dr. Barnhart concluded that section of his answer by saying, "That's why the Gestodene dose, for example, is lower than the norethindrone dose, but they're equally ultimately potent according to the body."
Is that true?
A No.
Q Why is it wrong?
A Because of the selectivity of different progestins for different receptors in the body. That is, these new progestins are designed to be, for example, less androgenic, bind to the liver with receptors with less avidity. So the effects are diffuse and simply increasing the dose of one is likely to result in adverse effects in another organ system.
Q Dr. Darney, let's review something here.
The progesterone -- the progestin acts on progestin receptors in the endometrium, correct?
A Yes.
Q And it also acts on the cervical mucous, correct?
A That's right.
Q It also acts on the hypothalamus in the brain, correct?
A Correct.
Q But I want to make sure what you're getting across to us

is clear.

Do oral contraceptives, specifically the progestin, also reach other receptors in parts of the woman's body other than just the brain, the cervix and the endometrium that are directly effected to try to prevent conception?

A Yes. Any drug that's given systemically is distributed in the blood stream and, in fact, the first effect on the liver, for example, in oral contraceptives is a very important one.

Q Is that why you have to care about how much of a particular progestin you give to a woman?

A Yes.

Q Now, by the way, when you prescribe -- I'm going to move now from designing to prescription.

When you prescribe as a doctor, as you've done for over 40 years, a combination oral contraceptive, do you consider the relevant potency of different progestins?

A Yes.

Q Okay.

So while you consider potency -- why do you consider potency in the prescription?

A Because potency of the progestin effects the three basic qualities of oral contraceptive pills that we described, any drug, efficacy, safety and tolerability or acceptability.

Q And has there been a trend in the '90s into the early

2000s time period away from norethindrone acetate and towards pills with the more potent progestins, such as second generation and third generation?

A Definitely.

Q Okay.

Can I have, Mr. Brooks, bring up Darney slide 27?

Is this a slide you helped us prepare, Dr. Darney?

A It is.

Q Now, the first line says, 1973 to 2005, 22 out of 41 progestins used norethindrone acetate or norethindrone, correct?

A Yes.

Q Okay.

Now, Dr. Barnhart, do you recall his testimony where he tried to create the impression that norethindrone acetate was still very popular in terms of development into the 1987 to 2005 time period?

A Yes.

Q Do you recall that?

Now, in point of fact, sir, how many regimens, new regimens, new regimens using norethindrone or norethindrone acetate were approved by the FDA between 1987 and 2005.

A The Estrostep that I list here, one.

Q Now, in contrast between 1987 and 2005, were all of the regimens that you've listed there that were approved, did they

use second- or third-generation progestins?
A All of these use second- or third-generation progestins.
Q What progestin does Ortho-Tri-Cyclen have?
A Norgestimate.
Q What did Ortho-Tri-Cyclen and I think you said Norgestimate, correct, Doctor?
A Yes.
Q What progestin did Desogen use?
A Desogestrel.
Q What progestin did Alesse use?
A Levonorgestrel.
Q What progestin did Mircette use?
A Desogestrel.
Q What progestin did Cyclessa use?
A Desogestrel.
Q What progestin did Yazmin use?
A Drospirenone.
Q Is Drospirenone a fourth-generation progestin?
A Yes.
Q What progestin did Ortho-Tri-Cyclen Lo use?
A Norgestimate.
Q And what progestin did Seasonale us ?
A Levonorgestrel.
Q Dr. Darney, in your expert opinion, does that slide help explain what the trend actually was as a matter of fact in the

1987 to 2000 time period, in terms of what progestins were being selected by skilled artisans who were actually making these contraceptives?

A Yes. This is a list of FDA-approved contraceptives and it was nine to one newer progestins over the first-generation progestins.

Q Okay.

I want to turn to another section of Dr. Barnhart's trial testimony, Dr. Darney.

Mr. Brooks, can you bring up the trial transcript day one?

MR. PAPPAS: Your Honor, at least in my copy, it's page 119, line 7 through 13.

Q Now, do you recall this testimony, sir, given in response to questions about whether or not half life mattered?

A Yes, I do.

Q And when Dr. Barnhart -- let's just read "The same goes for half life." This was after he did potency. "The half life is important in the progestin such that it's a long enough half life that you can take it once a day. If the half life is too short, you couldn't take it once a day, you would need two pills a day or three pills a day. All of the progestins we're talking about have a sufficient half life to allow once a day dosing."

Do you see that, sir?

A Yes.
Q I want to know what your response to that is? Is Dr. Barnhart correct or incorrect that half life does not matter for both efficacy and cycle control?
A No, for the reasons I've discussed, half life is very important for both efficacy and cycle control. That is acceptability.
Q Okay.
Why is half life of the progestin important for efficacy?
A Well, remember our discussion of the definition of half life and why it's important to have a long half life is that it allows the user to take the combined oral contraceptive pill with more latitude. That is, it's not as important to take it exactly the same time everyday in order to maintain efficacy, cervical mucous affect or a good bleeding pattern, endometrial affect.
The shorter the half life, the more critical it is to take it exactly on time and when these new progestins, as these new progestins were developed, beginning in the '70s, one of the reasons they're more and more commonly used as we just saw, is that all of us interested in oral contraception rejoiced at the longer half life of the new progestins. That's why they're designed that way.
Q All right.

Now, is the half life of the progestin important for cycle control?

A Yes, because of endometrial effects and the effect of withdrawing progestin on endometrial shedding.

Q Now, wrapping up this section of our examination, does the rate or dissipation of the progestin matter in cycle control?

A Yes, it does.

Q Why and in what way?

A The sooner the progestin is gone, metabolized by the liver, the sooner the endometrium senses a decline in serum progestin levels. And I mentioned that the endometrium, endometrial cells are exquisitely sensitive to changes in progestin. That's how they work. If they sense that there's -- the progestin is dropping, they begin to shed. So if you take a pill too late or miss a pill, then using a weak progestin, you're more likely to have irregular bleeding.

Q To wrap up this topic, do you agree with Dr. Barnhart that all of these different progestins are interchangeable so long as you adjust the dose?

A No, I do not.

Q And let me ask you this question. Can we have Darney exhibit 27 up?

Let's test Dr. Barnhart's assertion even further. If all these progestins were the same and all you had to do was

dose the woman up or give her a less dose, Dr. Darney, what explanation would there be for all these different progestins that have been used, Desogestrel, Gestodene, Norgestimate, Levonorgestrel, what explanation would there be?

A The explanation is that we've spent 40 years developing improved progestins.

Q So they're not interchangeable, are they?

A No.

Q And you can't simply adjust the dose, correct?

A No.

THE COURT: Are you going to another area?

MR. PAPPAS: I am.

THE COURT: Let's take ten minutes and we'll go right until about five to one.

THE CLERK: All rise.

(Recess.)

THE CLERK: All rise.

THE COURT: Have a seat.

P H I L I P D A R N E Y, previously sworn, resumes the stand.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Dr. Darney, I just -- before we move onto estrogen, I want to make sure we're clear on something. I may have asked you an imprecise question earlier.

Let me ask you more precisely hopefully. As opposed to

the design now of a progestin, after an oral contraceptive has been designed and is then considered by a clinician, is relative potency of a progestin relevant or is the OC instead considered as a whole?

A Well, previously we have been talking about the design of oral contraceptives, how you put these parts together to make a safe, effective and tolerable oral contraceptive.

After it's put together and undergone clinical trials and it's approved by the FDA, and clinicians begin to use it, that's not a consideration. The oral contraceptive has been demonstrated to have accounted for potency, balance, safety, efficacy and to a certain extent, tolerability.

Q And the actual dose of the particular progestin has been approved, correct?

A Yes, that's implicit in the design which clinicians then use as a completed combined oral contraceptive.

Q All right.

Now, I want to turn to a section of your examination that I told his Honor we would cover today, which is your opinion about the difficulty in lowering estrogen dose below 20 micrograms, even as late as 2005, okay?

A Yes.

Q Now, let me ask you, Mr. Brooks, to pull up testimony of Dr. Barnhart, day one.

MR. PAPPAS: Your Honor, this is at lines -- page

116, line six through page 117, line two.

Q Do you see that on your screen, Dr. Darney?

A Yes, I do.

Q Dr. Barnhart was asked, "QUESTION: Do you have an opinion as to how you and Dr. Darney have reached opposite conclusions in this case?

"ANSWER: I think the opposite conclusions have been reached because of the perspective. I think I've tried hard to give you my rational to take in the entire body of literature at the state of the late '90s and early 2000s, recognizing all the modifications that have already been made in the pill. Therefore, it's a very simple task to make this minor modification. My understanding from reading Dr. Darney's documents, he feels it's much more complicated if you start at the back, 1974 with Loestrin and used a 21-7 day pill.

"My opinion is we're well beyond that, we don't have to go back to look at that history, we don't have to look back at the respective and complicated times back in the '70s and '80s, trying to figure out what the right dose of estrogen and progestin is. That's already well known to everybody. There's a strong motivation to make these changes and based where you sit in the late 1990s, 2004, this is a modification that is only obscured if you try to put yourself back in the '70s and '80s."

Dr. Darney, do you agree with Dr. Barnhart that you are stuck in the '70s and focusing on irrelevant old technology?

A No.

Q Now, so why can't we, as Dr. Barnhart suggests, ignore the history of combination oral contraceptives from the 1970s and 1980s, if we are truly to understand why no one went below 20 micrograms of estrogen?

A Well, there are a number of issues here. We've talked about one of them that was the motivation to reduce the estrogen dose back in the old days that Dr. Barnhart's referring to here.

Among those motivations or resulting from those motivations to reduce the estrogen dose to make the pill safer, were new birth control pills in which the dose went as low as 20 micrograms by 1974. So I think it's instructive to look at the history of that effort as well as to recognize that most of the pills prescribed today are higher doses than the great majority.

I understand that the proportion of prescriptions written today for Loestrin 1/20 and its generic copies is less than two percent. The pills been around since 1974.

Q Okay.

Let me ask you, before we go, very briefly through the stages of estrogen development. Today, as we stand here or

sit here in this courtroom, other than Lo Loestrin FE, is there any approved combination oral contraceptive in the United States approved by the FDA that has less than 20 micrograms of estrogen?

A No.

Q Lo Loestrin FE is the only pill, correct, in the United States that has less than 20 micrograms of estrogen?

A That's correct.

Q Okay.

Now, Mr. Brooks, let's return briefly to Darney slide 20. I believe we showed that to his Honor before.

I just want to ask you a question about this so that we can orient ourselves.

Enovid was introduced in 1961, correct?

A That's right.

Q How much estrogen did it have?

A As we discussed before, it had 150 micrograms of estrogen.

Q All right.

Now, what estrogen was used then?

A There were two used then, ethinyl estradiol and mestranol.

Q Now, is 150 micrograms of mestranol or ethinyl estradiol a high dose by today's standards?

A Yes. We discussed earlier that it's five times the

standard dose today.
Q What led to the reduction in estrogen dosage now as we move forward, downward from 150 micrograms of either ethinyl estradiol or mestranol?
A The observation we discussed earlier, the epidemiologic observation that doses of estrogen that high were associated with an unacceptable risk of deep vein thrombosis and pulmonary embolism, life-threatening events.
Q Now, we've used the term "cycle control" several times today.
Let's just be clear as we go forward, when the literature refers to cycle control in relation to combined oral contraceptives, what are we talking about?
A We're talking about the degree to which a combined oral contraceptive is able to mimic the typical and expected menstrual cycle, the cycle that we described at the outset that occurs in normal women who aren't exposed to exogenous steroids.
Q Unscheduled bleeding?
A Another word for it, yes.
Q Or getting even more colloquial, it's the woman bleeding when she doesn't want to or should be bleeding, right?
A And doesn't expect it, right.
Q Very well.
Now, coming forward in time, '60s, '70s, '80s and even

up to the '90s, was there a generally-accepted proposition about what would happen to unscheduled bleeding or cycle control if you lowered estrogen?

A Yes. As we discussed, a motivation to lower estrogen was a really important one, deep vein thrombosis. So designers of oral contraceptives responded by progressively lowering the estrogen dose.

Example would be the one I, extreme example would be the one I referred to earlier, 1974, the marketing of a 20 microgram dose. That was an exception. Others reduced the dose to 80 from 150, then to 50, then to 35 and 30, depending on the progestin and observed that there was reasonably good cycle control at doses down to 25.

The experience with doses less than that showed poor cycle control.

Q All right.

Is there -- before we embark on this review, is there a physiological explanation why the lower the estrogen goes, the higher the incidents of break-through bleeding?

A Yes, a very clear explanation.

Q And what is that?

A That's the one we've discussed of the sensitivity endometrium to estrogen dose, that the estrogen has a stabilizing influence, that influence that was discovered when pills were first designed and inadvertently they contained

estrogen, but they had a lot better bleeding pattern than those that didn't.

Q Mr. Brooks, can I -- we put up plaintiff's trial exhibit 48?

Let me know when you have that in front of you, Dr. Darney, on your screen.

A I have it.

Q This is an article by Dr. Kaunitz, correct?

A Yes.

Q Entitled Oral Contraceptive Estrogen Dose Consideration?

A Yes.

Q And is the date of this, so we have it for the record, 1998?

A Yes.

Q This was prior art to the '984 patent, correct?

A Yes.

Q Now, I want to direct your attention to the second page of the article, page 16S, as in Samuel.

Do you see that paragraph there, Dr. Darney?

A Yes.

Q Will you read that for us and tell us what it means?

A Yes. "By providing endometrial support," that's the stabilizing influence I just talked about, "the estrogen component of combined oral contraceptives prevents break-through bleeding. As the estrogen doses decline,

therefore, cycle control also declines. Accordingly, 20 microgram ethinyl estradiol oral contraceptives have been found to have higher rates of break-through bleeding and spotting than 30 to 35 microgram formulations, an observation noted with norethindrone acetate as well as with Desogestrel formulations."

Q All right, sir.

Now, looking in particular at the second sentence that you read, "As OC," oral contraceptive "estrogen doses decline, therefore, cycle control also declines," how would an ordinary skilled artisan have understood that statement in April, 2005?

A Person of ordinary skill in the art would have read that as an admonition not to lower the estrogen content of the combined oral contraceptives.

Q Is Dr. Kaunitz's observation here a unique observation or was it considered to be well known to skilled artisans in 2005?

A No, he, I and many others have written about this issue. This kind of statement is ubiquitous in the literature.

MR. PAPPAS: Your Honor, I offer plaintiff's trial exhibit 48.

MR. GREEN: No objection, your Honor.

Q Now, Dr. Darney, have you prepared a slide of other literature likewise stating that as estrogen doses declines, so does cycle control?

A Yes, just a couple of examples.
Q Mr. Brooks, can we have Darney slide 21, please?
Now, we have -- let's take the first quotation.
Who is the author there?
A That's my writing about this issue.
Q And when was it written by you?
A 1997.
Q And what did you write there?
A "The frequency of break-through bleeding and spotting has been shown to increase as the estrogen dose decreases."
Q Is that generally understood to have been true in 2005?
A Yes.
Q In your opinion, is this something that was well settled and would have been understood by a skilled artisan in 2005?
A Absolutely.
Q Okay.
Let's move quickly to Mr. Akerlund in his article, published in 1993.
What does he tell us about the decrease in estrogen and cycle control?
A Akerlund here is describing his own study which demonstrated low pregnancy rates of the 150 Desogestrel 20 microgram and 150 Desogestrel 30 microgram of estrogen combinations and very little difference between them in general side effects.

"A difference which was demonstrated in this randomized double blind comparative investigation was the less effective cycle control with the 150/20 combination, leading to more drop-outs for that reason."

Q And finally, what did Professor Thorneycroft indicate about the relationship between lowering estrogen and cycle control that's in his article on Darney slide 21 that was published in July, 2001?

A Thorneycroft writes here, "However, when OC formulations with the same progestin component are compared," as in Akerlund's studies and others, "the lower the dose of estrogen, the more diminished is the cycle control."

Q Now, let's move then forward in time to 1974, with the introduction of Loestrin 1/20.

What is contained in the pill Loestrin 1/20, sir?

A Twenty micrograms of ethinyl estradiol and one milligram of norethindrone acetate given for combined preparation for 21 days followed by seven days of placebo or no hormones.

Q Now, do you have a slide that demonstrates that, sir?

A Yes.

Q Can we have Darney slide 22, Mr. Brooks?

A So at the top, the progestin norethindrone acetate, one milligram, 21 days, 20 micrograms of ethinyl estradiol and the seven days of no steroids to give us the standard 28-day administration cycle.

Q Dr. Darney, by the 1970s, had researchers settled on a conventional estrogen dose?
A By the 1970s?
Q Yes.
A Yes, I would think that by the 1970s, the conventional dose was 30, 35 micrograms ethinyl estradiol.
Q And so Loestrin 120 lowered that estrogen dose to 20 micrograms, correct?
A Yes.
Q In terms of cycle control and efficacy, what was learned by people of skill in the art about how Loestrin 1/20 performed, both in terms of cycle control and efficacy?
A Well, the admonitions we previously listed among others referred, in part, to the experience with Loestrin 1/20 with regard to irregular bleeding and increased rates of discontinuation because of unscheduled bleeding.

Subsequently, studies showed that Loestrin 1/20 was also less effective than other combined oral contraceptives.
Q All right.

Let's turn, if we can, Mr. Brooks, if you can bring up plaintiff's trial exhibit 10?

Do you see that article by Dr. Wally Bounds, Dr. Darney?
A Yes.

Dr. Bounds previously mentioned Dr. Vessey and Peter

Wiggins.

Q Now, publication date is 1979?

A Yes.

Q Let me direct your attention to page 328, the right-hand column directly under Discussion with the sentence starting with the word "Despite".

Can you read that first sentence and tell us what it discloses to a skilled artisan?

A "Despite the small sample size, the main finding in this clinical trial seems to be clear-cut. Loestrin 20 provides poor cycle," different name in U.K., "provides poor cycle control and as a result is a less acceptable contraceptive than Microgynon 30. There is also a suggestion that Loestrin 20 might be less effective than Microgynon 30, but the difference between the accidental pregnant rates does not reach statistical significance."

Q Let's turn our attention now to table two on page three 27 of that article.

Do you see that, sir?

A I do see it, yes.

Q What can you tell the Court is reflected in that graph or table actually about the discontinuation rate at 12 months for Loestrin 1/20?

A In the second column treatment group, L is Loestrin 20 and M is the 30 microgram estrogen preparation and you see

abnormal bleeding, simply go out to 12 months of use that there is a statistically significant large difference between abnormal bleeding rates of the 30 microgram preparation and the 20 microgram preparation. Twenty-seven percent in one case and about four percent in the other.

Q Twenty-seven percent is for what drug?

A Is for Loestrin 20.

Q Compared to?

A The 30 microgram preparation Microgynon, which has bleeding rate of 3.7 percent.

Q And how much estrogen does Microgynon have?

A Thirty micrograms.

Q This is a comparison of a 30 microgram estrogen pill to a 20 microgram estrogen pill, Loestrin 1/20, correct?

A Yes.

Q What's shown on the table with respect to continuation rate?

A Continuation rate, again, L and M, continuation rate of Microgynon the end of the year was 52 percent, but the continuation rate of Loestrin 20 was only 27 percent.

Q Can you tell from the table why the discontinuation rate for Loestrin 1/20 was higher than per Microgynon, 30 microgram pill?

A Well, the other factors that could affect the continuation rate were not significantly different. So

presumably the continuation rate differences can be attributed to the significant difference in abnormal bleeding.

Q Let me ask you to turn to --

MR. PAPPAS: Your Honor, if I haven't already, I offer plaintiff's trial exhibit 10 into evidence.

MR. GREEN: No objection.

MR. PAPPAS: Your Honor, at the same time, I failed earlier in the examination, summary exhibits under Rule 1006 to move in plaintiff's trial exhibits 21, one and 99. We move them in at this time.

MR. GREEN: For demonstrative purposes?

THE COURT: Yes, summary charts, 1006.

MR. PAPPAS: 1006. This is different and I'll be glad to be heard on this. I offer them under 1006 to actually come into evidence, not just as demonstratives.

THE COURT: I understand that. That's what 1006 does.

MR. PAPPAS: Thank you.

Accepted, your Honor?

THE COURT: Yes.

Q Let's now turn to plaintiff's trial exhibit 97.

Can we have that up on the screen, Mr. Brooks?

Do you have that, Dr. Darney?

A I do.

Q Okay.

It says, "WHO task force on oral contraceptives," titled "A Randomized Double Blind Study of Six Combined Oral Contraceptives Published in Contraception."

First of all, sir, who is WHO?

A The World Health Organization and in this study, they're attempting to determine which oral contraceptives ought to be recommended for use in worldwide family planning programs.

Q And the date on this is 1982?

A Yes.

Q So it's prior art?

A Yes.

MR. PAPPAS: I'd offer plaintiff's trial exhibit 97, your Honor.

MR. GREEN: No objection, your Honor.

Q Can we have page 233 up, Mr. Brooks?

Specifically, can you highlight preparation number five?

Do you see that, Dr. Darney?

A Yes. That's the preparation we have been talking about. The trade name is in the United States Loestrin 1/20.

Q Now, turning to page 238, if we can, Mr. Brooks, beginning with the sentence "In this instance" and reading through "the United Kingdom."

Dr. Darney, can you read that into the record and tell us what that is saying about the results of the World Health

Organization's study about Loestrin 1/20?
A "In this instance, the preparation with 20 micrograms of ethinyl estradiol and that with 400 micrograms norethindrone acetate can be considered as unsatisfactory because of the higher discontinuation rates. The former preparation was shown to be significantly less acceptable and effective than ethinyl estradiol 30 micrograms and Levonorgestrel 150 in a controlled clinical trial reported from the United Kingdom."
Q What does this article teach a skilled artisan about Loestrin 1/20's discontinuation rate?
A That it has higher discontinuation rates than the contraceptive to which it was compared.
Q What would a skilled artisan conclude about Loestrin 1/20 in terms of the reasons for the discontinuation?
A The conclusion would be that it was unsatisfactory because increase incidents of irregular bleeding led to high discontinuation.
Q All right.

Let's move to plaintiff's trial exhibit 93.

Can we bring that up, Mr. Brooks?

This is Szarewski and Guillebaud, Contraception Users' Handbook, 1998, date of that article?
A Yes.
Q Prior art?
A Yes.

MR. PAPPAS: Your Honor, I move in plaintiff's trial exhibit 93.

MR. GREEN: No objection, your Honor.

THE COURT: All right.

Q Now, what is this?

First of all, have you heard of Dr. Guillebaud?

A Yes, I know him well.

Q Have you reviewed any expert reports in this case from Dr. Guillebaud?

A Yes, I have.

Q Okay.

Do you know who he prepared those reports for?

A He prepared the reports for Lupin, Watson.

Q Okay.

Now, what does plaintiff's trial exhibit 93 generally concern?

A It's a handbook for couples, women, patients who are interested in using contraception. It's a users' guide.

Q Let's direct our attention to, if we can, pages 56 and 57. Mr. Brooks, can you bring that up?

Will you please read that highlighted language and tell us what it means to one of skill in the art, Dr. Darney?

A "Here's some suggestions for dealing with break-through bleeding on specific pill formulations." And under Loestrin 20, 20 micrograms of estrogen plus one milligram of

norethindrone acetate, he writes, "This advice, since this," that is break-through bleeding, "is almost universal, this pill has never been very popular. It will probably be sufficient to change to Mercilon, but if not, you can workup from there. Within the next year, there may be a new 20 microgram pill containing 100 micrograms of Levonorgestrel as its progestin." That is a slightly lower dose version of Microgynon, the pill that was examined before in the 30 microgram trial we discussed. "It is hoped that this might have better cycle control than Loestrin 20. The other pill, Mercilon, contains third-generation progestin Desogestrel."

Q And what is being indicated there or stated to a skilled artisan about what one would need to do with the estrogen dosage to Loestrin 1/20 to improve it?

A Well, there are two suggestions here. That is, move up to 30 micrograms or change to a pill with a more potent progestin.

Q Okay.

In view of that, let's find out what actually was done.

Are you familiar with what was done to Loestrin 1/20 in terms of the next generation pill?

THE COURT: By whom? What was done to it by whom?

MR. PAPPAS: By Parke-Davis, the one who made the pill in the first instance.

A Yes, I am.

Q Did you prepare a slide to demonstrate the reaction of Parke-Davis to the poor cycle control and efficacy we'll get to in a minute, of Loestrin 1/20?

Can we have Darney slide 25?

A I did prepare this slide. This demonstrates the response of Parke-Davis, now Warner Chilcott, to the problems of bleeding with the Loestrin 1/20 pill.

What they did was to increase the estrogen dose in a step-wise fashion. That is beginning with Loestrin 1/20 for the first, I believe five days, they went up to 30 micrograms and then went up to 35 micrograms and maintained, as shown in the orange bar, the norethindrone acetate dose at the one milligram.

Q What was the reason for increasing the dosage of Loestrin 1/20 to make Estrostep with more estrogen?

A To achieve a better bleeding pattern. That is, use the estrogen, additional estrogen to stabilize the endometrium, to discontinue -- to reduce discontinuation for irregular bleeding.

Q And just so we're clear, Dr. Darney, earlier I believe you had given an answer to one of my questions that Loestrin 1/20 has less than two percent of the market. You may have said that as of today.

Were you referring to today or as of April, 2005?

A That was 2005.

Q Now, we've covered, to some extent, the issue of cycle control.

I'd like you to tell us how important the issue of break through or unscheduled bleeding is to the actual design and use of an oral contraceptive?

A It's very important as some of the literature we reviewed shows.

Q Okay.

Let me -- can we have plaintiff's exhibit, trial exhibit 82A, please?

This is a Clinical Guide For Contraception. This is by you and Dr. Speroff, correct?

A Yes. This is our third edition.

Q Okay.

When -- do we have a date for the third edition?

A I believe it's 1995 or so.

Q Okay.

Is this the same book we mentioned earlier when we were covering your professional background today?

A Yes, actually 2001. 2001. So it was prior art.

A Yes.

MR. PAPPAS: I move into evidence plaintiff's trial exhibit 82A.

MR. GREEN: No objection.

Q Can I direct your attention to the top of page 94, Dr.

Darney, where you and Dr. Speroff wrote "A major" -- "Break-Through bleeding. A major continuation problem is break-through bleeding. Break-through bleeding gives rise to fears and concerns. It is aggravating and even embarrassing. Therefore, on starting oral contraception, patients need to be fully informed about break-through bleeding." Is that correct?

A Yes.

Q What would this sentence have disclosed to a skilled artisan in April of 2005, about the consequences of experiencing break-through bleeding?

A That it has important effects on both continuation of the birth control pill and the experience, quality of life of the woman using the pill that causes break-through bleeding, aggravating, embarrassing.

Q Dr. Darney, aren't women routinely counseled about the fact that there may be break-through bleeding or unscheduled bleeding with oral contraceptive?

A Yes, they are.

Q But do women still discontinue using the pills if they have unacceptable amounts of bleeding?

A Yes. For example, in the clinical trials we just examined, these women are very carefully counseled and still, the discontinuation rate for irregular bleeding was very high.

Q Now, Dr. Darney, I want to turn from cycle control to efficacy and so we're clear, efficacy is a term for whether or

not the pill actually works to prevent pregnancy, correct?
A Right.
Q In the 32 years between 1973 and 2005, did skilled artisans recognize a concern about Loestrin 1/20 contraceptive efficacy?
A Yes, several.
Q Did the prior art recognize these concerns?
A Several observations, comments in the literature about this issue.
Q I just want to be clear here because Dr. Barnhart has made certain comments about what years we're referring to. I want to make sure we're fixed in time.

During that 32 years, between 1973 and 2005, did it become known to skilled artisans that Loestrin 1/20, with 20 micrograms of estrogen, had a problem with efficacy?
A Yes, that became more obvious over time.
Q Okay.

Can I have plaintiff's trial exhibit 97, Mr. Brooks? We've already introduced this and can you please highlight or bring up on the screen page 238?

I direct your attention, Dr. Darney, to the sentence that is after contraceptive side effects or complication, reads, "In this instance, the preparation with 20 micrograms of ethinyl estradiol and that of 400 micrograms norethindrone acetate can be considered as unsatisfactory because of the

higher discontinuing rates."

Do you see that?

A Yes. This is the World Health Organization publication we just examined.

Q And then just to clarify, what were they referring to as the 20 microgram ethinyl estradiol regimen?

A That's Loestrin 20 in Europe and Loestrin 1/20 in the United States.

Q Now, going down further, Mr. Brooks, can you, to the sentence that says, "The former preparation was shown to be significantly less acceptable and effective than ethinyl estradiol 30 micrograms Levonorgestrel 150 micrograms in a controlled clinical trial report from the United Kingdom."

What is being indicated there that Loestrin 1/20 was less acceptable and effective?

A That's correct.

Q What does that mean to a skilled artisan?

A That with a 20 microgram dose of ethinyl estradiol, a birth control pill is likely to be less effective than one with 30 micrograms.

Q All right.

Let's look at plaintiff's trial exhibit 52, the Lammers article.

Have you reviewed the Lammers article?

A I have.

Q Directing you to the copyright page, when was it published?
A As I recall, it was 1992.
Q We're in the '90s now.
Is that prior art?
A Yes.
MR. PAPPAS: I offer plaintiff's exhibit trial 92 in evidence.
MR. GREEN: No objection.
Q Did this paper concern itself with Loestrin 1/20?
A Yes.
Q Let me direct your attention to page 71 and 72 under the heading Discussion.
Could you read that?
A Yes.
Q Just the first few sentences starting with the word "attempts" through "irregular bleeding" and tell us what that means.
A "Attempts have been made to reduce the estrogen content of combined oral contraceptives below 30 micrograms of ethinyl estradiol per tablet. Combination of 20 micrograms of ethinyl estradiol and one milligram norethisterone acetate. However, was shown in several studies to suppress the pituitary ovarian access insufficiently with relatively high incidents of unintended pregnancies and high rate of irregular bleeding."

Q Okay.

First of all, so we're clear, what's being referred to there as the 20 microgram ethinyl estradiol plus 1000 micrograms of norethisterone acetate?

A That's Loestrin 1/20.

Q And what does that disclose to one of skill in the art as late as 1992, about the efficacy?

A That unintended pregnancies occur.

Q What does it mean to say the combination oral contraceptives "insufficiently suppresses the pituitary ovarian access"?

A You'll recall our discussion of how pills work and their primary method of action is to have a central affect in the brain, the hypothalamus, and pituitary so suppress the signals to ovulate and release the egg and here, Paul Lammers is saying that that suppression is insufficient to accomplish effective contraception.

Q Would this publication reflect the views of a skilled artisan about the efficacy of the Loestrin 1/20 in April, 2005?

A Yes, it would.

Q Now, be clear, Dr. Darney, Loestrin 1/20 was approved as safe and effective by the FDA, right?

A Yes, it was approved in 1973.

Q Okay.

So what do we make of all this literature in the subsequent 32 years after its approval that indicates it had marginal contraceptive efficacy?

How do we square that?

A Well, it's been available for a very long time and in addition to the "pivotal trial" that resulted in FDA approval, others had the opportunity after it was marketed to conduct clinical trials and they observed unintended pregnancies and irregular bleeding. The several papers we've discussed summarize their observations.

Q Do the concerns about Loestrin 1/20 efficacy persist today?

A Yes, they do.

Q Just be clear, does Loestrin 1/20 have the same estrogen and progestin type, that is ethinyl estradiol and norethindrone acetate, as in the claimed invention of the '984?

A Yes.

Q And is the dosage of progestin, norethindrone acetate, in Loestrin 1/20, the same as in the narrower claims 6 through 9 of the '984 patent?

A Yes, one milligram norethindrone acetate in both.

Q But Loestrin 1/20 has ten more micrograms of estrogen, doesn't it?

A Yes.

Q So --

MR. PAPPAS: Your Honor, I noticed we're getting close to 1:00 so I'll finish with this question.

Q So what, in your opinion, would the problems with cycle control and unintended pregnancies tell skilled artisans in April, 2005, knowing that Loestrin 1/20 had unintended pregnancies and cycle control problems with 20 micrograms of ethinyl estradiol, would that lead to a motivation to cut the dosage in half to ten micrograms?

A Certainly not. The opposite would be the motivator.

Q Okay.

MR. PAPPAS: Your Honor, I know you said five of.

THE COURT: Good job. Let's take lunch.

We'll have you back here at let's call it 1:40.

THE CLERK: All rise.

(Luncheon recess.)

THE CLERK: All rise.

P H I L I P D A R N E Y, previously sworn, resumes the stand.

MR. PAPPAS: Your Honor, may I begin?

THE COURT: Yes.

MR. PAPPAS: Housekeeping matter. When I offered into evidence plaintiff's exhibit 21, one and 99, I misspoke in saying that that was the Darney summary slide 1006.

The summary slide which we would move in is Darney

slide 21, which is a 1006 summary slide, but we also wanted to move in the underlying articles. So I'd ask that the record be completed such that we have moved in the underlying articles, plaintiff's 21, one and 99 which have been accepted, but we also move in slide 21 as a 1006, again, aid to the Court because it's the select quotations and it's a summary and may assist the Court.

MR. GREEN: No objection, your Honor.

THE COURT: Not to be a nitpicker, I don't know if I would agree with you that slide 21 is a 1006 summary chart, but since the underlying articles are being accepted, it really doesn't matter.

MR. PAPPAS: Thank you, your Honor.

THE COURT: Now, before we get started, how are you doing in terms of time management?

MR. PAPPAS: Your Honor, I'm moving through the material I think at a much quicker pace. Depending on how long your Honor --

THE COURT: I'm going to leave that entirely to you and Dr. Darney and Joanne. Go as long as you think you can go today and I'm happy with it.

MR. PAPPAS: Let's watch how it's going.

THE COURT: I was just curious to know whether you're meeting your expectations in terms of time.

MR. PAPPAS: If I can, your Honor, let me see where

we are at three o'clock.

THE COURT: Okay.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Dr. Darney, let's pick up now and I want to ask you if you prepared a slide summarizing the literature that raised concerns about Loestrin 1/20's lack of efficacy.

Did you prepare such a slide?

A I have.

Q Mr. Brooks, can we have Darney slide 23?

MR. PAPPAS: If I may have a moment, I think I misplaced my copy.

THE COURT: Sure.

Q Dr. Darney, will you please review each of the quotes shown on Darney exhibit 23 and tell the Court what each of them indicates?

Let's start with DTX, a quote that comes from defendants' trial exhibit 507 by van Heusden.

A Here van Heusden and Fauser, in a 1999 article in Contraception, write that "The present data," they're reporting in this article, "suggest that a decrease in the ethinyl estradiol content as seen in the 20 microgram ethinyl estradiol containing oral contraceptive results primarily in larger follicles during the pill-free interval. Because follicles maintain the potential to ovulate, contraceptive efficacy in oral contraceptives should include the prevention

of dominant follicles."
Q What is -- what does this information communicate to a skilled artisan in April, 2005?
A That a lower dose of 20 microgram dose of ethinyl estradiol leads to larger follicles and because larger follicles may subsequently ovulate, in developing combined oral contraceptives, you should prevent dominant follicles and a way to do that is raising the estrogen dose.
Q And what 20 microgram pill was van Heusden referring to?
A Loestrin 1/20.
Q Let's move to the next quote by a gentleman named Teichmann.
MR. PAPPAS: By the way, your Honor, DTX-507 is already in evidence.
Q This is a quote that comes from DTX or defendants' trial exhibit 477, by Teichmann.
Can you read that and tell us what that would tell a skilled artisan as of April, 2005?
A Yes. That's a 1995 article in Gynecology & and Endocrinology and he writes, "It can be concluded that ethinyl estradiol dose in an oral contraceptive has a significant effect on follicular ovarian activity, and that reducing the dose to 20 micrograms is associated with a significant increase in follicle size."
Again, cautioning against reducing the dose of estrogen

to 20 micrograms because of possible decrease in efficacy.
Q And again, what pill is Teichmann referring to?
A He's looking at the Loestrin 1/20.
Q Let's move to the third quote that comes from JTX-16, which is already in evidence.
This is the '940 patent, correct?
A Yes. The writers of the patent observe, "confirmed in several studies, of slighter ovarian suppression for the preparation that contains 20 micrograms of ethinyl estradiol represents another clinically important problem. Obviously, for many women this very low estrogen dose," 20 micrograms, "can result in maturation of follicles as has been detected in ultrasound studies or hormone studies."
Q Do you know what product was being referred to in JTX-16?
A Yes. They had reviewed the literature in writing their patent about Loestrin 1/20 and report here in the patent that it's a clinically important problem when estrogen doses reduced to 20 micrograms because of the maturation of the follicles and perhaps unintended pregnancy.
Q Can you call up the '940 patent, Mr. Brooks?
Let me direct your attention, Dr. Darney, to column two, line 61 through 67.
Do you see that?
A Yes.
Q Okay.

Now, just let me ask you to review that and ask you whether the '940 is referring there to Loestrin 1/20 or the Mercilon product?

A It's referring to Mercilon. Contains 20 micrograms of ethinyl estradiol, but contains 150 Desogestrel rather than 1000 of norethindrone acetate.

Q What does the patent conclude with the sentence, beginning "Obviously"?

A "This low estrogen dose can result in a maturation of follicles as has been detected in ultrasound studies or hormone studies."

Q So was it known in 2005, that 20 micrograms dosages of estrogen could lead to increased size follicles?

A Yes, I believe the date of this patent is 1999.

And the writers are making that observation with a low estrogen dose, even with a relatively potent progestin, Desogestrel, whether than the weaker progestin, norethindrone acetate, leads to maturation of follicles.

Q Okay.

Now, in the van Heusden article, do you have that up there with you, DTX-507?

Actually, let me have you pull up the cover or first page of DTX-507 which is already in evidence.

Dr. Darney, is this a comparison between Mercilon and Marvelon, one having, Mercilon having --

A Yes, Mercilon is a 20 microgram pill and Marvelon is a 30 microgram pill.

This study they compare both have 150 micrograms of Desogestrel and that's the comparison they're making. It's not with norethindrone acetate.

Q Once again, in your opinion, what would that have told one of skill in the art though in April of 2005, about what you could expect with a 20 microgram pill?

A You'd expect a greater degree of follicular enlargement.

Q And what would you expect then if you tried to go below 20?

A They don't look at going below 20. They look at using 20 with Gestodene and Desogestrel and comparing that with 30 to Desogestrel and find enlargement with 20.

A person of ordinary skill in the art reading this would think that you'd have even greater degree of enlargement of follicles and, therefore, a greater risk of unintended pregnancy if you used ten micrograms or 15 micrograms.

Q Let me ask you to direct your attention to DTX-477, the Teichmann article.

Front, first page of the article, the abstract, what compounds were being compared there with 30 and 20 micrograms of estrogen?

A In this case, they were making a comparison of 30 micrograms of ethinyl estradiol and 17 micrograms of Gestodene

in one group and in the other group, 20 micrograms of ethinyl estradiol and 150 of Desogestrel.

Q Let's bring up PTX-83, Mr. Brooks, please.

Is this your portion of your Clinical Guide to Contraception, fourth edition, that you co-authored with Dr. Speroff?

A Yes, it is.

Q Do you know when it was published?

A I believe this was published in 2005.

Q Do you believe it reflects the thinking of the state of the art by skilled artisans as of April, 2005?

A I believe it does, yes.

Q Okay.

Can we turn to page 39?

MR. PAPPAS: By the way, your Honor, I offer PTX-83.

MR. GREEN: No objection, your Honor.

Q Now, if you look at page 39, it's a very short phrase starting with the words "We are."

Can you read that and this is from your book, tell us what it means, as of April, 2005?

A "We are probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy. Metabolic studies with the multiphasic preparation indicate no differences or slight improvements over the metabolic effects of low dose monophasic products. Low dose oral contraceptives

now include products with ethinyl estradiol, daily doses of 20, 25, 30 and 35."

The implication is that those are the lowest doses that can be achieved without sacrificing efficacy based on studies like the ones we just reviewed.

Q Now, how would this portion of your Clinical Guide to Contraception that was published in 2005, in your opinion, be understood by a skilled artisan in 2005?

A Such a person would have concluded that you can't go below 20, 25, 30, without -- 35, without sacrificing efficacy.

Q Sir, do you think it was true in April, 2005, that the "we are probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy"?

A Yes.

Q Now, Dr. Darney, let's examine on this question of whether or not a skilled artisan would have even been motivated to try to go below 20 micrograms as of 2005.

Let's examine what happened in the wake of Loestrin 1/20.

Have you prepared a chart of what took place in the market during that period of time?

A Yes, I have.

Q Okay.

Now, we may have covered this before, but if we do, I'll move quickly through it.

Between 1973 and 1993, did any company introduce a regimen in the United States with the same 20 micrograms EE dose as Loestrin 1/20?

A No, they did not.

Q What did they do?

A Should we put the chart up?

Q Let's put the chart up.

Can we have Darney slide 24?

MR. PAPPAS: Your Honor, I would represent to you that I understand that you and I may have disagreed on the last chart, but I will offer this as a 1006. I can, if you need to hear from me, I will, but I do think this is the classic sort of summary slide that collects data from a variety of sources.

This is the chart entitled Daily Estrogen Dose of FDA-Approved Oral Contraceptives, 1973 through 2005. We'll avoid having to introduce all of the underlying articles. I would offer it.

MR. GREEN: No objection.

Q Do we have it up there?

THE COURT: For what it's worth, I agree with you. I think this is.

MR. PAPPAS: Thank you.

Q First of all, let's start, will you explain what's on the X axis and what's on the Y axis?

A Along the horizontal axis are -- is time, 1970s moving up to 2000s, through the generational development of progestins and on the vertical axis is the ethinyl estradiol dose on both sides, ranging from ten to 30.

What the chart shows in the orange segment is condenses 1974 through 1995, 20 years of contraceptive development and documents the introduction of 15 new FDA-approved regimens and they were all at 30 micrograms or higher.

Q Before we go any further, Dr. Darney, I want to start with the very left-hand side.

We have Loestrin there, 1/20, correct, in 1973?

A That's right.

Q And we have covered, have we not, I think in some detail, the articles that indicate there was a problem with cycle control and efficacy with Loestrin 1/20, correct?

A Yes.

Q So now, moving forward then, left to right, between 1974 and 1995, were there any 20 microgram oral contraceptives introduced in the United States?

A No. During that 20-year period, after the introduction of Loestrin 1/20, there were no pills less than 30 micrograms.

Q Do you have an opinion as to why, without covering each one of these individually, there was a movement after the Loestrin 1/20 experience, to 30 microgram pills or higher?

A Yes, there were at least three factors --

Q What were those?
A -- involved.
One was that subsequent epidemiologic studies failed to show that reduction of the estrogen dose below 30 to 35 resulted in further reduction in DVT risk. So there wasn't a clear benefit to further reduction of the estrogen dose.
As we've discussed, however, there were clear risks to that reduction. First, that several studies, and we reviewed some of them, documented a worse bleeding pattern with 20 microgram pills, both Loestrin 1/20 and those that had been marketed in Europe.
In addition, we've also discussed, cited references showing that Loestrin 1/20 had higher failure rates than higher dose pills, Lammers, World Health Organization, so on.
So those were the three primary reasons, I think, and I think a person of ordinary skill in the art would have thought that no more 20 microgram pills were introduced. That is, more risk and no benefit.
Q Now, moving then left to right, the next pill is Estrostep, which I believe we covered already, correct?
A Right.
Q That increased the estrogen?
A Yes. It was the only pill introduced subsequently to use a first-generation progestin and it increased the estrogen dose to an average of about 30 micrograms daily. Remember, it

was a step-wise increase.
Q And can you explain, just so the record is clear, I know his Honor gets it, but what do the colors of the dots or the circles mean on this? I need to have a clear record.
A Well, purple means norethindrone acetate, first generation, weak progestin.
Q Okay.
What is the deep red or maroon.
A That represents the later generation progestins, which accounts for all of the subsequent introductions. Within the 20 microgram pills that were introduced, Mircette, Levonorgestrel and Desogestrel and the slightly higher dose pills, Cyclessa, Desogestrel, Yazmin, Drospirenone, Ortho-Tri-Cyclen Lo, Norgestimate and Seasonale was Levonorgestrel.
Q Okay.
Now, does the chart then depict the oral contraceptives moving past Estrostep, left to right, that were approved by the FDA up to the 2005 year?
A Yes, up to 2005, these were the newly-approved contraceptive preparations.
Q I believe we covered this earlier, but can you please just identify the six pills and what progestin they used, beginning with Alesse?
A Alesse, Levonorgestrel; Levonorgestrel, Desogestrel,

Desogestrel, Drospirenone, Norgestimate, Levonorgestrel. So they all use --

Q Can you simply put the progestin with the pill for the record?

A Yes.

Q So Alesse?

A You mean I went too fast?

THE COURT: He just did that.

MR. PAPPAS: He just read the pill. The progestins without tying them to the pill. I just wanted the record to be clear.

A I see -- yes. All of these pills that I just mentioned, all of these here?

Q Right.

A Used the third -- second, third and fourth generation progestins, Levonorgestrel, Gestodene, Norgestimate, Drospirenone.

Q Now, do you see that on this chart, the dates of the '394, '490, '940 patents are plotted as of the date they were issued?

A Yes, I do.

Q What, if anything, does this chart indicate about notwithstanding the ranges of estrogen disclosed by the patents, how artisans, skilled artisans reacted in terms of pills that they actually made?

A Well, skilled artisans would have been aware of these patents. They're progestins and the ranges and their preferences and claims and the products that were produced in light of that knowledge resulted in six pills, all 20 micrograms or above, and all using second, third and fourth generation progestins.

Q Now, what, if anything, does that -- does this chart -- let's take it one-by-one, indicate about whether or not there was a preference or a desire by skilled artisans after 1996, to use norethindrone acetate for oral contraceptives?

A None of them, none of the new pills developed did that. They all used later generation progestins.

Q And what does the Darney exhibit 24 show was the reaction of skilled artisans with respect to the estrogen doses not withstanding the fact that ranges -- well, even in light of the ranges disclosed in the '394, '490, '940 patents?

A Well, the ranges of estrogen are indicated here.

Q Are they all between 20 and 30 micrograms with the exception of --

A They're all between one to 35 and none of the new products went below 20. Two did and four wen above 20.

Q All right.

Now, do you have an opinion why no combined oral contraceptives were introduced in the United States between 1996 and 2005, that contained a dose of estrogen lower than 20

micrograms?
A Yes. The persons of ordinary skill in the art and developers of new combined oral contraceptives were aware of the experience around the world with 20 microgram pills and didn't want to take the chance of decreasing the estrogen dose further because that could result in the poor bleeding patterns and decreased efficacy that we've seen in the literature we've reviewed.

In addition, the thought in developing new pills, they would use later generation progestins for better control of bleeding and better efficacy, in addition to other virtues of those progestins.

Q Now, let's talk about Minesse for a minute.

Was that product ever approved in the United States?
A Minesse is a 15 microgram ethinyl estradiol pill as shown here on the cart which uses another third generation potent progestin Gestodene. It was approved in Europe in 2001, but has not been approved in the United States.
Q And at a dose of 15 micrograms, Minesse did not use norethindrone acetate, correct?
A No, it used Gestodene.
Q Which is a third-generation progestin, right?
A Yes. It is the most potent of the progestins available.
Q Do you have an opinion as to whether or not the use of the most potent progestin, Gestodene, affected the ability of

Minesse to go to 15 micrograms?
A Yes, I do.
Q What is that?
A I think that in the case of Minesse, using Gestodene helped to improve its efficacy and its bleeding pattern.
Q All right.
Let's turn now --
MR. PAPPAS: Your Honor, we're transitioning now to the detailed reasons for Dr. Darney's various opinions of non-obviousness that we previewed earlier today.
Q Can we have Darney slide 11, Mr. Brooks?
Let's turn to the first reason that you have advanced as to why the '984 patent claims were not obvious in view of the prior art.
Do you see A, prior art taught difficulties of lowering ethinyl estradiol below 20 micrograms?
Do you see that, sir?
A Yes, I do.
Q Okay.
I believe we have covered your reasons already about demonstrating the prior art taught difficulties of lowering the estrogen below 20 micrograms, correct?
A Yes.
Q Now, I'd like to turn then to the second opinion that the prior art taught use of a more potent progestin than

norethindrone acetate if one wanted to try to lower ethinyl estradiol below 20 micrograms.

First, let's start, do you believe Minesse is an example that demonstrates what the prior art taught?

A Yes, I do.

Q Now, let's examine, in connection with that second opinion, you have as to why the '984 claims are not obvious in light of the prior art, norethindrone acetate for a moment.

Was that known to have poor cycle control and be weak in terms of efficacy? I'm talking about the progestin now, norethindrone acetate.

A Yes, it was.

Q Was that recognized in the prior art as of 2005?

A Yes.

Q Can we have plaintiff's trial exhibit 112, Mr. Brooks, please?

This is a patent, U.S. patent 4292315, correct, Dr. Darney?

A Yes.

Q Is this one you have reviewed with the inventor Vorys?

A I have, dated 1981.

Q Well, before the prior art date, correct?

A Yes.

Q Let me ask you to direct your attention to column three, line 17 through 37.

Now, can you read that and explain that for us?
A Yes.
Q As to what's being disclosed by Vorys, the inventor to one of skill in the art?
A "Weaker progestins, such as norethindrone and norethindrone acetate, were also formulated with low dose estrogen pills and combination." He's talking about Loestrin 1/20 here.

"These latter formulations in several dose levels, however, were associated with break-through bleeding and unpredictable uterine bleeding in 40 to 50 percent of the cases. Because of this clinical fact, their acceptance has been minimal. Hints, because of the prior art approach in developing new and more potent steroid molecules, a principle characteristic is the various combination contraceptive steroid formulations in the market today, 1981, is that the design of each is predicated on the potency of the progestin molecule used in the combination with its inherent ability to allow a reduced dosage of estrogen. To wit: The more potent the progestin administered, less estrogen in combination with the progestin is required to achieve effective contraception and menstrual cycle control. However, when a less potent progestin is administered in combination with a reduced dosage of estrogen to adapt to adverse metabolic effects, menstrual cycle disruption results."

Q Okay.

Now, what would a skilled artisan in 2005, understand from that passage, from Vorys?

A That if you're going to produce the dose of estrogen in designing a new combined oral contraceptive, you ought to use a more potent progestin and not first generation, weak progestins.

Q All right.

So let's focus right on this case.

2005, we've already covered the demonstrated problems of going below 20 micrograms of estrogen, correct?

A Yes.

Q I want to ask you to assume hypothetically that a skilled artisan decided that he or she wanted to try to lower the dose of estrogen to let's say 15, correct, all right?

A Yes.

Q Assume that?

A Yes.

Q Would that skilled artisan, based on this and other teachings we'll cover, have used norethindrone acetate?

A No.

Q What would they have had to have done if they wanted to lower the estrogen below 20 micrograms?

A Well, we have one actually marketed product, Minesse in Europe, and the skilled artisans there used Gestodene.

Q The most potent progestin?
A The most potent progestin and we've seen that all of the other pills marketed, even if their dose of estrogen was at 20, used potent progestins.
Q Now, is the passage you just read from the Vorys patent, does that make the connection between the lower the estrogen, the more powerful the progestin?
A Yes, it supports all of the other observations in the -- supported by all of the observations in the literature which we've already reviewed.
MR. PAPPAS: Your Honor, I move PTX-112 in.
MR. GREEN: No objection, your Honor.
Q Mr. Brooks, can you bring up PTX-78, please?
Now, this is an article by David Serfaty, correct?
A Correct. Published in 1990.
Q So that was prior art, correct?
A Yes.
Q Now, directing your attention to the beginning of the article, what was this about in general terms? In other words, what were they studying?
A This is about a pill we described in the three earlier studies about follicular development and that's a 20 microgram ethinyl estradiol, plus 150 microgram Desogestrel pill called Mercilon in Europe, never marketed in the United States.
Q All right.

MR. PAPPAS: Your Honor, I mover into evidence, PTX-78.

MR. GREEN: No objection, your Honor.

Q Let me direct your attention to page two of this article, left-hand column, starting with the words "It was logical to try."

Do you see that?

Will you read that short passage and then tell the Court and us what is being communicated to a skilled artisan?

A "It was logical to try to reduce the estrogen dose still further by comparison to the low dose combined pills already in existence and, for example, to use pills with 20 micrograms of ethinyl estradiol in the hope of further increasing the acceptability of oral contraceptives and further reducing the vascular risk of this contraceptive. This was first tried by combining a first-generation progestin, norethisterone, 20 micrograms norethisterone acetate, one milligram plus 20 micrograms of ethinyl estradiol" and he gives two references for that.

"Then with a second-generation progestin, Norgestrel, 20 micrograms of ethinyl estradiol with 300 micrograms of Norgestrel or 15 micrograms of ethinyl estradiol, with 400 micrograms of Norgestrel or 20 micrograms of ethinyl estradiol and 500 micrograms of Norgestrel." He cites the reference to document that attempt.

"However, the first 20 microgram or 15 microgram ethinyl estradiol pills were rapidly abandoned due to inadequate contraceptive efficacy and/or poor cycle control resulting above all in unacceptably irregular bleeding. The appearance of the third-generation progestins, Desogestrel in 1982, led to the possibility of once more developing a combined oral contraceptive pill containing less than 30 micrograms of ethinyl estradiol."

Q What does this passage say about the lack of success of 20 and 15 micrograms dose?

A Well, he says that Preston, Bounds, documented in their studies that these 20 microgram pills with norethindrone and then with Norgestrel, that the performance was poor with regard to bleeding and that they were abandoned.

Q And what does it suggest or teach will be necessary if you want to go below 30 micrograms in the future?

A Serfaty is saying that you need to employ a third-generation progestin and the example he provides is Desogestrel, which as you'll recall was, in fact, used in introduction of low dose pills in the United States subsequently.

Q Would a person of ordinary skill in the art have agreed in 2005, with his characterization of norethindrone acetate?

A Yes.

Q Now, I want to turn to the point in support of your

second opinion that if you wanted to go below 20, you would need a more potent progestin and focus on the issue of half life, the concept we discussed earlier today.

Do you remember that?

A I do.

Q Can we -- as of April, 2005, were there other progestins thought to provide better cycle control than combined oral contraceptives with norethindrone acetate?

A Yes, there were.

Q Okay.

Let's look at PTX-73.

An article by Dr. Rosenberg, The Effect of Desogestrel, Gestodene and Other Factors on Spotting and Bleeding.

Do you see that?

A Yes.

Q Have you reviewed this?

A Yes, I have.

Q When was it published?

A I believe it was published in 1996, and I think this is in Contraception.

Q So this is prior art?

A Yes.

MR. PAPPAS: Your Honor, I move in plaintiff's trial exhibit 73.

MR. GREEN: No objection, your Honor.

Q Let me direct your attention to the abstract.

Can you explain what the authors were studying?

A Yes. They did a large trial, nearly 3,000 women in order to examine spotting and bleeding, common side effects with low dose oral contraceptives and they say a prime determinant of whether a new user will continue to use oral contraceptives. They describe Desogestrel and Gestodene as new progestins, that is third-generation progestins that were developed to minimize the occurrence of these side effects.

They go onto say that they're conducting the study analyzing data from two comparative multi-center clinical trials of the 3,000 women nearly that I mentioned. In one study, 75 micrograms of Gestodene and 30 of ethinyl estradiol was compared with 150 of Desogestrel and 30 of ethinyl estradiol.

Other study compared the same Gestodene preparation with 150 of Desogestrel and 20 micrograms of ethinyl estradiol. Both studies found a higher risk of spotting or bleeding in all cycles among users of the Desogestrel containing preparation with the differences ranging between 20 and 70 percent higher.

Q Let me direct your attention to page one, right-hand column, second full paragraph.

What do the authors report as to their rational for the development of newer progestins?

A They cite to a study supporting the rational for the development of newer progestins to improve cycle control. However, comparing effective different progestin components, phasing and other characteristics, is difficult for a number of reasons and they go onto list those reasons.

Q So it's even -- it can even be a challenge with the newer progestins?

A Yes, to make the comparison.

Q All right.

Now, in April, 2005, do you have an opinion as to whether or not skilled artisans believed that newer progestins did improve cycle control?

A I believe that persons of ordinary skill in 2005, believed that new progestins improved cycle control based on the literature presented here and other information.

Q Now, Dr. Barnhart, when you reviewed his testimony, did you see the portion where he said that the vast majority of products developed between 1973 and 2005, used norethindrone acetate as opposed to the newer progestins?

A Yes, I recall that statement.

Q Okay.

And I think, as we've demonstrated on slide 27, if we can have that up again, Mr. Brooks, is that correct, that the vast majority of COCs developed in that time period used norethindrone and norethindrone acetate?

A Yes. You'll see here that in the 25 years, that about half of the regimens actually did use -- 25 years up to 2005, about half of the regimens did use norethindrone and norethindrone acetate, but in recent years, 1987 to 2005, the overwhelming majority of new regimens used second-, third- and fourth-generation progestins.

Q Okay.

Now, I want to cover a point we at least alluded to with respect to Minesse.

Can we have plaintiff's trial exhibit 32, Mr. Brooks?

Have you reviewed this article before?

A Yes, I have.

Q And who is the author?

A Frank Fruzetti, an Italian Study of Contraception.

Q And what is he addressing in that article?

A The investigators here are looking specifically at effects on blood clotting of a 15 microgram ethinyl estradiol pill with 60 micrograms of Gestodene. That is Minesse. And examining at the same time cycle control of this pill.

Q And when was this published?

A 1990. Let's look down there at the page. I believe 1995.

Q Bring that up, Mr. Brooks?

A At the top, 2001, isn't it?

Q All right. Let's just verify that.

A Yes, 2001. That's right.
Q That's prior art?
A Yes.
MR. PAPPAS: I move in PTX-32, your Honor.
MR. GREEN: No objection, your Honor.
Q Was he studying the performance of Minesse?
A Yes, with regard to cycle control and hematologic parameters.
Q I'd like to direct your attention to page 306, the left-hand column. It starts with Discussion.
There's a very short passage there. Can you read that and tell his Honor and us what this would have told skilled artisans in 2005, about the relationship between the amount of progestin and the type of -- I'm sorry, the amount of estrogen and the type of progestin used?
A Yes. "The reduction in EE," ethinyl estradiol "dose, is one of the major goals in contraception research. Until now, the lowest available dose was 20 micrograms. The availability of a potent progestin such as Gestodene makes possible a further decrease in the estrogen dose to 15 micrograms without compromising the contraceptive efficacy of the preparation."
Q What would that disclosure by Fruzetti 2001, have told a skilled artisan in 2005, about what you need to do if you're going to take estrogen down below 20 micrograms?
A It would have told the person of ordinary skill that if

you reduce the dose below 20, then if you don't use a potent progestin, third-generation progestin like Gestodene, you'll compromise the contraceptive efficacy of the preparation.

Q So what do you do if you don't want to compromise contraceptive efficacy and you want to take estrogen down below 20 micrograms?

A Use a potent progestin.

Q And, sir, just so we're clear, that would not be norethindrone acetate, would it?

A No, we're talking about second, third-generation progestins here.

Q Let's be clear about something.

In your opinion, would anyone in 2005, have referred to norethindrone acetate as a powerful progestin?

A No.

Q Would anyone have referred to norethindrone acetate in April, 2005 as a progestin with a long half life?

A No.

Q Now, one article before we get to the alleged pill scare.

Let me ask you to bring up, Mr. Brooks, PTX-7. This is an English translation article by Bianchi that was published in France.

Do you see that?

A Yes.

Q That's 2001 or 2000?

A It says acquisitions, 2000, so 2000.
Q All right.
This was prior art as well?
A Yes.
Q Okay.
MR. PAPPAS: I offer PTX-7, your Honor.
MR. GREEN: No objection, your Honor.
Q Now, what is generally being discussed in this article, sir?
A This is a review of what's new in the field of contraception and includes a review, as you see in the key words, of low dose estrogen plus progestin. That is combined oral contraceptives.
Q Let me direct your attention to page 109, right-hand column starting with the words "The regularity." Just read that and tell us what this would mean to a skilled artisan in April of 2005?
A "The regularity of the cycle decreases when the estrogen dose is reduced. If the progestin can change the situation, it is the case for Gestodene, which also seems to be more effective than other progestins in the stabilization of the endometrium."
This is saying that this particular third-generation progestin results in a more acceptable menstrual pattern when it's combined with a low dose estrogen pill. I should say

combined in a low dose estrogen pill.
Q All right.
By the way, was Minesse a pill with 21 days of combined oral contraceptive and seven days pill free or was it some other regimen?
A No, Minesse is 24 days of the same dose of estrogen and progestin, that is 15 micrograms of ethinyl estradiol and 60 of Gestodene, for 24 straight days followed by four days of placebo with a total of 28 days.
Q All right.
Now, did you, when you reviewed Dr. Barnhart's testimony, did you read those sections about the pill scare, as he called it?
A Yes, I did.
Q Okay.
Now, specifically, did you review that portion of Dr. Barnhart's testimony that the pill scare in the mid '90s would have led a skilled artisan to use norethindrone acetate?
A I did.
Q Do you agree with that?
A No.
Q Well, let's test it. Let's see which version is correct.
Can we have Darney slide 30, Mr. Brooks?
Now, is this something you helped us prepare?
A Yes, it is.

Q Now, the shaded area, should be shaded, I'm not sure it is on the screen. I hope yours is shaded between 1995 to 1999.

Do you see that?

A Yes.

Q Is that the period in which there was what has been, I guess generically, referred to as a pill scare?

A Yes. That was after the 1995 publication of a World Health Organization, controversial World Health Organization report that some progestins resulted in an increased relative risk of deep vein thrombosis compared to the progestin Levonorgestrel.

Q Okay.

And which progestins specifically were the subject of the pill scare?

A Gestodene and Desogestrel.

Q Was Norgestimate the subject of the pill scare?

A No, it was not.

Q Now, let's look at the chart that has the pill scare.

Was it generally conceded that any concern about Desogestrel and Gestodene was over by 1999 at that time?

A Do you mean that the controversy had subsided by 1999?

Q Had it subsided by 1999?

A Well, it had cooled down. It remained a controversial issue.

Q Okay.
A But additional studies, additional reassuring studies had been reported that counteracted the findings of the World Health Organization and the Liddegard study.
Q So it took place between '95 and '99 and then cooled down.
Is that your testimony?
A Yes.
Q Okay.
But starting from the period of 1999, and even let's include the cool-down period, however long that lasted, is there any oral contraceptive introduced in the United States that used norethindrone acetate?
A No. Estrostep was introduced, we discussed that and the reasons for its introduction.
Shortly after the advent of the pill scare, but following that, there were no, as you see here, no pills introduced using norethindrone acetate or norethindrone.
Q Right.
So prior -- yes, prior to the invention of the '984, there were four pills introduced, Cyclessa, Ortho-Tri-Cyclen Lo, Seasonale and Yazmin?
A Yes.
Q Are we correct that not one of those used norethindrone acetate?

A That's right.
Q Not one of those used norethindrone?
A Right.
Q So let me ask you, sir, as a matter of fact now, did this pill scare over Desogestrel and Gestodene, based on the actual facts, lead to Dr. Barnhart's testimony that there was -- that that would have led people to use norethindrone acetate instead of second- or third-generation progestins?
A No, none of the subsequent pills that went on to develop testing, approval by the FDA used norethindrone acetate.
Q Did doctors continue to prescribe Desogestrel and other second- and third-generation progestins after the pill scare?
A Yes, they did.
Q Now, have you prepared a slide that summarizes your opinions about why the pill scare would not have led a skilled artisan in 2005, to use an EE dose of less than 20 micrograms with norethindrone acetate?
A I have.
Q Can we have Darney slide 29, Mr. Brooks, please?
Now, take your time, Doctor, and describe for us, I believe there's five reasons up there about why the pill scare would not have encouraged anyone to use norethindrone acetate with a sub-20 microgram EE dose, even though Warner Chilcott ultimately did it with Lo Loestrin. We're talking now about the ordinary man or woman of skill in the art. Go ahead.

A Yes. I mentioned that the first publications were surprising regarding the physiologic basis for thrombosis which was thought to be associated solely with the estrogen component. The increased risk calculated in the studies which showed an affect was small, on the order of 1.3 to 2.4, as I recall, and since the event, as we discussed at the outset at our session today, was a rare event.

If you applied the relative risk to patients who were actually using these products, small proportion of pill users were affected. That was, it was not clinically relevant even if you were convinced by the data and other studies, Dinger and others, demonstrated different results. That is, no increased relative risk.

Then the FDA did not ban either progestin. It continued to approve of the pills that contained Desogestrel. The British authority which started the scare which said Desogestrel and Gestodene containing pills ought not to be prescribed when they saw additional data from Dinger and Spitzer, for example, retracted their advice from four years earlier and we marked that in our previous chart with the subsidence of the pill scare, was part of it.

The prior art that Lupin has asserted in this proceeding here actually recommended using Gestodene and Desogestrel, even after the concerns arose. That is, that patents and publications written by experts in the field

continued to recommend those two progestins, even during and after the, quote, pill scare.

Q Let's pause there and let's have a little flash back to Darney exhibit 30.

Can you bring that up?

You have down there the '490 and the '940 patents, two of the patents relied on by Lupin in this case are shown there, right?

A Yes.

Q And they're toward the latter part of the initial pill scare, right?

A Yes.

Q Now, are you familiar -- what progestins are the preferred progestins by the inventors of the '940 patent?

A In both of those patents, the preferred progestins are Gestodene, which was implicated in the pill scare, and Levonorgestrel, which was not.

Q Did the '940 patent recommend Levonorgestrel and Gestodene?

A Yes.

Q Did the '490 patent recommend or prefer as progestins, Levonorgestrel and Gestodene?

A Yes.

Q Okay.

So we're clear then, during this pill scare, is it

accurate to say that not only were the subsequent pills not made with norethindrone acetate, but two of the patents on which Lupin relies as prior art taught people that the preferred progestins were Levonorgestrel and Gestodene, right?

A That's correct.

Q Let's return then to the summary slide, sir.

I think you were just finishing describing Lupin's asserted patents recommending using Gestodene and Desogestrel.

I take it that slide should be corrected, we have Gestodene and Levonorgestrel, correct?

A Those are the preferred progestins, Desogestrel is listed in those patents.

Q Okay.

How about the fourth reason?

A The fourth issue is one we've already covered and that is that the new combined oral contraceptives that were introduced after the pill scare used these third-generation progestins, Gestodene and Desogestrel, that were implicated in the pill scare and those examples in the U.S. were Mircette and Cyclessa in Europe, Minesse.

Finally, the World Health Organization, the Liddegard and Jick studies did not implicate Norgestimate or Levonorgestrel, two additional second- and third-generation potent progestins in the controversy. In fact, Levonorgestrel was the standard against which the others were judged and the

calculation of relative risk. Even if you believed that two of the third-generation progestins were implicated with increased risk of DVT and as I said, that issue was controversial, still available to use in new pill -- new combined oral contraceptives were the third-generation pills Norgestimate -- third-generation progestins, Norgestimate and Levonorgestrel and, in fact, they were used along with Desogestrel and Gestodene in all of the new pills that were developed after the pill scare.

Q So, based on that, do you have an opinion that even with what's been called the pill scare, in April, 2005, what would a person of ordinary skill have done in terms of their choice of progestin if they wanted to reduce the estrogen below 20 micrograms?

Let's further assume they just decided to play it really safe and not to use Gestodene and Desogestrel because of the pill scare, what progestins would they have used?

A Norgestimate and Levonorgestrel, for example.

Q Second generation?

A Yes.

Q Stronger, more potent progestins than norethindrone acetate, correct?

A Yes.

Q Levonorgestrel and Norgestimate, longer half life progestins than norethindrone acetate, correct?

A That's right.

MR. PAPPAS: I'm about to go to a new area. Is this an appropriate time for a short break?

THE COURT: Sure. Whatever you think.

How long do you want to go today?

MR. PAPPAS: Your Honor, to get -- I am past the halfway. A little bit further, perhaps if we can go another 45 minutes after the break, is that acceptable?

THE COURT: Let's take a break and come back and she'll tell us when it's time to stop.

THE CLERK: All rise.

(Recess.)

THE CLERK: All rise.

MR. PAPPAS: Your Honor, after consultation with your court reporter, 3:15.

THE COURT: Okay.

MR. PAPPAS: If that's okay with you?

THE COURT: It's okay with me. Believe me, at this point in the process, I relinquish control over the machinery.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Dr. Darney, let's move to the third opinion you have as to why the '984 patent is not obvious in light of the prior art.

THE COURT: By the way, I'm paying attention to this, I want you to know that.

MR. PAPPAS: I assumed that, your Honor.

THE COURT: I am.

MR. PAPPAS: That has been my observation as well.

Q The third opinion you had -- can we go back to Darney slide 11, Mr. Brooks?

Your third reason, Dr. Darney, was the prior art did not teach shortening the hormone-free interval and giving ethinyl estradiol alone before placebos to lower ethinyl estradiol below 20 micrograms.

Do you see that?

A Yes, I do.

Q Let's explore that now for the time we have remaining.

In general terms, why do you say that shortening the hormone-free interval would not by itself permit the lowering of an ethinyl estradiol dose below 20 micrograms in 2005?

A We've discussed the design of oral contraceptive pills and we're aware that the conventional 21-7 day administration remains the most popular kind of oral contraceptive.

It's the first 21 days that provide most of the contraceptive efficacy of the pills in terms of suppressing the pituitary, ovarian hypothalamic access and changing cervical mucous viscosity.

The addition to ultra low dose pills of additional combined oral contraceptives, that is teaching -- that is shortening the hormone-free interval without regard to giving

estrogen alone is not sufficient to compensate for the dramatic reduction in estrogen doses we are contemplating. The prior art didn't teach that it was.

In addition, turning now to the place of the additional estrogen before the placebos, the prior art actually taught when that was going -- if that was done, the most effective place to do it in the 28-day cycle was immediately prior to the combined pills, that is after the placebo.

So on both counts, shortening the hormone-free interval and using estrogen before the placebos, the prior art spoke against the ability of those changes to render an ultra low dose estrogen pill effective.

Q Let's unpack that a bit.

The term you used, "ultra low dose," when you use the term "ultra low dose," what amount of estrogen are you talking about?

A We're defining low dose as the typical definition, is 20 to 35 micrograms. Those are classified as low dose pills, along that continuum.

Ultra low dose means going below 20.

Q All right.

Now, let's start -- before we get to the order of how you do it, if you were going to do it, let's start just with the first part of your testimony about shortening the hormone-free interval that was normally seven days.

Are you with me?
A Yes.
Q Okay.
Now, can we agree that it was recognized that there were some potential advantages to shortening the steroid-free interval from seven days, some advantages, correct?
A Yes.
Q And that would have been known in April of 2005, correct?
A That's correct.
Q Okay.
Now, here's the question: Would a person of ordinary skill in the art, in 2005, have believed that by simply shortening the hormone-free interval of seven days, you would be able to overcome the expected problems with going below 20 micrograms of estrogen?
A No.
Q Why not?
A Because the principle efficacy of low dose pills occurs, principle action occurs in those first 21 days. If you've given an ultra low dose of estrogen with the first 21 days, simply extending the regimen is not going to resolve the follicular growth that you've already had in the first 21 days with an additional dose, an additional administration of the combined pills for three more days.
It is the three days is a small proportion of the

combined regimen and birth control pills work by -- through continuous administration. We discussed how that prolonged administration results in prolonged suppression. Simple addition of three more days wouldn't make enough difference to overcome 21 days of too little estrogen. That would be the perception of a person of ordinary skill in the art and I think that's backed up by pills that were marketed up to 2005.

Q Now, Dr. Darney, just to move -- I want to orient us in time again on our timeline.

Mr. Brooks, can we have Darney exhibit 24, which I believe has been admitted?

Do you see that, sir?

A Yes.

Q Beginning with Estrostep in 1996, and moving forward up to the time of the '984 patent, were any of those pills -- well, were all of those pills 21-7, with one exception?

A That's right. The exception was Mircette.

Q Let's be clear because this has to do with some of Dr. Barnhart's testimony about what the trend was.

Am I correct that Alesse, Cyclessa, Ortho-Tri-Cyclen Lo, Yazmin, Seasonale were all 21 days of combined oral contraceptives and seven pill-free days, correct?

A Yes, as was Estrostep.

Q That's right.

THE COURT: Excuse me, a pill-free day was not an

estrogen alone day, was it?

THE WITNESS: No. No, it's a day in which you take a placebo or not take a pill at all.

THE COURT: So the estrogen-alone dose is not part of the hormone-free interval?

THE WITNESS: No, it's not.

THE COURT: Thank you.

Q Now, let me ask you, was Seasonale an 84-day pill?

A Yes, Seasonale is unique in being continuous administration for three times 84 days -- three times 28 days, 84 days.

Q And then a pill-free?

A Then a pill-free interval.

Q Let's be clear because Judge Pisano raised a good point.

When I say "pill free," there's a period of time when the woman gets no estrogen or progestin when we say pill free, right?

A Right. That's the pill-free interval.

Q So the record is clear then, Estrostep, Alesse, Cyclessa, Ortho-Tri-Cyclen, Yazmin, were 21 days of progestin and estrogen followed by seven days where the woman either took a placebo, a clear pill with nothing in it or took no pill at all, right?

A Exactly.

Q Okay.

Seasonale, she took drugs, the progestin, estrogen for 84 days and then had a pill-free period with no drugs, correct?

A Right.

Q Okay.

May be we can conclude for today on this one note. But there was one pill called Mircette that what was the regimen of Mircette?

A Mircette used 20 micrograms of ethinyl estradiol combined with Desogestrel in the same regimen we've examined that was approved in Europe and we discussed in several papers in the literature called Mercilon.

Q All right.

A To that Mercilon was added five days of unopposed estrogen, after two days of placebo, 21 days of -- and I believe I have a slide illustrating pills.

Q Yes, bring up Darney slide 32.

Will this aid you in explaining the Mircette regimen?

A So --

Q Is this the Mircette regimen?

A Yes.

Q All right.

Now explain what Mircette did.

A Orange and purple are the 21 days of the combination, 150 Desogestrel, 20 micrograms of ethinyl estradiol, followed by

two days of placebo, followed by five days of estrogen alone. So the pill-free interval is shortened by five days. Normally it's seven, it's shortened by two and administered during the latter part of the pill-free interval immediately before the combination or ten micrograms of ethinyl estradiol.

Q I may have handed you the wrong slide. My error, Dr. Darney.

Let me ask you to look at Darney exhibit 26. Is this the slide you made up on Mircette?

Can we have that instead?

A The other just represented the pills, but this is the same thing showing the combined pill, purple and orange together for 21 days and then two days of placebo and then five days of ten micrograms of ethinyl estradiol, half the dose in the combined preparation to make up the full 28 day package of pills.

Q Okay.

A And then as the previous slide showed, immediately after finishing the ethinyl estradiol, so immediately before the combination, the ethinyl estradiol ten micrograms is taken.

Q All right.

In other words, it repeats the next 28 days?

A Yes.

Q Okay.

So Mircette, prior to 2005, was the only product in the

United States that had some combination of placebo and unopposed estrogen after the 21 days, correct?

A That's correct.

Q And Mircette put the placebo after the combined oral contraceptive and then it was followed by unopposed estrogen, correct?

A Yes, it was the only such pill in the world.

Q That was the regimen disclosed by the '940 patent, correct, or the '843 patent, correct?

A Yes.

Q Pasquale patent?

A The '843 patent.

Q Mircette was not the regimen of the '984 patent dose, is it?

A No.

THE COURT: Okay.

MR. PAPPAS: Your Honor, it's 3:15 and I'm reminded --

THE COURT: Finitio.

(Trial adjourned until Wednesday morning, October 16, 2013, at 9:15 a.m.)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CIVIL NO. 11-5048 and 12-2928

WARNER CHILCOTT CO., LLC, Plaintiff, -vs- LUPIN LTD. and LUPIN PHARMACEUTICALS, INC., Defendants.	TRANSCRIPT OF PROCEEDINGS TRIAL
WARNER CHILCOTT CO., LLC, Plaintiff, -vs- WATSON LABORATORIES, INC., Defendant.	

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Trenton, New Jersey
October 16, 2013

B E F O R E:

THE HONORABLE JOEL A. PISANO
UNITED STATES DISTRICT COURT JUDGE

Pursuant to Section 753 Title 28 United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above-entitled proceedings.

S/Joanne M. Caruso, CSR, CRR
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WITNESS	DIRECT	CROSS	REDIRECT	RECROSS
PHILIP DARNEY				
By Mr. Pappas	772			
By Mr. Green		875		

October 16, 2013.

THE CLERK: All rise.

THE COURT: Good morning.

Have a seat.

I guess if nothing happens today, tomorrow we're volunteers of America.

P H I L I P D A R N E Y, previously sworn, resumes the stand.

THE COURT: Good morning, Doctor.

THE WITNESS: Good morning.

THE COURT: Okay.

The only thing I need to say in terms of scheduling is I have to take a call at noon, so wherever we are at noon, I'm just going to ask for a break and do something on the phone.

Go ahead.

MR. PAPPAS: Good morning, your Honor.

THE COURT: Mr. Pappas, good morning.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Good morning, Dr. Darney.

A Good morning, Mr. Pappas.

Q Let me ask for Darney slide 11 to be put up, Mr. Brooks. I want to return to where we left off on yesterday afternoon, which is your third reason, Dr. Darney, for why it is your opinion that the '984 patent claims are not obvious in view of

the prior art.

Do you see letter C, that the prior art does not teach shortening the hormone-free interval and giving ethinyl estradiol alone before placebos to lower EE below 20 micrograms?

Do you see that, sir?

A Yes, I do.

Q In general terms, sir, why is it your opinion that shortening the hormone-free interval would not permit lowering the estrogen dose below 20 micrograms?

A Further reduction of the dose of estrogen for 21 days, for the 21 days of the combined preparation could not be compensated for merely by shortening the hormone-free interval.

Q All right.

Now, when we say "shortening the hormone-free interval," do you include in that extending the number of days of the combination pills or adding unopposed estrogen pills or both?

A Yes, you could do either or both.

Q Okay.

A The placebo period would be shorter than the conventional seven days.

Q As of 2005, Dr. Darney, were there any perceived benefits of shortening the hormone-free interval and if so, what were

they?
A As of 2005, there was one product which we discussed yesterday, that did shorten the hormone-free interval and the benefit presented in arguing for that approach was possibly more suppression -- was stabilization of the endometrium by the additional estrogen.

The approach taken in that product was to add additional days of estrogen five days prior to the combination in the hope that that would both suppress follicular development and stabilize the endometrium.

THE COURT: What was that product?

THE WITNESS: That product was Mircette, which we discussed yesterday.

MR. PAPPAS: Thank you, your Honor.

That was a question I was going to ask next.

Q Now, Dr. Darney, had the concept of shortening the hormone-free interval been known before 2005?
A It had been described in patents dating, for example, dating way back.
Q Approximately how far back?
A Well, I don't remember precisely, but I'm thinking 1980s, '81.
Q And yet, since between 1981 and 2005, only Mircette was the only product that shortened the hormone-free interval?
A Yes.

Q Now, let's take a look at two prior art references.

First of all, Mr. Brooks, can I have PTX-112, plaintiff's trial exhibit 112?

Do you have that in front of you, sir, on the screen?

A Yes. This is the 1981 patent that I recalled.

Q All right.

Can I ask you to return your attention to Example 9 of the '315 patent.

Mr. Brooks, can you blow that up?

A Here's what Vorys and the author of this patent depicts in figure six. Remember yesterday we talked about the follicular stage, when the estrogen is stimulating the endometrium and the luteal stage, when the corpus luteum is growing so he's using that reference for the first 15 days, 12 plus three, and the last 13 days, six plus seven.

And what's done here is a placebo period, days one through three, that is no exogenous steroids, either nothing or the placebo pill. First 12 days, example suggests norethindrone and then in the last -- the next six days, in the luteal stage, norethindrone plus ethinyl estradiol in 20 micrograms and then for the last seven days of the preparation, norethindrone and 35 micrograms of ethinyl estradiol.

At the bottom, he has the total dose of norethindrone and the total dose of ethinyl estradiol given over the 28

days.
Q All right.
Now, so is this an example of shortening the pill-free interval from the 21-7 pill?
A Yes, it's shortened here down to pill-free interval is three days.
Q Now, other than Mircette in the United States, after that patent in 1981, did anybody ever make a product that shortened the pill-free interval, other than the Mircette product?
A You mean up to the relevant date, 2005?
Q Correct.
A No.
Q All right.
A No.
Q Let me show you JTX-15 next, Dr. Darney.
Can we have that, Mr. Brooks, please?
What's the date of this patent, sir?
A This is 1990, and it's Sam Pasquale's patent, the one that actually led to Mircette years later.
Q All right.
And was he a prominent figure in oral contraceptive?
A Yes, I actually knew Sam very well. We did clinical trials, not of oral contraceptives, but other contraceptives together and he was a West Virginia coal miner's son and a very nice guy.

Q He's passed away, hasn't he, sir?
A Yes.
Q He's no longer with us?
A He died about seven years ago.
Q Now, sir, I think you testified this is like the '724, this is the patent that covers Mircette. Is that correct?
A Yes.
Q All right.

Now, let's bring up slide, Darney slide 24 very briefly.

Dr. Darney, just before leaving this particular topic, with the Vorys patent which is PTX-112, that has been introduced earlier, as you look at Darney exhibit 24, which is our chart of what happened from 1970 up to just prior to the invention of the '984 patent, other than Mircette, did anybody shorten the pill-free interval?
A Mircette shortened the pill-free interval in a 28 day, the typical 28-day package.

Seasonale shortened it by just continuously giving the pills over a three-month period. That is, there were no pill-free intervals, it wasn't shortened, there were simply no pills.
Q Do you understand from my recent question, I'm excluding Minesse, the European product, we're just talking about the U.S. now?

A Right. I was just looking at the U.S. products marketed between 1970 and 2005.

Q So, Dr. Darney, now that we've I think a good grasp on the history and the fact that Mircette was the only one used any shortening of the pill-free interval, do you have an opinion as to what the significance of those facts would have been to a skilled artisan in 2005, who was trying to make a pill that lowered the dose of estrogen in terms of whether or not shortening or lengthening the pill-free interval would be enough to compensate for the shortening of estrogen?

A Person of ordinary skill in the art would have been aware that dating way back to the Vorys patent in 1981, which is not shown on this chart, it's obscured under the orange stripe, would have been aware that although that idea had been suggested in patents, it hadn't been adapted to Mircette and Mircette was the only example of doing that.

Such a person would not have thought that shortening the pill-free interval was a great leap forward.

Q Dr. Darney, specifically, would a skilled artisan in 2005, thought that shortening the hormone-free interval, whether by placebo or unopposed estrogen or both, would have been enough to compensate for what would have happened to a woman if you dropped the estrogen below 20 micrograms?

A No. A person of ordinary skill in the art would not have considered that and wouldn't have thought that could possibly

overcome the effect of a drastic reduction in estrogen dose, either with regard to efficacy or cycle control.

Q All right.

Let's turn then to the issue of what we know or what the prior art has described happens when you go from a 21-7 regimen to a 24 day, four-day regimen, all right, Dr. Darney?

A Yes.

Q Let me ask you, has Lupin pointed to any data or evidence demonstrating that extending the combination dose from 21 to 24 days would, by itself, enable lowering the daily EE dose below 20 micrograms while still maintaining adequate cycle control and contraceptive efficacy?

A No.

Q Are you aware of any such data?

A No.

Q Mr. Brooks, could I have PTX -- before we go there, I want to ask you a follow-up question, sir.

Has Lupin pointed to any data or evidence that extending the combination dose from 21 to 24 days would, by itself, enable a skilled artisan to lower the daily EE dose below 20 micrograms while still using norethindrone acetate and yet, maintain adequate cycle control and adequate contraceptive efficacy?

A No.

Q Are you aware, based on your position as a reviewer of

the New England Journal of Medicine and the Contraception magazine, of any data where it has been demonstrated that extending the combination dose from 21 to 24 days would, by itself, enable a skilled artisan in 2005, to lower the daily EE dose below 20 micrograms with the progestin being norethindrone acetate and yet, maintaining adequate cycle control and adequate contraceptive efficacy?

A No.

Q Let's turn now to plaintiff's trial exhibit 91.

Could I have that, Mr. Brooks? This is -- Dr. Darney, you should have that on your screen?

A Yes.

Q This is the article by Sullivan, et al, effective 21-day and 24-day oral contraceptive regimens containing Gestodene, 60 micrograms and ethinyl estradiol, 15 micrograms on ovarian activity.

Do you see that, sir?

A Yes, in Fertility and Sterility in 1999.

Q And that would be prior art?

A Yes.

Q Have you reviewed this in connection with your work in this case?

A Yes.

MR. PAPPAS: Your Honor, I offer PTX-91 into evidence.

MR. GREEN: No objection, your Honor.

Q What is this article generally about, sir?

A It's about the pill we discussed earlier, Minesse, 15 micrograms of ethinyl estradiol with Gestodene 60 micrograms specifically examining ovarian activity. That is the growth of follicles in the ovary.

Q All right.

I understand, Doctor, this comparison was of Gestodene products, correct?

A Yes. One 21-day and one 24-day, both the same preparations, subjects followed for five cycles, that is five months.

Q All right.

Let me direct your attention to page 118 of the article and ask if you can read the highlighted language and tell us what the study found regarding cycle control in comparing the 21-day and the 24-day regimens?

A Yes. "Cycle control. Overall break-through bleeding, it was more substantial than spotting occurred in 16, 21 percent of 75 treatment cycles in the 21-day group and 35, 42 percent of 84 treatment cycles in the 24-day group.

The third treatment cycle, break-through bleeding occurred in six, 25 percent of 24 subjects in the 21-day group and 12, 42 percent, 28 subjects in the 24-day group.

Three women in the 21-day group and one woman in the

24-day group failed to bleed in the seven days after ingestion of the last active pill.

The mean duration withdrawal bleeding was four days in the 21-day group and five days in the 24-day group. The median intensity of bleeding was light in both groups.

Q So what does that mean?

A Perhaps I should say that break-through bleeding, it was more substantial than spotting means usually break-through bleeding that requires sanitary protection, the pad or a Tampon.

The conclusion person of ordinary skill would draw from this is that the incidence, frequency of occurrence of break-through bleeding was actually greater in the 24-day group.

Q Now, so it was worse on the 24 days than the 21 days, correct?

A Yes.

Q Now, would this article encourage a skilled artisan, in 2005, to shorten the hormone-free interval and lower the dose of estrogen to below 20, let's say to 15 micrograms?

A No. A person of -- such a person reading this article would think, well, it made the bleeding worse, didn't help.

Q And further, would this article have encouraged or discouraged a skilled artisan, in 2005, to reduce estrogen below 20 micrograms using norethindrone acetate as the

progestin at one milligram?
A No, such a person would have looked at this article and thought, there's a real problem in both groups with reducing the estrogen to 15 and this is with the most potent progestin.
So such a person would certainly not consider, a person would think the problem would be a lot worse, whether it's 21 or 24 days, using one milligram of norethindrone acetate. Such a person would have known that Gestodene has powerful effects on the endometrium, much more powerful than those of norethindrone at one milligram.
Q All right.
Let me ask us to turn now to another study. Mr. Brooks, can we have -- can you pull up plaintiff's trial exhibit 37, sir?
MR. PAPPAS: Your Honor, before we go to PTX-37, I believe I moved into evidence PTX-91, but I'm not positive, so I'd like to.
THE COURT: That was the last one.
MR. PAPPAS: Last one.
MR. GREEN: No objection, your Honor.
Q Thank you.
What is PTX-37 that is now on the screen?
A This is an article from the European Journal of Contraception Reproductive Healthcare, November, 1999, titled New Parodyne For Low Dose Oral Contraceptive.

Q Prior art, sir?
A Yes.
MR. PAPPAS: Your Honor, I move it into evidence, plaintiff's trial exhibit 37.
MR. GREEN: No objection, your Honor.
THE COURT: All right.
Q Now, what was compared in this article, sir?
A This is an examination by a group of investigators called the Gestodene study group, of the cycle control, safety and efficacy of a 24-day regimen of Gestodene 60 of ethinyl estradiol 15, that is European Minesse, and a 21-day regimen of Desogestrel, a different but potent progestin with ethinyl estradiol of 21 micrograms. That is it's Minesse versus Mercilon.
We discussed the Mercilon product, which was approved in Europe at that time, but not approved, it's never been approved in the United States. We discussed that yesterday.
Q All right.
Can I direct your attention to the right-hand column of page 20?
Can you tell us what the author found in terms of the cycle control when the two regimens were compared?
A So here they're comparing -- remember, 24 days, Gestodene and 15 of ethinyl estradiol. The 21 days Desogestrel and 20 of ethinyl estradiol and it's fairly large numbers of cycles,

3,000 in the Gestodene group and 3,000 in the Desogestrel 21-day group and the total percentage of normal cycles was lower in the Gestodene group, the 24-day group, than in the Desogestrel group, the 21-day group.

Do you want me to read?

Q No, I think that's fine. That's a good summary.

Now, which group had better cycle control, the 21-7 or the 24-4?

A The 21-7 had better performance than the 24-4.

Q Let me ask you, Dr. Darney, based on the Sullivan and Gestodene study group articles, do you have an opinion as to what this would have taught a skilled artisan, in 2005, about whether or not they could compensate for lowering estrogen below 20 micrograms by simply extending pills into the hormone-free interval?

A This would have taught a person of ordinary skill that the bleeding was actually worse when you went from 21 to 24 and would have counseled against making that kind of change.

Q And, sir, what would the Sullivan and Gestodene articles have taught the skilled artisan, in 2005, about whether he or she should consider lowering the dosage of estrogen below 20 while using norethindrone acetate at one milligram as the progestin?

A Well, in this study, two potent progestins were used, Gestodene and Desogestrel. Person of ordinary skill would

have thought that the situation would have been much, much worse if norethindrone acetate, one milligram, were used with these lower doses.

In addition, there had already been a lot of experience with the bleeding pattern of one milligram of norethindrone acetate and 20 micrograms of estrogen and the Loestrin 1/20 product marketed in 1973.

A person of ordinary skill in the art would have also been aware of that long experience of bad bleeding.

Q All right.

Let me ask you to turn now to plaintiff's trial exhibit 83.

Can we have that, Mr. Brooks?

This is from your -- the Clinical Guide to Contraception, fourth edition, of which you're one of the authors.

A Yes, Leon Speroff and I wrote this in 2003, 2004, published in 2005.

Q Now, let me ask you to turn to page 40, sir.

Read that language and tell us what it would have told a skilled artisan in 2005.

A "Reduction of the pill-free interval is a strategy aimed at the concern that pill omission," that is failing to take all your pills or more likely not starting a new package on time with low dose oral contraceptives, "might more readily

result in escape ovulation. Utilizing a four day pill-free interval rather than the usual seven days is associated with greater ovarian suppression. Another approach adds estrogen for five of the usual seven pill-free days," and we've talked about that approach when we talked about the only product that did that, Mircette.

"However, these approaches have failure rates in break-through bleeding rates that are comparable to the standard regimens and no clear-cut advantage for these alterations can be established."

Q Did you include the same statement in 2001, third edition of the Guide to Contraception, PTX-82A and just to be sure, can we have that, Mr. Brooks, page 39, just so you can confirm this, sir?

A Yes. It's just the same.

Q All right, sir.

MR. PAPPAS: Your Honor, we move --

A Mr. Brooks hasn't shown it yet.

Q Mr. Brooks, have you put it up? There it is.

A There, same statement.

Q Okay.

This is from the third edition that was the Clinical Guide to Contraception that was published in 2001. Is that correct?

A Yes. The difference is the reference numbers because in

each edition, we change the number of references.

Q All right.

Now, sir, again taking the Sullivan article with the Gestodene study and your quotes and Dr. Speroff's from the Guide to Contraception, can you tell us in 2005, what would have been the lesson or the message to the skilled artisan as to whether or not they should consider lowering estrogen below 20 micrograms per day while using a progestin of norethindrone acetate of one milligram?

A There is no such instruction.

Q Any suggestion to do that?

A No such suggestion. In fact, caution against that.

Q Okay.

Now, let me ask you to turn to PTX, plaintiff's trial exhibit 33, the Gaspard article.

Can we have that up on the screen, Mr. Brooks?

Are you familiar with this article, sir?

A Yes, I am.

Q And when was it published?

A It was published in May, 2000.

MR. PAPPAS: Your Honor, I move in PTX-33.

MR. GREEN: No objection, your Honor.

Q Directing your attention to the summary on the first page, in general, what is this about?

A This is a review of new methods of hormonal

contraception, including oral contraceptive implant contraception, inter-uterine contraception.

Q Okay.

And what oral contraceptives were compared?

A This is a comparison of 24-day ethinyl estradiol Gestodene, that is Minesse, and I believe this describes the experience of the Gestodene study group as well as other experiences.

It says -- and they're writing here about new methods, so they also are looking at subcutaneous implants containing keto-desogestrel, that's a derivative of Desogestrel which is used in birth control pills, and the Levonorgestrel releases in the uterine system.

Q Now, let's turn to page 289, the second page of the article, with the highlighted language with the rate of spotting.

What were they comparing and what did they find?

A Here, they are comparing Minesse 15, Gestodene 60 for 24 days to Mercilon 20 ethinyl estradiol and 150 of Desogestrel for 21 days and describing that the -- there were a higher proportion of normal cycles, which is the aspiration of birth control makers, of course.

In the 21-day preparation, 78 percent were normal than in the 24-day preparation, where 65 percent were normal.

Q All right.

Now, what would a skilled artisan, in April, 2005, had concluded from this report about cycle control in low estrogen formulations, sir?

A Twenty-four days was worse than 21 days.

Q Would this reference have encouraged a skilled artisan, in your opinion, in 2005, to combine 15 micrograms of daily estrogen dose with a one milligram norethindrone acetate pill?

A No, the effect would be exactly the opposite. A profound discouragement.

Q Similarly, would this reference have encouraged a skilled artisan, in 2005, to combine ten micrograms of ethinyl estradiol with one milligram of norethindrone acetate, as was done years later by the '984 patent?

A No.

Q Dr. Darney, before I move on to the next topic, I want to ask you to return for a moment to the guide that we had just looked at, which was exhibit 82A.

A Yes, Clinical Guide For Contraception.

Q All right.

Can we have that language up again, Mr. Brooks?

Now, in conjunction with these -- is this page 39, Mr. Brooks, the Clinical Guide, fourth edition?

A Yes.

Q Specifically, what would a skilled artisan, in your opinion, in 2005, have concluded from the statement, "We are

probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy," and then it goes onto identify ethinyl estradiol doses of 20, 25, 30 and 35 micrograms?

A Person of ordinary skill would have concluded that you can't reduce estrogen any further than in these low dose preparations without sacrificing -- without causing unacceptable bleeding or sacrificing the efficacy of the oral contraceptive.

Q All right.

Now, let's turn, Doctor, to the product called Loestrin 24, about which Dr. Barnhart has testified.

You read that testimony, sir?

A Yes.

Q Are you familiar with the Loestrin 24 product?

A Yes, I am.

Q Is it another product sold by Warner Chilcott?

A Yes.

Q What's the regimen?

A It's a regimen that adds estrogen to the previous Loestrin 1/20 that we discussed a lot yesterday. It adds four additional days -- three additional days; 21 plus three is 24. Three additional days of the combined pill. So increases the estrogen dose and progestin dose for three additional days.

Q Dr. Barnhart testified that Loestrin 24 is prior art.

Are you familiar with his testimony given in this court last week?
A Yes.
Q As far as you know, would a skilled artisan have known, according to Dr. Barnhart, that Loestrin 24 was approved by the FDA as of April, 2005?
A No, it was approved four or five years later than that.
Q So a skilled artisan certainly couldn't have known of FDA approval because it hadn't taken place yet, right?
A Right.
Q Now, Dr. Barnhart testified, I believe, that it would have been known what the results were of Loestrin 24's clinical trials as of April, 2005.
Do you remember that?
A Yes, I do.
Q Do you have any evidence that it was publicly known what was happening with the clinical trials of Loestrin 24?
A No. As far as I'm aware, there is no such evidence.
Q In reviewing the transcript of Dr. Barnhart -- did Dr. Barnhart produce any actual factual evidence in terms of documents that proved that it was well known as prior art in terms of publications in libraries or medical facilities as to what the results were of the clinical trials of Loestrin 24, as of April, 2005?
A No.

Q Was there any evidence offered by Dr. Barnhart that the regimen of Loestrin 24 was known generally to persons of skill in the art in April, 2005?

MR. GREEN: Objection, your Honor. He's asking for a legal conclusion as to evidence.

MR. PAPPAS: I'll alter that question, your Honor. I'll amend that.

THE COURT: Okay.

Q Did you read any facts from Dr. Barnhart's testimony as opposed to opinion, facts that disclosed that skilled artisans and members of the public generally had available to them, in April, 2005, information about the regimen of Loestrin 24?

A No.

Q Now, I want you to assume for my next question or two, Dr. Darney, that the Loestrin regimen, Loestrin 24 regimen was known, okay? I want you -- I'm asking you to accept that hypothetically, all right?

A Yes. I don't understand that. I don't believe it was known in 2005, but you want me to assume that it was?

Q Just for the sake of my question, yes.

A Okay.

THE COURT: You want him to assume what?

MR. PAPPAS: Your Honor, I'm asking him now to assume that Dr. Barnhart's -- that Loestrin 24 was known, the regimen was known in April, 2005.

THE COURT: What's the patent from which Loestrin 24 is derived?

THE WITNESS: '394.

THE COURT: Okay.

Q Thank you.

Is the Loestrin 24 regimen similar to the Estrostep regimen that we discussed yesterday?

A Yes, it is.

Estrostep that we discussed added estrogen by increasing the estrogen dose over the 21 days.

Loestrin 24 adds estrogen by adding it at the end of the 21 days and shortening -- thereby shortening the hormone-free interval.

Q So does Loestrin 24 give the woman on a monthly basis more estrogen than Loestrin 1/20?

A Yes, in the same way that Estrostep did.

Q Okay.

Now, keeping with that assumption that I've just asked you to make hypothetically, if a skilled artisan decided to modify Loestrin 24 in April, 2005, to design an ultra low dose oral contraceptive with less than 20 micrograms per day, would that person have thought that adding two days of unopposed estrogen would compensate for cutting the daily doses of estrogen in half for the 24 days of combined administration?

A Absolutely not.

Q Why not?
A That's a dramatic reduction in daily and total estrogen dose. It couldn't possibly be compensated for by adding a little more estrogen in two days.
Q Let me sharpen that question more.

If a skilled artisan decided to modify Loestrin 24 to design an ultra low dose oral contraceptive with ten micrograms of ethinyl estradiol per day, as was ultimately done by the '984, would that person have thought that adding two days of unopposed estrogen would compensate for cutting the daily dose of estrogen in half for the 24 days of combined administration that ultimately became the '984?
A No, such a person would have thought that it would be impossible to overcome the problems of bad bleeding and compromised efficacy of cutting the dose in half with adding a lit bit of estrogen.
Q All right.

Same question, but since the range is five to 15 in the '984 patent, would a skilled artisan, in 2005, have thought that adding two days of unopposed estrogen would compensate for a 25 percent reduction in the daily dose of the 24 days of combined administration by going from 20 micrograms to 15 micrograms?
A No, for the same reason.
Q Okay.

Now, I want to turn now -- can I have slide 11, Mr. Brooks, Darney slide 11?

I'd like to turn to the fourth reason now for your opinion that the '984 patent claims were not obvious in view of the prior art where you said, "defendants' hindsight use of portions of prior art does not render the claimed invention obvious."

Do you see that, sir?

A Yes.

Q Okay.

Now, in engaging in your obviousness analysis so that you could come here prepared to testify, did you understand that skilled artisan in April, 2005, would have had to consider all the available prior art, not just two or three patents?

Did you understand that?

A Yes, I did.

Q All right.

And were you also told by counsel that you can't just read patents in bits and parts, but you must read the patent or any other reference as a whole to see what it describes or teaches?

Were you told that?

A Yes, I understand that.

Q And did you apply those principles as they were given to

you by counsel?
A I did.
Q Okay.
Now, let's turn then to the '490 patent. Can we have JTX-12, which I believe is already in evidence, your Honor, on the screen.
Now, you have read the trial testimony, correct, Dr. Darney?
A Yes, I have.
Q And are you aware that it's Lupin's contention that the '490 and '940 patents read as a whole would disclose the patented invention?
A I'm aware of that, yes.
Q Did you agree with that?
A No, I don't.
Q Are you aware that Dr. Barnhart opined that the claims of the '984 patent would have been obvious over the '490 patent?
A Yes.
Q Do you agree with that?
A No, I do not.
Q Did you prepare a slide to summarize the reasons why you do not believe the '984 patent would have been obvious in light of the '490 patent?
A I have.
Q Okay.

Can we have, Mr. Brooks, Darney slide 42, please?

Okay, sir. We'll state briefly and we'll get into then in some detail, though, the four reasons you have that support your opinion that the '490 patent would not have rendered the '984 patent obvious.

A Yes. That patent clearly emphasizes potent progestins, Levonorgestrel and Gestodene.

Next, that patent prefers 15 to 25 micrograms, not five to 15 micrograms of ethinyl estradiol and it actually doesn't mention norethindrone acetate in the patent. There would be no reason for a person of ordinary skill to disregard the patent's failure to include placebos. It's continuous administration.

Finally, the patent, if you do consider all of the alternatives it presents or even if you limit the alternatives to its preferences, gives a huge number of possible regimens.

Q All right.

Let's explore each of those.

By the way, before we get there, so that we stay tethered to the real world, was a product ever developed, to your knowledge, pursuant to the '490 patent?

A No.

Q Now, have you, before we get into detailed analysis of this patent, you did mention the large universe of regimens encompassed by the claims of the '490 patent.

Have you formed an opinion as to how many potential oral contraceptive regimens a skilled artisan could derive from the disclosures of the '490 patent?

A Yes, I have, based on Dr. Thisted's calculations.

Q Now, did you provide Dr. Thisted with certain assumptions to make in his calculations of amounts of progestin, estrogen and so forth as in the claims?

A I did.

Q Okay.

Let me ask you to look at plaintiff's trial exhibit 151, which is already into evidence.

Just tell his Honor if this is the document summarizing the assumptions for each of the patents that had been cited by Lupin that you provided to Dr. Thisted?

A Yes, it is.

Q Okay.

Now --

THE COURT: 151 speaks about the '940 patent. I thought we were on '490?

MR. PAPPAS: We are, your Honor.

Q Can we go to the next page?

So you did it for the '940 patent and the '490, correct?

A Yes. There's a group of assumptions for each of the patents. This is '490.

Q Let's go through the document so we know.

What other patents did you provide assumptions to Dr. Thisted for, in addition to the '940 and the '490?

Can we have the next page, Mr. Brooks, after '490?

A Yes. It's '607, '394, '724. Here's '394, the patent we mentioned a moment ago. '251.

Q All right.

Now, would you characterize -- how would you characterize the assumptions that you gave to Dr. Thisted -- let me back up.

Did these assumptions that you made include every conceivable numerical regimen within the range or did you limit them in some way?

A They're limited.

Q Okay.

And the assumptions you used, would you characterize them as conservative or aggressive?

A Conservative.

Q Now, in --

MR. PAPPAS: One moment, your Honor.

(Pause.)

Q The question arose earlier in the trial with Dr. Thisted, Dr. Darney, about one of the patents as to whether or not you based your assumptions on the preferences alone, either the '490 or '940. This was the patent that preferred Gestodene or

Levonorgestrel.

Can you tell his Honor why you did not limit the combinations to the preferred --

A Yes.

Q -- progestins?

A With these patents, if you limited the possibilities to the preferred progestins, you immediately exclude the '984 patent. And so in order to include the possibilities presented there, I didn't limit it just to the preferences.

Q And that's true with at least with respect to the patents that claimed Levonorgestrel and Gestodene as the preferred progestins, correct?

A Right.

Q Now, have you prepared a slide then to set forth the number of regimens that would be possible for the '490 patent, based on these assumptions?

Can we have Darney slide 34?

What was the total number of regimens possible with the '490 patent?

A '490 was on the order of 16 million based on Dr. Thisted's calculations.

Q Okay.

Now, Dr. Darney, as we continue down this path of what these patents would or would not disclose to someone of skill in the art, who was actually in the process of trying to

design an oral contraceptive, I want to return for a moment to slide, Darney slide 18.

Can we have that, Mr. Brooks?

Now, you earlier identified all the choices for the designer of a COC, combined oral contraceptive.

My question, to you, sir, is: Are those six variables, estrogen type, estrogen dosage, progestin type, progestin dosage, hormone-free interval and order of administration, do they operate independently or are they interdependent on one another when a skilled artisan attempts to design a regimen?

A They're interdependent on one another.

Q What does that mean, sir?

A That is that the type of estrogen and the estrogen dose you give would influence the progestin dose; that the order of administration would influence the other factors and so on and so forth.

That is, each one isn't considered separately in putting together out of it's component parts a combined oral contraceptive.

Q Can you -- can a skilled artisan simply change one of those six design choices without considering the effect it would have on the other parts of the oral contraceptive regimen?

A No, all of the literature we've discussed speaks against that approach, that can't be done.

Q Is that principle, that all six parts are interdependent, well known in the contraceptive art as of April, 2005?
A Yes.
Q Have you ever, in your review of literature, in your 44 years of experience, have you ever read an author who says in considering the design of a contraceptive pill, you can make one change and ignore everything else?
A No, never have.
Q So would it be fair to say that that principle is well settled among those who design oral contraceptives?
A Absolutely.
Q Okay.

Let's return to the '490 patent, sir.

Mr. Brooks, can we have JTX-12? Let me direct your attention to column two, lines 50 through 62.

Do you see that, Doctor?

A Yes.
Q Now, please read that and tell us, in your opinion, what that passage of the '490 patent would have disclosed to one of ordinary skill in the art, in April, 2005?
A That if you lower the estrogen to low as 20, you'll have problems with too much bleeding, I was thinking of the Akerlund study, and with efficacy, that is you wouldn't adequately suppress the development of follicles.
Q All right.

In particular, when the patent said "The preparation," and I'm quoting, "was the lowest dosed amount of estrogen at this time is marketed as Mercilon and contains 20 micrograms of ethinyl estradiol in combination with 150 micrograms of Desogestrel in each daily dosage unit over 21 days, followed by a seven day pill-free interval" and what is that disclosing in terms of what was the lowest dose product at the time?

A They're commenting here that the pill, Mercilon, which was available in Europe then, that was the one that Gaspard and the Gestodene study group and the earlier studies he reviewed, said was better than the 15 microgram pill, Minesse, in cycle control. They're commenting that that pill has a worse bleeding pattern than other birth control pills.

Q And what does the inventors of the '490 patent warn about in the last sentence when they wrote, "Obviously, for many women, this very low estrogen dose can result in the maturation of follicles, as has been detected in ultrasound studies or hormone studies"?

What's being disclosed there to the skilled artisan as of April, 2005?

A The writers are cautioning against going as low as 20.

Q Now, by the way, I just want to pause on this because this may for a moment be important later.

This patent reports that the maturation of follicles can be detected in ultrasound studies or hormonal -- hormone

studies. Is that correct?
A Yes.
Q So if one really, such as Lupin, wants to really demonstrate what's happening with the follicles, that can be measured, correct?
A Yes.
Q Okay.
We'll come back to that.
Now --
THE COURT: May we take a break?
MR. PAPPAS: Certainly, your Honor.
THE COURT: Let's take ten minutes.
THE CLERK: All rise.
(Recess.)
THE CLERK: All rise.
THE COURT: Thanks, have a seat.
How are we doing Mr. Pappas?
MR. PAPPAS: Moving through it, your Honor.
P H I L I P D A R N E Y, previously sworn, resumes the stand.
DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:
Q Dr. Darney, let me direct your attention in the '490 patent to column three, line 16 through 37.
Do you have that, sir?
A Yes.

Q Let me ask you about the first sentence, first about the sentence at the bottom, reads, "Contraceptive protection is thus jeopardized. The risk of pregnancy is, therefore, high, especially in the case of intake errors below the 20 microgram ethinyl estradiol preparations."

What is the inventor disclosing to the skilled artisans there, sir, about the references above?

A That these references say that if you lower the estrogen dose, you reduce contraceptive protection, that is efficacy. That that is especially true if you're using 20 microgram pills -- using less than 20 micrograms and having to not take the pill on time or not begin a new package of pills when you should.

Q All right.

If you go up a little bit, is there a reference in the highlighted language above to the Pasquale '843 patent, sir?

A Yes. The last line refers to Sam Pasquale's '843 and applies to the re-issue '724.

Q Is this the patent that covers Mircette?

A Yes, those patents cover Mircette.

Q And I think we covered yesterday that the '843 patent discloses dosing unopposed estrogen immediately before the combination phase, correct?

A Yes, that's where Pasquale administers the five days of unopposed estrogen, right before the combination.

Q So what does this '490 patent indicate to one of skill in the art, even about the '843 patent, if you go below 20 micrograms of estrogen?
A It's cautioning you that you'll compromise efficacy, even when you had that extra estrogen before the combined preparation.
Q All right.
Let's turn to the example on columns five -- starts at the bottom of five and goes up through column six of the '490 patent.
Can we have that up on the screen, Mr. Brooks?
Do you see that, sir?
A Yes.
Q Is this the only example provided in the '490 patent?
A Example 1 is the example.
Q Does this example give a recommended estrogen dose in the first three phases?
A Yes.
You want to highlight that?
Q Yes, can you highlight, that Mr. Brooks?
So this is the only example in the '490 patent and it is a four-phase structure, correct?
A Yes. It's a complex scheme, with four phases, five with these four phases, five days, seven days, 12 days and four days of estrogen.

Q All right.

Now, for how many phases is the woman in this example would she be given a combination oral contraceptive containing an estrogen and progestin?

A That's for 24 days.

Q And then followed by four days of what?

A Of estrogen alone.

Q Okay.

Now, during that combination phase, all three combination phases, how many estrogen or what amount of estrogen is disclosed in this example?

A This example discloses in the first five days, 20 micrograms; in the next seven days, 25 micrograms; and in the next 12 days, 20 micrograms or it discloses, the line below discloses doses of natural estrogen 17 beta estradiol.

Q Now, in combination oral contraceptive phases for 24 days, does this example disclose an amount of estrogen below 20 micrograms?

A No. In fact, it discloses 20 and an amount greater, 25 and then 20.

Q And then in the fourth phase, it purports, does it not, to cut the estrogen at least by 50 percent when it's alone; ten instead of 20 micrograms, right?

A Yes. As in the Mircette patent which the writer of this patent was criticizing.

Q Now, what -- let me ask you, what progestins are disclosed in the '490 patent? First of all, what progestins are used in the example?
A Gestodene and the doses are given and Levonorgestrel, and the doses are given.
Q Were these the preferred progestins in this patent?
A Yes.
Q Now, is there any disclosure in the '490 patent, in your opinion, Dr. Darney, that would suggest to a skilled artisan that he should pare 15 micrograms of ethinyl estradiol with norethindrone or norethindrone acetate?
A No, there is no such disclosure in the preferences or in the example.
Q Now, is there any data at all in the '490 patent that would show a skilled artisan that a range of estrogen from five to 15 micrograms would be effective contraceptively or have good cycle control when pared with one milligram of norethindrone acetate?
A Well, the writers of the patent do present other studies, which speak against doing that.
Q Okay.
So the studies disclosed in the patent, in your opinion, speak against doing that, correct?
A Yes.
Q But I want to understand as well that in addition to the

studies that speak against it, is there any data or studies cited in the '490 patent which, in your opinion, would be read by a skilled artisan, in April, 2005, to suggest or motivate them or make them believe that if you made a pill with five to 15 micrograms of ethinyl estradiol and only one milligram of norethindrone acetate, that it would be effective contraceptively and have acceptable cycle control?

A Absolutely none.

Q Now, I want to stay with that example for a moment.

Does the '490 patent teach or suggest that the same amount of ethinyl estradiol should be used in each phase or stage?

A No, it does not. In fact, it varies the doses as we've seen over the stages, over the phases.

Q Now, is there any suggestion in the '490 patent that you could keep the amount of estrogen the same in the combination phases of the pills as well as in the unopposed estrogen?

A No.

Q What does the '490 patent teach in the only example that they give?

A Example, as in the '843 patent, reduces the estrogen to half or more than half of the estrogen dose in the combined phases.

Q Is that what Mircette did?

A Yes.

Q But is there any -- so is there any suggestion or teaching at all in the '490 patent that one could pick a particular dosage of estrogen, such as ten or 15 micrograms, and use that estrogen dosage throughout the pill-taking period with the progestin and then you would go to unopposed estrogen and keep the same amount of estrogen?

Is there any suggestion of that?

A No.

Q In fact, they cut it in half, right?

A Yes.

Q Okay.

Now, sir, let me turn to the '940 patent.

Mr. Brooks, could I have joint trial exhibit 16 up?

Dr. Barnhart, you've -- I'm sorry, Dr. Darney, you've reviewed Dr. Barnhart's testimony that the claims in the '984 patent would have been obvious in light of the '940 patent, correct?

A Yes.

Q Do you agree with that opinion?

A No.

Q All right.

Have you prepared a slide that summarizes the reasons for your opinion that the '984 patent would not have been obvious in light of the disclosures of the '940 patent?

A I have.

Q Can we have, Mr. Brooks, Darney slide 43 on the screen, please?
A First, the '940 patent emphasizes potent progestins as did the '490. There are no data in the '940 patent to show a person of ordinary skill that five to 15 micrograms of ethinyl estradiol and one milligram of norethindrone acetate would be effective or have good cycle control.

There would be no reason for a person of ordinary skill reading the '940 patent to ignore its teachings on the order of administration, which specifically require placebos before the unopposed estrogen.

Finally, there is no reason for a person of ordinary skill to arrive at the '984 patent given the huge number of possibilities that the '940 patent includes.
Q All right, sir.

Before we turn to each of those reasons in some detail, did the '940 patent ever result in a marketed product?
A No, it did not.

THE COURT: Why is that? Why, in your view, did the '940 and the '490 not result in a product?

THE WITNESS: I think it's because of the practical experience with other products, for example, Mircette, that attempted other ways of doing the same thing. That is, that those products weren't particularly successful and that the standard 21-7, 25 to 35 microgram products continued to

dominate the market and provide good, safe, effective contraception with no indication that further reducing the estrogen dose would confer important benefits, particularly with regard to deep vein thrombosis.

THE COURT: So how did the '490 and the '940 run into difficulty? That's a terrible question.

What about the '490 and the '940 leads you to conclude that the product was not going to be developed? It just didn't work or it wasn't enough of a difference from the previous products which were marginal?

THE WITNESS: Well, it would be too big of a risk without enough chance of benefit in the market or benefit to individual patients who use them, to reduce the estrogen even as low as these patents suggest, which is on the order of 20, 25 as we saw in the '490, and as we'll see in the '940, that there was no clear health benefit to doing that, and when it had been done in the marketplace, Mercilon, for example, had clearly worse bleeding than its 30 microgram equivalent Marvelon.

So I think from the point of view of the company, same company produced both of these patents, they thought, well, it's not worth spending 30 or $40 million to do a clinical trial when there's not going to be a really clear benefit.

THE COURT: Okay. Thank you.

MR. PAPPAS: Your Honor, if the Court please, may I follow-up on your questions?

Q Let me explore, Dr. Darney.

So is it -- are there women in our great country who present themselves to gynecologists and say, I want the lowest estrogen pill you can give me, Doctor?

A There are.

Q Okay.

A Yes, I've had patients ask for that.

Q Are there women who present a medical picture to a physician, a gynecologist, such that their symptoms indicate very real sensitivity to estrogen, synthetic estrogen such that the doctor would be inclined to give them the lowest dose estrogen product available?

A Yes, or change to a --

Q Or change to an IUD?

A Yes, to a different method of contraception.

Q Now, so in light of that, those two facts, women who either want estrogen because they simply want the lowest amount, or they need to take the lowest amount of estrogen due to their constitution, their body, just can't tolerate estrogen, in view of that, what you've just told his Honor is that the companies were the same that invented the '490 and the '940 patent were not motivated by their own inventions to make an estrogen pill that only had ten micrograms. Isn't

that correct?
A Right.
Q Okay.
Now, I think we've reviewed earlier that the disclosure in the '940 patent is very similar to the '490 patent, correct?
A Yes.
Q The basic specification, before we get to the claims?
A Yes.
Q Okay.
Before I get into it, because Lupin has put the '490 and the '940 together for their obviousness case, is there any teaching in the '490, '940 patents taken together that would have led a skilled artisan, in 2005, to make an oral contraceptive with ten or 15 micrograms of ethinyl estradiol with one milligram of norethindrone acetate?
A No, both patents prefer the potent progestins, Levonorgestrel and Gestodene.
Q Okay.
I want you to assume now, sir, this person of ordinary skill in the art, which we know is a hypothetical person, and he is sent into a room and told by his boss to review all of the prior art in oral contraceptives as of April, 2005, but to come out of that room with a pill that has 15 or ten micrograms of ethinyl estradiol and that produces acceptable

cycle control and contraceptive efficacy.

Do you have an opinion whether that person of ordinary skill in the art, looking at all the art available, would say, I'll do it with norethindrone acetate in 2005?

Do you have an opinion whether anybody would think that, other than the inventor in this case?

A No, no one would think that.

Q Why not?

A All, literally all of the prior art, if you were required to do what you're demanding of that person would tell you to use a more potent progestin.

Q And the '490 and the '940 clearly prefer Levonorgestrel and Gestodene, which are more potent progestins than norethindrone acetate. Is that correct?

A Yes.

Q Let's return to the '940 patent, Doctor.

Similarly, as you had done for the '490 patent, did you give a series of assumptions to Dr. Thisted to determine how many possible regimens could come -- could be made from the '940 patent?

A I did. Using the same approach as we described for the '490.

Q And just so we have for the record what number you came up with, Mr. Brooks, can we have Darney exhibit 34, please?

What number, based on your assumptions, did Dr.

Thisted calculate as the possible regimens that would emanate from the claims of the '940 patent?

A 6.2 million.

Q All right.

Now, Doctor, let me direct your attention to column two, lines 55 through 67 of the '940 patent.

I don't see a necessity to repeat. All I'd like you to do is establish for the record that the highlighted language is the same here in the '940 patent as you've already testified about in the '490 patent.

A Yes.

Q All right.

Let me ask you to direct your attention to column three, line 17 through 39 of the '940 patent, sir.

Again, is this the same language that was in the '490 patent?

A Yes, same language, same references.

Q Okay.

And this is the passage concerning the risk of pregnancy being high from 20 microgram preparations, correct?

A Right.

Q Let me ask you to turn to column five, lines 20 -- 22 through 24.

Sir, is that the same disclosure as the '490 patent, thereby telling the skilled artisan, in April, 2005, that

Gestodene and Levonorgestrel are the preferred progestins?
A Yes, it is.
Q Now, let's turn to column five of the '940 patent, lines 30 through 54.
In this area, does the '940 patent provide any examples?
A Yes, it provides its example in a more complex format than the previous table from '490 in which the days are represented on the first line and the composition of the tablet is represented on the second line and there are four lines for the four weeks of administration.
The examples two, three and four, in addition to one, are presented in the bottom four lines by virtue of changing the length of either estrogen combination or placebo administration.
Q What do the examples disclose about the estrogen dose?
A About the order of the estrogen?
Q No, just the estrogen dosages that they use?
A The preferred doses of 15 to 25, we'd have to look at another table to show what the examples prefer.
Q Yes. I'm just talking about the examples, sir.
Let me ask you this way, maybe this will make it streamline.
Does the '940 patent provide any examples or data showing successful reduction below 20 micrograms with any

particular regimen?
A No.
Q In your opinion, sir, does the '940 patent teach or suggest using a five to 15 microgram dosage of EE with norethindrone acetate?
A No.
Q All right.
Now, let's move to another subject.
Are you familiar with Dr. Barnhart's testimony that he says it would have been obvious, in view of the '940 patent, to deliver the same estrogen dose in the combination phase as in the unopposed estrogen phase?
Are you familiar with that?
A I'm familiar with that, yes.
Q Is that issue -- first of all, does the '940 patent teach or suggest that you can use the same estrogen dosage in each stage, including the unopposed estrogen phase?
A No, it does not.
Q Does the '940 patent address that issue at all?
By "that issue," I mean the amount of estrogen used in the combination phase and the amount used in the unopposed estrogen phase?
A I'd have to look more closely at the patent to see if that's --
Q Okay.

Well, can we have the examples up, Mr. Brooks, from the '940 patent?
A What we need are the doses in the examples rather than the pattern of administration, which is in the example table.
Q Well, does the '940 patent provide any examples containing specific estrogen doses?
A No.
Q I see.
Perhaps that's why we're having trouble finding it?
A Yes.
Q Now, let's turn to the order of administration.
The '940 patent discloses a particular order of administration. Is that correct?
A That's right.
Q What is it?
A That's what that example was about.
Q Okay.
And this order of administration disclosed by the '940 is disclosed in the examples, correct?
A Yes.
Q Okay.
And what order of administration is disclosed in the '940 patent?
A Estrogen before combination phase.
Q And does the -- are there any examples in the '940 patent

of unopposed estrogen before the combination phase or after the placebo phase?

A No.

Q Now, does the '940 patent tell us or tell one of ordinary skill in the art, in 2005, why it should be combination pill followed by unopposed estrogen -- sorry -- excuse me.

THE COURT: Do I have it right, Doctor, that the '940 teaches 24 days of combination, followed by two days of placebo, followed by two days of unopposed estrogen?

THE WITNESS: Yes, it does teach that. That is 24 days.

THE COURT: That's the '940, right?

Now, it is suggested that it would have been obvious to reverse the unopposed estrogen and the placebo stages.

Do you agree with that?

THE WITNESS: No, I do not.

THE COURT: Why?

THE WITNESS: Because none of the prior art suggest doing that.

THE COURT: What physiological difference does it make, or does it make a physiological difference, rather, if one were to administer the unopposed estrogen prior to the placebo?

THE WITNESS: Yes. The physiologic rational is presented in patents and elsewhere in the literature in the

'843 patent, for example, the Pasquale patent, explaining why you're likely to have a better bleeding pattern and better efficacy if you administer the unopposed estrogen right before the combination.

THE COURT: But the '984 does not do that?

THE WITNESS: The '984 reverses the order of administration.

THE COURT: Now, I believe Dr. Barnhart testified that in his view, it didn't make a difference. Do you disagree with him?

THE WITNESS: Yes, I do.

THE COURT: Why?

THE WITNESS: Because of the physiologic rational and demonstrated success that a person of ordinary skill in the art were to see in the Mircette example, for example.

THE COURT: Putting Mircette aside for the moment, we have -- you just talked about the '940 and you talked about the Pasquale, which teach administering the placebo before the unopposed estrogen?

THE WITNESS: That's right.

THE COURT: Your statement is that to reverse it, resulted in a better product?

THE WITNESS: My statement is that a person of ordinary skill in the art would have not been motivated to reverse the order because the prior art, including prior

products, prior patents and research, said that the best place to put it, "it" would be the estrogen, is before the combination.

THE COURT: Having now spoken that there was not a motivation to make the switch, having made the switch in the '984, what, if anything, is obtained?

THE WITNESS: Well, an unexpected efficacy.

THE COURT: How, how so?

THE WITNESS: That with that low a dose of estrogen and with such a weak progestin, one would not have expected efficacy no matter what else you did, extending the dose of the combination or adding that estrogen, but for unexplained reasons, it turned out to be more effective than expected.

THE COURT: Whether it's an unexplained reason or for other reasons, is it physiologically beneficial?

THE WITNESS: I don't know because there are no data to show that it's physiologically beneficial.

THE COURT: Did it result in an efficacious product?

THE WITNESS: It --

THE COURT: Is Lo Lo an efficacious product?

THE WITNESS: Yes, the FDA approved it and that's the evidence from the pivotal trial that it's effective.

THE COURT: Thank you.

Forgive me, but I was getting lost in the weeds, Mr. Pappas. I had to extricate myself, however inartfully I may

have done it.

MR. PAPPAS: Very well, your Honor. I think that can be helpful.

Q Following up on his Honor's questions, is there an explanation in the '940 patent as to why the inventors there tell the skilled artisan to start with the combination phase, then go to the placebo and then go to the unopposed estrogen?

A Yes.

Q Okay.

Let's see what they told the world.

Can we have column six, lines 33 through 39, Mr. Brooks?

This is in JTX. What do the inventors tell the world and skilled artisans in April, 2005, about why the unopposed estrogen should come after the placebo and before the next cycle?

A They say you'll have better cycle control from the first package of pills that are used, you'll get reliable break-through bleeding if you have the intake pause before the estrogen and combination.

It will also help reduce amenorrhea and that line six says point six, I should say point six says that it improves cycle control in the very low incidence of amenorrhea will result in a higher compliance. That is that patients, women will be able to use the pill more successfully, which of

course, is important to avoiding unintended pregnancy, the objectives of taking combined oral contraceptives.

Q Now, let me show you Dr. Barnhart's testimony -- before we do that, you've covered that with the Judge.

I want to ask you about the concept of priming the progestin receptors.

What does that mean?

A That concept results from studies showing that the presence of estrogen induces the receptors for progesterone in various places in the body, including in the uterine lining, the endometrium as well as centrally, hypothalamus.

So if you give the estrogen right before the combination phase, that estrogen will induce more receptors of the progestin and the progesterone and the progestin which binds with the progesterone receptors will have a greater action and result, therefore, in a better bleeding pattern, which is what they're describing here.

Those studies, although they don't cite them, is the basis for this statement and it's the basis for Sam Pasquale's statement in his patent.

Q All right.

A That's the physiologic explanation we were talking about.

Q Is that the physiological explanation that is disclosed by the '940 patent?

A Yes.

Q So they say, after the combination pill, do the placebo and then the unopposed estrogen, which then is immediately followed by combination estrogen again in the next cycle, right?
A Yes. Because you just got the estrogen, you have the maximum concentration of progesterone receptors.
Q And is that what's disclosed by the '940 patent as the physiological reason for doing it in that order?
A Yes.
Q Okay.
Now, was there other prior art, in addition to the '940 patent, that agreed with that proposition?
In other words, that the physiological advantage of priming the progestin receptors took place if you did it combination pill, followed by the placebo, followed by unopposed estrogen and then combination estrogen?
A Yes.
Q And was that the Pasquale patent you referred to, '843?
A Right.
Q And was that physiological rational present in the one product we have in the United States?
A Yes.
Q Mircette?
A That actually resulted in a product, Mircette.
Q All right.

And one moment, your Honor.

(Pause.)

Let me ask you to -- are you familiar with another article by Killick that supports this physiological principle?

A Yes.

Q Can we have --

A Some of the prior art.

Q Mr. Brooks, can we have plaintiff's trial exhibit 50? This is the 1998 article by Killick.

Do you see that, sir?

A Yes.

Q This is prior art.

MR. PAPPAS: I move that into evidence, your Honor, PTX-50.

MR. GREEN: No objection, your Honor.

Q Let me ask you to direct your attention to page S-24 of this article.

Can you read that paragraph and tell us what that would have disclosed to one of skill in the art about the order of administration that the '940 patent and Mircette practiced?

A They're supporting Sam Pasquale, Sam Pasquale's idea. "The results of this study appear to validate the rational for the administration of ten micrograms of ethinyl estradiol during the last five days of the seven day nominally hormone-free interval of the Mircette regimen." That is,

immediately before the combination. "On the basis of the findings here, Mircette regimen maintains more effective suppression of follicular activity while lowering the total estrogen load administered during each treatment cycle."

Q So what is that telling the skilled artisan, as of April, 2005, about why it's better to have combination phase followed by the unopposed estrogen, followed by the placebo and then the combination phase?

A Well, if you want to lower the estrogen dose to 20, with a potent progestin like Desogestrel, you'll get -- you're likely to get better efficacy if you administer the estrogen right before the combination pills. That is, the estrogen plus Desogestrel pills.

Q All right.

So, just to sum up this portion, Dr. Darney, as of April, 2005, you have the '940 patent, the '843 patent, the product Mircette and Killick article telling the skilled artisan, if you're going to do unopposed estrogen and placebo in a pill, go combination phase, placebo, unopposed estrogen and then start over, right?

A That's right.

Q Okay.

Was there any teaching prior to the invention of Lo Loestrin FE to reverse that order?

A None.

Q In your review of the literature, as an editor of the New England Journal of Medicine and editorial board of Contraception, did anybody even every write an article suggesting that you should reverse the order and still get the priming of the progestin receptors affect?
A No.
Q Okay.
A I don't want the record to say that I'm the editor of the New England Journal.
Q I'm sure.
You're a peer reviewer?
A I'm an editorialist.
Q Okay.
Let's stick with the '940 patent.
Is there any disclosure in the '940 patent anywhere that you could adopt the order that Warner Chilcott did in the Lo Loestrin patent?
A No, the opposite is true.
Q So is there anywhere in the '940 patent where, after the inventors there extol the virtues of the order that's given there, they write, well, alternatively, you could reverse the order?
Is that disclosed in the '940 patent?
A No.
Q Do they tell the skilled artisan that he or she might

want to consider reversing the order?
A No.
Q And is it fair to say, Dr. Darney, that the '984 invention is about lowering estrogen while unexpectedly getting good results with one milligram of norethindrone acetate and that's all part of the regimen that also include the order of administration?
A Yes.
Q And would it be fair to say, Dr. Darney, based on your earlier testimony, that if you're going to change the order of administration or even contemplate it, that's one of the six factors, you then have to consider the progestin dose, the estrogen dose, what type of progestin, what type of estrogen, correct?
A Correct, they all interact with one another.
Q So you can't just change one part of the regimen without understanding what you have in the rest of the regimen. Is that correct?
A That's right.
Q Now, I want to -- have you been shown or are you aware of any patent in the United States, other than Lo Loestrin, the '984 patent, that teaches an order of administration, combination oral contraceptive followed by unopposed estrogen, followed by placebo as done in the '984?
A No.

Q Now, I want to go to slide Barnhart slide 19. Can I put that up, Mr. Brooks?

Have you seen this before, sir?

A Yes, I have.

Q Okay.

And you're aware, from your review of the testimony, this was put up by doctor or created or used by Dr. Barnhart, correct?

A Yes.

Q Can you tell from this what, if anything, one is trying to convey with slide 19 -- strike that.

Do you understand that Dr. Barnhart used this slide in his testimony to support his opinion that the '984 invention was obvious?

A Yes, I do.

Q Okay.

Now, I want to start by looking at the slide.

Is there information that would need to be on this slide for it to have any utility whatsoever to a scientist or contraceptive designer?

A No, the slide is not -- doesn't show parameters of anything, nor is it based on studies which would support it.

Q So my question may have been unclear.

Are you saying that you would need real data to make any sense out of this chart?

A Yes.

I'm also adding that there are no data.

Q All right.

What is it missing, sir? Does is disclose the estrogen type in that drawing?

A No, it doesn't disclose any of the factors that are important in designing oral contraceptives.

Q Does it disclose the estrogen dose?

A No.

Q Does it disclose the progestin used?

A No.

Q Does it disclose the progestin dose?

A No.

Q Does it disclose the actual FSH amounts, which is follicular stimulating hormone?

A No.

Q Does it disclose the follicle size?

A No.

Q By the way, can you even tell from this drawing what is supposed to be the follicles?

A Well, the follicles are the little circles at the top.

Q Is there any data to support the size of those follicles?

A No.

Q Would the size of the follicles depend on the amount of progestin and estrogen used?

A Absolutely.
Q Is there any legend on that chart that tells you the size of those little gray circles or I guess they become ovals at some point?
A No.
Q For one of skill in the art to draw any conclusions, sir, from just looking at slide 19, would you need to know that information, estrogen type dose, progestin type dose, actual amounts of FSH and the follicular size?
A Yes.
Q Why?
A Because all of those factors would determine any conclusion about the validity of these representations.
Q Now, something else I'd like to cover with you.
You see the bottom artistic drawing called two-day PFI. Do you see that?
A I do.
Q Do you see it appears to have 24 blue dots, two pinkish dots and two white dots?
Do you see that?
A Yes.
Q I think it indicates, purports to indicate that the pink would come before the white, which is PFI, for pill-free interval, right?
A Yes.

Q Okay.

Now, to the extent the blue dots, if we assume it's combined oral contraceptive and the pink is unopposed estrogen, that's the order of the '984 patent, isn't it?

A Yes, it is.

Q Okay.

And this drawing says it's adapted from DTX, I can't read from there.

DTX-824, right, the defendants' exhibit?

A Yes.

Q And was that a Warner Chilcott marketing document in 2010?

A Yes, it was.

Q Well, 2010 is after the critical date, right?

A Right, the critical date is 2005.

Q And 2010 was after Warner Chilcott had the data and knew that Lo Loestrin worked, right?

A That's right.

Q Okay.

So, so we're clear, this chart, such as it is, Barnhart-19, does not reflect prior art certainly as to the bottom drawing, does it?

A No.

Q Something else that intrigued me. It says, supported by JTX-16.

Do you see that?
A Yes, I do.
Q Well, JTX-16 is the '940 patent, correct?
A That's right.
Q Does the '940 patent anywhere disclose what's drawn on that drawing on the lower phase?
A No. We just discussed how it discloses the opposite position --
Q So --
A -- of the pill-free interval and the unopposed estrogen.
Q In your capacity as a physician, as a scientist, would it be fair to say that that lower drawing is not supported by the '940 patent, correct?
A That's right, it's not.
Q Let's take a look at Barnhart slide 20.
Now, Doctor, does this suffer from the same deficiencies of the Barnhart slide 19?
A Yes, it's precisely the same representation and lacks validity for the same reasons.
Q Does it disclose the estrogen dosages or the estrogen types on the drawing itself?
A No.
Q Does it disclose the progestin dosages and progestin types?
A No.

Q Does it disclose the amounts of follicular stimulating hormone on a daily basis?
A No.
Q Doesn't that affect what the size of the follicle will be, sir?
A Absolutely.
Q And is the size of any of those follicles shown?
A No.
Q Is there any data that shows the size of the follicles on that drawing?
A No.
Q Now, I think I asked you a question earlier and I said we might come back to it.

One of the prior art references says you can do tests to measure the size of the follicles in a woman, can't you?
A Yes, it's --
Q So --
A -- common practice in any contraceptive trial now.
Q So if Lupin intended to bring a chart to the courtroom for the aid of his Honor that actually told you something about the follicular size, which depends on the amount of estrogen, which depends upon the amount of progestin, it could have been tested, there's data for that, right?
A Yes.
Q Okay.

Now, I want to direct your attention, Dr. Barnhart, to a passage of doctor -- Dr. Darney, to a passage of testimony by Dr. Barnhart.

Mr. Brooks, can we have trial day number one, lines -- page 99, lines ten through 21?

There Dr. Barnhart was asked the following question: "In April, 2005, was amenorrhea considered to be a good or bad side effect?

"ANSWER: Well, you're going to hear a lot about bleeding with the pill. One is the scheduled bleeding and the other is one when you don't want something called unscheduled break-through bleeding. Admittedly that's a problem. By the time you want your period, if you get a light period or no period, that's really not considered a problem. Many women would prefer that. Many pills are designed to do that, so amenorrhea, while it is a very fancy name, is not necessarily an undesirable side effect."

Do you see that, sir?

A I do.

Q Do you agree with that?

A No.

Q As of 2005, was amenorrhea considered an unwanted side effect by women in general?

A Yes.

Q And why is that, sir, and why was that true in April,

2005?
A Because amenorrhea is considered a sign of being pregnant. The reason you take a contraceptive is not to be pregnant. So if you don't have a period, you're concerned that I might be pregnant, my contraceptive isn't working.
Another factor is that having regular menstrual periods is a sign of normal health, normal physiologic function, and women expect that. Birth control pills are actually designed and one of their big advantages, as opposed to some other methods of contraception, is that they do actually provide regular withdrawal bleeding rather than amenorrhea.
Q And, indeed, if we can go back to the '940 patent for a moment, Mr. Brooks, column six, lines 33, 39.6.
What do inventors of the '940 patent say about amenorrhea, Dr. Darney?
A They say that their aspiration with this patent is to reduce the rate of amenorrhea and that --
Q Why?
A The low incidence of amenorrhea results in higher compliance.
Q Well, don't we want higher compliance when women take pills for contraception?
A Yes.
Q So are they indicated that if you have low incidence of amenorrhea, you're going to get higher compliance, the women

are going to stay on the pill, right?
A Right. What happens with methods of contraception, for example, if you have an oral contraceptive with -- that caused amenorrhea, women would think I'm pregnant, I'd better stop the pill because maybe these pills would affect the pregnancy I have. They stop the pill and then they actually do become pregnant.

So that's how amenorrhea has an important affect on the very objective of using, designing and using oral contraceptive pills, preventing unintended pregnancy.

Q Now, would it be fair to say that some women don't mind amenorrhea, some?
A Oh, I have, in counseling women to use various methods of contraception, if a method will cause amenorrhea, for example, injectable contraceptive Depo-Provera, I tell them that and some women do say well, I wouldn't mind that.
Q All right.

But aside from those women, my question to you now is, in 2005, would a skilled artisan consider it a design goal to arrive at a regimen that was not expected to cause amenorrhea if they're trying to design a pill for general applicability throughout the United States, to all of the women who desire contraception?
A No, you certainly wouldn't want to build amenorrhea into a pill.

Q You would not want to?
A You would not want to.
Q Okay.
Now, we've covered, in following up some of the questions from his Honor, the affect that the '940 order has on the prime progestin receptors in advance of the next combination cycle, correct?
A Yes.
Q And that's the physiological explanation for the '940 order of administration, following the combination pills with the placebo and the unopposed estrogen, right?
A Yes.
Q Okay.
Now, do you have an opinion as to whether or not a skilled artisan, in 2005, would have thought that if you reversed the order and give the unopposed estrogen before the placebo, which is then followed by the combined phase, would you have gotten that same effect on the priming of the progestin receptors?
A A person of ordinary skill in the art would have thought, no, you wouldn't have the same effect.
Q Okay.
Now, let's turn to the '251 patent, Dr. Darney.
Can we have, Mr. Brooks, joint trial exhibit 13 on the screen, please?

Now, do you recall Dr. Barnhart's testimony that this patent, the '251 patent, supports the notion that a skilled artisan would have been motivated to use the '984 order of administration which is combined pill, unopposed estrogen and placebo?

Are you aware that's his testimony?

A Yes, I am.

Q Do you agree with that?

A No, I don't.

Q Have you prepared a slide that summarizes the reasons in support of your opinion that the '251 would not teach one to reverse the order?

A Yes.

Q Mr. Brooks, can we have Darney slide 35, please?

A First, the title of this patent is natural estrogen. It's not concerned with synthetic estrogen. That's important because you can use much higher doses of natural estrogen without causing serious side effects, DVT, than of synthetic estrogens, but even if the patent did concern itself with ethinyl estradiol, it's not relevant to the '984 patent's administration scheme because it presents a very complicated administration scheme with two separate unopposed estrogen phases. That is, both before and after.

And then the '251 patent prefers progestins other than norethindrone acetate. I should add that this -- we know what

this patent was aiming at because there's actually a product marketed not too long ago in the United States from which -- used this patent.

Q What product was that?

A Natazia.

Q All right.

Now, did you read this patent as a whole, as you're supposed to do?

A Yes.

Q What struck you about what this patent is basically all about when you read it, and I'm referring now to the '251 patent, joint trial exhibit 13?

A Well, from the title on, it's all about using more estrogen and natural estrogen.

Q Okay.

Let's turn to columns one, the '251, line six through seven.

What do they say in the first sentence about the '251 patent?

A Right there there's the title, Based on Natural Estrogen. "Present invention relates to a multistage contraceptive preparation based on natural estrogens."

Q Okay.

Have any of the patents we've looked at any time during the case concerned natural estrogen?

A The '490 and '940 mention natural estrogen as a possibility, but they aren't specifically focused on it like this patent is.

Q So this is the first patent and the only patent in this case that anybody's raised the focus on natural estrogen. Is that right?

A That's right.

Q Is that a fundamentally different project using natural hormones with high doses than synthetic estrogens with low doses?

A Yes.

Q And how so, sir?

A Well, the natural estrogens, because of their very different effects in the liver, we talked about estrogen receptors throughout the body, the liver being particularly important, natural estrogens don't have the adverse effects in terms of plotting parameters that synthetic estrogens do. They don't affect the liver.

So you're not concerned about the risk of increasing the risk of deep vein thrombosis and, therefore, you can give more estrogen, which as we've discussed many times over the past two days, more estrogen means a better bleeding pattern and greater efficacy.

Q Now, does the '251 patent contain any example regimens?

A Yes.

Q Okay.

Mr. Brooks, can we highlight column four, line 32 through six, column nine?

A Example 1.

Q And what estrogen is used there?

A Estradiol valerate, estradiol is 17 beta estradiol. That's the estrogen that the ovary makes itself from the follicle mostly and they simply add a valerate to it to make it active orally.

Q Is that a natural estrogen?

A Yes, natural estrogen.

Q Let's look at Example 2.

Does that use a natural --

A Yes.

Q -- estrogen?

A This is a different approach to using the estrogen that everybody's ovaries makes, keeping it orally active by micronizing the estrogen particles. It, too, uses estradiol 17 beta estradiol of the same thing.

Q Let's look at Example 3, does that use a natural estrogen as well?

A Yes. Conjugated equine estrogen is the natural estrogen that has been used traditionally for hormone replacement therapy in menopausal women.

Q Let's look at Example 4.

Does that teach using a natural estrogen?
A Yes, Example 4 is the same conjugated equine estrogen, a natural estrogen product.
Q And does it, Example 5, the last example, also disclose or suggest a natural estrogen?
A Yes. In fact, as in the first example, estradiol valerate is used.
Q Now, is there a teaching in the '251 patent about being able to lower the dose of a synthetic estrogen while using norethindrone acetate?
A No, that's not what the patent is concerned with.
Q All right.
Now, would it even be safe to take the numbers of dosages of natural estrogen and simply plug in ethinyl estradiol, a synthetic estrogen?
A No, because of the vastly different affects on the liver.
Q What do you mean by that?
A I mentioned that synthetic estrogens, ethinyl estradiol, have very different affects when they're metabolized in the liver and affect clotting parameters adversely. Natural estrogens don't do that.
So if you gave enough ethinyl estradiol to have an equal dose to these natural estrogens, you might cause serious problems.
Q All right.

Now, what is the -- let's turn to the second bullet point on slide -- can we have Darney-35 up again, please?

Where you said even if the patent were relevant, it does not teach '984 patent's administration scheme, but teaches two separate unopposed ethinyl estradiol phases?

A Yes.

Q Can you describe what administration scheme is disclosed in the '251 patent?

A Didn't I prepare -- this is the most complicated administration scheme of any birth combined oral contraceptive, so it probably would be worth looking at a figure.

Q Did you help us a prepare a figure that would help you explain this?

A Yes.

Q Okay.

And can we have Darney-36 up, please?

Now, before we even get started, is the -- I want to start with what we might call first principles in life.

Is the '251 order of administration the same as the patented '984 order of administration?

A No.

Q Is it just minor differences or is it fundamentally different in what they're accomplishing in the '251?

A It's profoundly different.

Q Profoundly, okay.

Now, with that, can you explain to us in Darney-36, what the order of administration is claimed there and in so doing, you can tell us how it's different than the '984?

A Here I'll use my welcome capacity to draw.

Q Okay.

A So it starts with natural estrogen unopposed.

Q That's the purple pill we'll call it?

A Prior to the first combination pills, which are in a different dose, represented by dose two of the natural estrogen and progestin.

That's followed for the next two weeks by a different dose, dose three, of natural estrogen and progestin. That continues for three days of the last week of administration.

Then comes the two pills containing still a different dose of the natural estrogen and then comes the two represented here in green, placebo pills and then you start the next package of Natazia, and you get the natural estrogen again prior to the first combination pill, and so on and so forth for subsequent cycles.

In this preparation, the natural estrogen in the preceding combination is in a different dose than the natural estrogen preceding the next combination pills here.

Q So does the '251 actually provide an additional stage of hormone administration as compared to the '984?

A Well, it provides two, at least two additional stages, because the combination is dosed differently as well as the unopposed estrogen, which is in two doses in two stages.

Q Now, Dr. Barnhart has opined in his direct testimony that a skilled artisan in 2005, would have been motivated to apply the teaching of the '251 patent concerning the placement of unopposed estrogen.

Do you agree with that?

A No.

Q Why not?

A There is no way a person of ordinary skill in the art would pluck out of this natural estrogen-based patent, with five different phases, just that portion that happens to put the natural estrogen before the placebo, followed then by more natural estrogen in a different dose before the combination. Just wouldn't, just wouldn't happen. There would be no motivation to do that.

Q So are we clear that in the '251 patent four-stage scheme, they provide unopposed estrogen both before and after the combination phase, correct?

A Yes.

Q And in the '984, the unopposed estrogen is just provided before the placebo and then you go right to the combined pill, not to unopposed estrogen, right?

A Correct.

Q Now, does the -- let's go to your third point.

Even assuming the skilled artisan was looking at '251 in that room all by himself or herself with all the prior art, what does '251 say about the preferred progestins?

If we can, let's have column three, lines 49 through 53.

Does this '251 patent disclose the preferred or advantageous progestins?

A No, it doesn't mention norethindrone or norethindrone acetate, and it prefers advantageously, as it says, the progestins from the 19-Nortestosterone gonane family, Desogestrel, dienogest, Gestodene and Levonorgestrel and then it mentions some progesterone itself derivatives. It actually used in its marketed product dienogest.

Q Dr. Darney, let me ask you this question: Do you have an opinion as to whether or not a person of ordinary skill in the art, after reading the '251 patent that disclosed four phases of steroid administration instead of three, that it proposes or teaches unopposed estrogen both before and after the placebo phase, which discloses combination pills in two different doses at two different times and natural estrogen doses of two different doses at two different times, and prefers progestin, the progestins Gestodene and Levonorgestrel, in all of that teaching, do you have an opinion whether or not '251 would have taught the skilled

artisan in 2005, anything about making a ten or 15 microgram synthetic estrogen pill ethinyl estradiol, not natural, with one milligram of norethindrone acetate in a three-phase administration?

A There is no way that would have been taught from this '251 patent.

THE COURT: Mr. Pappas, I need to go and take a call that I made reference to.

How much longer do you think you'll be with the witness?

MR. PAPPAS: Thirty to 40 minutes.

THE COURT: Do you want to do it before we break for lunch or take lunch now?

MR. PAPPAS: I think since we have been going this morning, it might be beneficial to take lunch now, if that's okay with your Honor.

THE COURT: Does anybody mind?

MR. PAPPAS: And to the court reporter?

MR. GREEN: That's fine with us.

THE COURT: We'll see you back here at 12:45.

THE CLERK: All rise.

(Recess.)

THE CLERK: All rise.

P H I L I P D A R N E Y, previously sworn, resumes the stand.

THE COURT: Have a seat.

Mr. Pappas, go ahead.

MR. PAPPAS: Thank you, your Honor.

DIRECT EXAMINATION CONTINUES BY MR. PAPPAS:

Q Good afternoon, Dr. Darney.

A Good afternoon.

Q I want to cover a couple of points that I missed asking about on the priming progestin receptors.

Can I have the '940 patent, Mr. Brooks, column three, line 17 through 24?

Do you see the reference to Pasquale U.S. patent 4921843?

A Yes.

Q Is that the Pasquale patent that you referenced in partial answer to some of the Judge's questions about supplying a physiological rational for putting unopposed estrogen before the combination phase?

A Yes.

Q Let's turn to the Pasquale patent, JTX-15, column three, line 65 continuing onto column four.

Can you just read that passage and explain to us and to his Honor if this is part of the Pasquale patent that explains the priming of the progesterone receptors?

A "Estrogen administration at this early stage of the menstrual cycle also prevents recruitments of the dominant

follicle, thus allows a reduction in the dose of the estrogen and progestin in the combination oral contraceptive needed between days seven and 28 of the menstrual cycle to prevent conception. Additionally, estrogen stimulate progesterone receptor sites. Stimulation of progestin receptors early in the menstrual cycle, estrogen administration allows a reduction in the incidence of intermenstrual bleeding. That is break-through bleeding and spotting or minimized with the low dose oral contraceptives of the present invention."

Q All right.

From this passage, from the Pasquale patent that is specifically referred in the '940 patent, if a skilled artisan, in April of 2005, was trying to decide where to place the unopposed estrogen, either before the placebos or after, what would he have concluded was the best way to proceed from what Pasquale says?

A That it's important to give the estrogen to induce the progesterone receptors immediately before you give the progestin that's going to bind those receptors.

Q All right.

Is there anything in JTX-15, that Pasquale patent, that says that one could achieve the same effect on progestin receptors by giving the placebos after the unopposed estrogen and before the combination tablets?

A No.

MR. PAPPAS: Your Honor, I don't know if I did, but just out of my abundance of caution, we offer JTX-15 into evidence.

MR. GREEN: No objection.

Q Now, Dr. Darney, before we cover our last patent, I want to -- are you familiar with the testimony from Dr. Barnhart about this order of the placebos and the unopposed estrogen?

A Yes.

Q Mr. Brooks, can I have day one of the transcript, page 105, line 21 through 106, line five? This is part of Dr. Barnhart's answer to what his opinion was.

See where it he testified, "We also know you can use it in combination. You can take both of these amendments 24 days and put estrogen in the pill-free interval. You're really left with not that many options left. It's been disclosed you can go to 24 days for four days of placebo. It's been disclosed you can go to 24 days with four days of estrogen. It's been disclosed you can go to 24 days with two days of estrogen and two days of placebo. The only thing that's not disclosed is where you do put the estrogen in relation to the placebo."

Do you agree with that statement?

A No.

Q If Dr. Barnhart were right, would contraceptive development have ceased in April, 2005?

A Yes.
Q Has that happened or has contraceptive development continued?
A It has continued.
Q Now, even if you assume 28-day regimen, Dr. Barnhart, with 24 days of combined administration and you have to decide what to do with the last four days, do you agree with Dr. Barnhart that the '490 and '940 patents cover all but one of the possible combinations of those four days?
A No.
Q Well, for example, could you have made a regimen back then that was 26 days of combination followed by two days of natural estrogen?
A Yes, you could have.
Q Could you have made a 26-pill combination followed by two days of placebos?
A Yes.
Q And that wasn't invented, was it?
A No.
Q Could you have made 24 days of combination estrogen with four days of unopposed estrogen?
A Yes, you could have.
Q Now, how about if you decided to go outside the 28-day cycle, like Watson did, with 56 days, would there be additional regimens that you could come up with not described

in the art?
A Absolutely.
Q In fact, a 56 day regimen was one of the five tries Watson made when it was trying to discover Warner Chilcott's invention but failed, right?
A That's right.
Q So I could go on with many, many more examples but I think these establish the point.
The fact is, is it not, Dr. Darney, that the way Warner Chilcott did it, was not the only way it could be done in 2005, right?
A Yes, that's right.
Q Okay.
Now, let's turn to the '394 patent.
MR. PAPPAS: Your Honor, I think that's the last patent that was the subject in this case.
Q Can you bring up JTX-10, please, Mr. Brooks?
You're aware, Dr. Darney, that Dr. Barnhart has opined that the claims in the '984 patent would have been obvious over the '394 patent?
Do you agree with that opinion?
A No, I do not.
Q Let me have -- did you prepare a chart that would illustrate your opinions as to why the '984 patent in this case is not obvious in light of the '394 patent?

A I have.
Q Okay.
Can we have Darney chart 38, please?
Will you go through the reasons for the Court as to why the '394 patent would not have motivated anyone to make the '984 invention?
A Well, Gary Hodgen, the writer of this patent, whom I knew, based the patent on his experiments in ten cynomolgus monkeys.
Q In any event, for short, monkey study?
A Yes.
Q Okay.
Continue, Dr. Darney.
A So there is no data about the performance of the claimed regimens in women. There is no evidence that it's appropriate to do what Gary Hodgen did, that is to convert the doses he used in the monkeys to humans.
In many places in the prior art it says that monkeys metabolize the steroids differently.
The conversion factors that he used to determine the dose in women were clearly wrong. He used an average woman weighing ten times more than the monkey, when actually the weight of women in 2005 was considerably more than 110 pounds and the multiplier should have been adjusted accordingly.
He didn't present any evidence that the doses were

tolerated by the monkeys. Obviously, you can't collect such data from monkeys.

Actually when a product was developed, as it was from this patent, it selected a dose higher than the monkey data suggested and that is one milligram norethindrone acetate and 20 micrograms of ethinyl estradiol doses that we've justified before.

Q Now, do you have an opinion then as to whether or not a skilled artisan reading the '394 patent would have been motivated in 2005 to make the Lo Loestrin invention?

A Yes.

Q And what is that opinion?

A Would not have been so motivated.

Q Now, in the Lo Lo -- in the '394 patent, am I correct that norethindrone acetate is disclosed as one of the preferred progestins?

A Yes, it is.

Q All right.

And how, if at all, does that stated preference affect your opinion that a skilled artisan would not have seen a reason to select norethindrone acetate along with an EE dose of 15 micrograms or less in 2005?

A A person of skill in the art would have been aware of the extensive experience with Loestrin and that the dose of estrogen below 20 micrograms, combined with a milligram of

norethindrone acetate would be unlikely to be effective and would not have satisfactory bleeding pattern.

Q All right.

Between 1994 and 2005, was there a trend away from norethindrone acetate to more potent progestins?

A Yes. We looked at that trend yesterday.

Q That's a trend of a POSA, person of order skill in the art would have been aware of in 2005, right?

A Yes.

Q Let's turn to the monkey example, the monkey data.

Have you prepared a slide summarizing the basis for your opinions that the monkey data and the conversion factors would not shed any light on the claimed invention in the '984 patent?

A I have.

Q Can we have Darney slide 38, please, Mr. Brooks?

THE COURT: I thought we went through this already, didn't we?

MR. PAPPAS: I'm sorry, I don't mean 38, your Honor. I misspoke, your Honor. It's Darney slide 39.

Q Now, let's take these one point -- one of these points at a time.

Does monkey data tell a skilled artisan how a regimen will perform in the female body?

A No.

Q Are monkeys considered a standard reliable way to measure efficacy for cycle control in women?

A No.

Q And are you aware of any evidence that a dose for human women can be determined merely based on multiplying the dose given to monkeys?

A No, I'm not.

Q Now, the next thing you had said on your slide was the conversion factors used to determine dosage in women were plainly wrong.

What does that mean, sir?

A Yes. Even if there were a simple conversion factor and we knew what it was, the conversion factor that Gary Hodgen used was clearly wrong. As you see in the lines, first line for example of this table, he gave 1.2 micrograms of ethinyl estradiol to the ten monkeys.

The monkeys weighed, on average, 11 pounds and then he assumed that women weighed 110 pounds, multiplied the dose by ten and came up with about 12 micrograms of ethinyl estradiol.

If you use data from 2005 about what women's fertile age range actually weighed, you'd get 18 micrograms, that is approximately 20. Same with the dose of norethindrone acetate. If you multiply .06 by the appropriate weight of women, you come up with approximately one milligram of norethindrone acetate.

And as we've observed, those doses are what the actual marketed product used.

Q When you reference to the document, was that a document shown to Dr. Barnhart in his deposition in this case where he acknowledged that 163 pounds was the average women weight in America?

A Yes.

Q Okay.

And that came from the CDC?

A Yes, it's one of their annual publications tracking the obesity epidemic for the weight of Americans.

Q Okay.

Now, let's go back to the fourth bullet point on your slide where you stated there was no evidence that pills were well tolerated by monkeys.

What's your basis for this?

A There are additional factors concerning the administration of contraceptive steroids that indicate side effects that might make them difficult to use and there were no data presented in the patent about how monkeys, to say nothing of women, tolerated this particular preparation.

Q Why is that? Why is there no evidence about break-through bleeding or breast tenderness or nausea or any of the other side effects that can affect compliance with monkeys?

A These are, obviously, difficult to quantitate in monkeys.
Q Does it matter that there was no evidence about -- from the monkeys about whether or not the regimen they were given was well tolerated if you're trying to figure out a pill and design one for a woman?
A Yes, a person of ordinary skill in the art would understand that monkeys aren't a good measure of what's likely to happen if you try the product in women.
Q Now, your last point was in the real world, the product that was ultimately developed based on the '394 patent was Loestrin 24, correct?
A Yes.
Q So -- by the way, the '394 patent is the one that discloses a range of estrogen anywhere between one microgram and 35 micrograms, right?
A Right. One to 35.
Q So when it came time for someone to actually make the product, from a patent that disclosed a regimen from one to 35, what dosage of estrogen was chosen?
A Twenty.
Q And I think, by the way, I think as I get close to the end of the examination, is there one area where I think you and Dr. Barnhart do agree on these dosage patents that notwithstanding at times very wide dosages, that everybody of skill in the art knows that there are amounts within those

dosages that wouldn't work, even if they're disclosed?
A Yes. Most of the patents we've reviewed, all include ranges that would clearly not provide contraception.
Q Okay.
One final point on the monkeys.
Is the bleeding data that was collected from monkeys sufficient to determine the cycle control of a regimen in women?
A No. What was used were vaginal swabs, no quantitation of duration of bleeding or quantity of bleeding, break-through bleeding, spotting or break-through bleeding, so on.
Q Very well.
Let's turn now to my penultimate topic, progestin-only pills.
Are you aware, from your review of the transcript, that Dr. Barnhart testified that the existence of a progestin-only pill contraceptive would provide a reasonable expectation of success in using low doses of ethinyl estradiol with norethindrone acetate, as was done in the '984 patent?
Are you familiar with that?
A Yes.
Q Do you agree with that opinion?
A No.
Q Okay.
Let's start out, first, by describing what is a

progestin-only pill?
A Well, one such pill is marketed in the United States, which uses norethindrone in a dose of 35 micrograms of estrogen, with a progestin without any estrogen and those pills are always given continuously.
Q Okay.
Can you explain how progestin-only pills work in comparison to what we have been hearing about the entire trial, which is combination oral contraceptive that has progestin and estrogen?
A Yes. They have a very different mechanism of action. With no estrogen and that low dose of progestin, ovulation is unreliably suppressed.
So the mechanism of action of a progestin-only pill, which most pills are not widely used in the United States, is to depend on the constant presence of a low concentration of the progestin in the serum and the effect on cervical mucous that we previously discussed. That is that it makes the cervical mucous thick and viscous and sperm can't penetrate.
We also discussed the exquisite sensitivity of cervical mucous glands to flucuations in progestin level. That means that if you don't take a progestin-only pill exactly on time, progestin level begins to fall, cervical mucous quickly returns to its normal state, that is able to conduct the sperm up to the egg. Since the ovulation is not suppressed, the egg

may be there waiting and pregnancy results.

Consequently, progestin-only pills are less effective than combined oral contraceptive pills.

The other issue is that with all progestin-only methods, including progestin-only pills, irregular bleeding is a constant problem and that mitigates against their wide use. The bleeding is, for most women, simply intolerable.

Q Who is the typical audience for progestin-only pills, 20 to 30 something?

A No, progestin-only pills are used in women who are breast feeding, because estrogen suppresses lactation. If you're lactating, you really don't need a very good contraceptive, you just want to be sure that just in case you ovulate, you'll have some protection. So progestin-only pills are good in that situation. That's the most common example for their use.

Q Now, Micronor is a progestin-only pill approved in the United States, corect?

A Yes. That's the one that's approved in the United States.

Q It has no estrogen, correct?

A Right.

Q How much progestin does it have?

A .35 milligrams.

Q So that would be 350 micrograms of progestin?

A Yes.

Q Now, do you believe the existence of progestin-only pills provides or would have provided a skilled artisan, in April, 2005, with a reasonable expectation of success in creating a combination oral contraceptive with five to 15 micrograms of EE and one milligram of NA, which was the invention of Lo Loestrin?

A No.

Q Did you prepare a short slide to summarize your reasons why the progestin-only pill would not create any expectation of success?

A Yes.

Q Let me have Darney slide 40, please.

Can you please explain your reasons why you disagree with Dr. Barnhart and believe that progestin-only pills provide no reasonable expectation of success for a combination oral contraceptive with five to 15 micrograms of estrogen, one milligram of norethindrone acetate?

A This slide summarizes what I just said, and that that is the progestin-only pills are less effective than combined oral contraceptives. The FDA would have different standards for judging their efficacy.

I mentioned that they -- that's true because they operate through different mechanisms of action. We count on the combined oral contraceptive pills, as we discussed extensively, to suppress ovulation. Progestin-only pills use

cervical mucous effects for the most part to account for their efficacy.

And, finally, they have poor cycle control as do all continuously-administered low progestin dose contraceptives. Some of those, like contraceptive implants and Levonorgestrel, IUD are, however, very effective while the -- because they're sustained release systems, while the progestin-only pill counts on a daily oral dose. So it's much, much less effective than its progestin-only counterparts.

Q All right.

Let me ask you to direct your attention to plaintiff's trial exhibit 92, which is a chapter on progestin-only pills from a book by Swareski and Guillebaud.

Do you have that sir?

A Yes.

Q Have you reviewed that?

A Yes.

Q When was it published?

A As I recall, 2002.

Q Bring that up, Mr. Brooks.

MR. PAPPAS: Just a moment, your Honor.

Q In any event, it was prior art, sir?

A Yes.

Q Okay.

What's the general topic of this reference?

A Well, this is -- the general topic is a guide to using contraception and this is chapter six about the progestin-only pill.

Q Let me direct your attention to page 85 and read that brief sentence that tells us about the efficacy of progestin-only pill?

A "Progestin-only pill does not have such a high success rate as the combined pills since it does not always stop ovulation, but it is not compared badly failure rate" and so on.

Q What's the last paragraph say with the graph?

A "It is clear that the failure rate above the age of 30 is acceptable, quite acceptable and under two per 100 women use. However, as regards younger women under the age of 25, the failure rate is around four and the graph rises rapidly. The failure rate in teenagers may perhaps be too high for it to be a good choice."

Q So what would this graph have told one of ordinary skill in the art who was trying, in 2005, to make a pill such as Lo Loestrin FE?

A That a dose of progestin, norethindrone, norethindrone the pill they're talking about here, is unlikely to be generally useful.

Q Okay.

Now, let's turn to the last opinion that you had as to

why the patent was not obvious.

Can we have slide 11?

This is the one, Dr. Darney where you said "objective indicia, unexpected results and skepticism further demonstrate non-obviousness."

I just want to cover with you the unexpected results and your opinions on that and skepticism.

Have you formed any opinions regarding the unexpected results from the claimed invention?

A Yes, I have.

Q What is that opinion?

A My opinion is that the resulting product, Lo Loestrin, was unexpectedly effective. That is, one would not have expected it to be successful.

Q All right.

Let's talk about the Pearl Index of the regimen.

I don't know if I asked you this question. If I have, I apologize.

What is the Pearl Index?

A It's the conventional measure of contraceptive efficacy based on the number of women per 100 woman years of use who become pregnant using a particular contraceptive.

Q Let me ask that we turn our attention to plaintiff's trial exhibit 233, which is already in evidence. This is the FDA statistical review of Lo Loestrin.

Do you see that, sir?
A Yes.
Q Okay.
Now, directing your attention to page or table three, I think would be the easiest way to find it, Mr. Brooks, what did the FDA reviewers conclude the Pearl Index was for Lo Loestrin?
A The FDA reviewers concluded that the Pearl Index was 2.9.
Q Now, did the FDA conclude that Lo Loestrin was safe and effective?
A Yes.
Q And were they aware of the Pearl Index as stated in the document?
A Yes.
Q Now, as of April, 2005, before the invention of Lo Loestrin FE and before any data was generated, would a skilled artisan have expected Lo Loestrin would be sufficiently contraceptively effective to obtain FDA approval?
A Ask the question again. Do you mean prior to this determination?
Q Yes, prior to the determination?
A No.
Q In April, 2005?
A No.
Q Would a skilled artisan have expected that Lo Loestrin,

with 15 micrograms of ethinyl estradiol and one milligram of norethindrone acetate would have been sufficiently contraceptive to obtain FDA approval?

A No.

Q What is your opinion?

A I would not have expected it to be contraceptively --

Q And why is that?

A Because it's too little estrogen and a weak progestin.

Q Why would the skilled artisan then have been surprised by Lo Loestrin's contraceptive efficacy?

A For those reasons, wouldn't expect a pill with that little estrogen, using such a weak progestin, to be effective, especially in light of what we already knew about the marginal efficacy of Lo Loestrin 1/20.

Q I may have misspoken earlier.

When I said Lo Loestrin had 15 micrograms, it has ten micrograms, correct, of ethinyl estradiol?

A Yes, it has ten.

Q Now, Lo Loestrin was compared to Loestrin 24 by the FDA, correct?

A Yes.

Q And have you examined the similarities in the two studies?

A I have.

Q Can we have Darney slide 41?

Will you please explain what you have captured there in terms of comparing the studies of Lo Loestrin and Loestrin 24?

A Two studies were basically the same. The inclusion, exclusion criteria were the same. The efficacy assessment, Pearl Index was the same. The standard for removing subjects from a study, that is using some of their contraceptives while they're participating was the same. Subject populations demographically, ethnically were the same. They were sponsored by the same company so it was the same kinds of forms, format for the reporting forms was the same. And they were reasonably close in time, that is 2004 versus 2008.

Q And, Dr. Darney, this was a comparison of Lo Loestrin and Loestrin 24 that you did, not the FDA, correct?

A Yes.

Q All right.

Now, I want to turn to skepticism. You already testified as to your skepticism.

I want to ask you a series of questions. Did you review the Patel testimony, the corporate representative from Watson?

A Yes, I did.

Q Okay.

Now, have you prepared a chart to briefly explain why you believe Watson was also skeptical of the Lo Loestrin

invention?
A Yes, I have.
Q Can we have Darney slide 33?
Can you briefly explain what is demonstrated on Darney slide 33?
A Well, Watson knew from a statement from Warner Chilcott that they planned to introduce a low dose pill. So Watson, as Patel explained, wanted to get a jump on this and went through various iterations of the low dose pill that Watson thought Warner Chilcott was likely to produce.
This is simply a listing of those iterations.
Q Okay.
I think we can move through this very quickly.
How many options did Watson try?
A Five in all.
Q And did they vary at one point or another the amount of progestin used?
A Yes. You can see they varied it from .5 up to one milligram of norethindrone acetate.
Q Did they vary the number of combination pills?
A Yes. They used the usual 21, 21 and then 24, 24 and finally 52 days. That is a cycle twice as long as normal.
Q Did they make different assumptions about whether or not to use unopposed estrogen in the regimen?
A Yes, they did. In the first three iterations, they

didn't use unopposed estrogen, but in the subsequent iteration, two iterations they did.

Q Did they use different assumptions about the length of the hormone-free interval or whether even to have one?

A Yes. First two examples, they were typical hormone-free interval and then they reduced it to four days and then they eliminated the hormone-free interval all together with the addition of the four days of ten micrograms of ethinyl estradiol.

Q Did they make -- did they experiment with any estrogen dosage other than 20 micrograms?

A No, they left the estrogen dose constant throughout all five experiments, 20 micrograms.

Q And of the five possibilities that Watson tried, did any of them reduce the total amount of estrogen that would have been given to a woman on a monthly basis?

A No. Three of them, the last three actually increased the monthly dose of estrogen.

Q Which ones were those?

A That would be the 24-day regimen, and the two which added estrogen during the usual hormone-free interval, the last three.

Q Are you aware of how Watson ultimately learned or came upon the formulation of Lo Loestrin that became part of their NDA?

A Yes. As I recall, Patel said that they reviewed documents that went to the FDA and they saw the information about Lo Loestrin.

Q Now, there's been some question in the trial raised about whether or not Watson would know more or less than a skilled artisan.

Do you remember that testimony?

A Yes.

Q All right.

Based on reading Mr. Patel's testimony about Watson's use of publicly-available information and going to the patent office, do you have a view as to whether or not Watson was in a better position than a skilled artisan to make certain assumptions about the invention that's disputed here as opposed to a hypothetical person of skill in the art who wouldn't have known anything about Warner Chilcott and nothing about the press release?

MR. GREEN: Your Honor, I need to object to that, simply calls for speculation --

THE COURT: Sustained.

MR. GREEN: -- on behalf of the witness.

MR. PAPPAS: Let me check for a moment, your Honor.

(Pause.)

MR. PAPPAS: Your Honor, subject to moving in some exhibits which I think we can do at the end of the day as a

THE COURT: Mr. Leonard, Miss Hiatt.

MR. COBB: Mr. Cobb.

MR. CONDE: Your Honor, plaintiff's next and last witness will be Dr. Kagan who will provide testimony regarding how clinicians prescribe oral contraceptives that are best suited for the patients.

She also will provide testimony regarding the skepticism concerning the Lo Loestrin product and finally, she will provide testimony as to why Lo Loestrin fulfills an unmet medical need.

Your Honor, plaintiffs call Dr. Risa Kagan.

R I S A K A G A N, sworn.

Direct Examination By Mr. Conde:

Q Good morning, Dr. Kagan.

A Good morning.

Q Mr. Brooks, can you please pull up PTX-128?

Dr. Kagan, PTX-128 is also in your exhibit book in front of you.

Could you please tell us what PTX-128 is.

A Yes, this is my CV.

MR. CONDE: Plaintiffs move into evidence plaintiff's exhibit 128.

MR. WEZOWSKI: No objection.

THE COURT: Dr. Kagan is your problem?

MR. WEZOWSKI: She is.

THE COURT: I don't mean to be glib about that. We have a one lawyer per witness rule.

Q Mr. Brooks, can you please go to slide two?

Dr. Kagan, could you please tell us about your educational background?

A Sure. I went to New York University and I graduated in 1974, where I got my bachelors degree in an alternate education program as a multi-disciplinary nature, somewhat like psychobiology.

I subsequently went to Albany Medical College of Union University, and I graduated. I was there from 1974 to 1978, at which time I graduated and then I matched at UCSF, San Francisco, University of California, San Francisco in obstetrics and gynecology where I did my internship and residency from 1978 to 1982.

Q Could you also please tell us the licenses that you hold and your board certifications?

A Yes. I am licensed to practice in the State of California and I am board certified by the American Board of Obstetrics and Gynecology.

Q I see on slide two, you have professional organizations.

What's the significance of being part of the American College of OB-GYN/fellow?

A Well, to be a fellow in the American College signifies you were board certified and it is our main organization that

all board certified OB-GYN'S belong to. Sets the standard of care for our practice and our specialty.

Q Mr. Brooks, could you please go to Kagan slide three?

Dr. Kagan, can you please tell us about your academic appointments?

A Yes. When I finished my training, and I stayed for almost a year at UCSF, I was given the title of associate clinical professor, which is a teaching appointment, not a full-time faculty academic appointment mostly related to teaching.

When I left the university, I continued with that teaching appointment as an associate clinical professor, so that was from 1982 to 2005, and then in 2005, I was promoted to clinical professor in the department of OB-GYN at UCSF and I still maintain that appointment.

Q And what are your responsibilities as a clinical professor, Dr. Kagan?

A Well, it's changed over the years. In my earlier years, I used to attend as a gynecology faculty teaching medical students and residents, both in the out-patient clinic of OB-GYN, mostly at San Francisco General and then I would also attend and supervise the residents in the operating room.

More recently, we have a resident at our local hospital in Berkeley, California, and it's a third-year resident that I teach in the operating room. And then I also have medical

students that either shadow me or I observe them and teach them in clinical practice in our practice.

Q In terms of shadowing your practice, does that include teaching them about how to prescribe oral contraceptives?

A Absolutely. I mean, a large part of gynecology practice is evaluating patients and prescribing oral contraceptive pills.

Q Dr. Kagan, could you please tell us more about your clinician practice?

A Yes. When I graduated from my residency in 1982, I decided to stay in the full-time faculty at UCSF practicing and attending in OB-GYN.

I subsequently was whisked away to a group in the East Bay, OB-GYN fertility specialist medical group, which was an all male clinical practice and I was the first woman to practice OB-GYN in the East Bay of the bay area. And I stayed and became a partner in that practice, which grew and developed and then merged with a few other groups to now be part of something called the East Bay Physicians Medical Group, which is a part of a foundation, which is where I now practice.

It's a very large multi-specialty, but our department itself has 15 OB-GYN'S with a number of nurse practitioners.

Q So you have been a clinician prescribing oral contraceptives during this entire 30-year period?

A Yes, absolutely.
Q Could you give us an estimate as to how many patients you see with regard to prescribing oral contraceptives?
A Well, I work full-time. Somewhere in the 1990s, I stopped practicing delivering babies or obstetrics and seeing pregnant women. So I exclusively practice gynecology, which is surgery and out-patient, working full-time which is four days a week.

When I'm not in the operating room, I am in the office seeing 15 to 20 patients a day, depending upon how many new patients. I take more time with new patients. I take the liberty of my senior status to do that, and teach and so six weeks' vacation a year and work full-time four days a week and so I see a lot of patients and a lot of those patients are for birth control, prescribing birth control, helping people make choices and I am now, I'm happy to say, actually taking care of some of the women I delivered years ago.
Q So you're now taking care of the children who were your patient's children?
A That's correct.
Q Could you please give us an estimate as to the range of ages of your patients?
A Yes. I will see young women, even in adolescence. I'm referred from pediatricians many a time.

My youngest patient I think was 11 or 12, people with

abnormal bleeding, young adolescence all the way to my eldest patient right now is 92. I actually saw her just last week.

Q Dr. Kagan, could you please tell us whether you have served as a consultant with pharmaceutical companies?

A Yes, I have.

Q And what role did you serve as a consultant?

A I have been asked over the years to be a consultant in many scientific advisory boards and when I stopped practicing delivering babies obstetrics, I became more involved with clinical research.

So I am related to some of the pharmaceutical companies in doing clinical research and also consulting on these boards.

Q Dr. Kagan, have you testified as an expert in patent cases before?

A Yes, I have.

Q Approximately how many?

A Four or five.

Q And, Dr. Kagan, how much time per year do you serve as an expert testifying in patent cases?

A Very little.

MR. CONDE: Your Honor, plaintiffs offer Dr. Kagan as an expert regarding clinical aspects of gynecologic practice and contraception management.

MR. WEZOWSKI: No objection your Honor.

THE COURT: All right.

Q Mr. Brooks, can we please go to slide four?

In the next two slides, Dr. Kagan, I'd like you to briefly summarize the opinions that you'll be providing this morning, starting with slide four.

A I think I'm here as a clinician and an expert clinician, having been in practice since 1978.

In trying to give an expert opinion of how a clinician prescribes or helps patients make choices about their contraception and also how to prescribe a birth control pill and trying to find the right pill that works for that woman.

Q Mr. Brooks, can you please go to Kagan slide five?

Dr. Kagan, can you please summarize the final two opinions that you'll be offering this morning?

A Yes. I also would like to clarify in my opinion has -- how marketing does not cause a clinician to prescribe a certain product. Again, explaining that I think the proof is in the pudding, which is a product has to work very well for it to keep increasing if it's prescriptions.

And then also specifically about the clinical benefits of Lo Loestrin FE, which is now the lowest dose birth control pill on the market and, in my opinion, has really met, fulfilled an unmet need for some women, that up until now could not use combination oral contraceptives.

Q And just to put a finer point on that, there's some women

who before the Lo Loestrin regimen were unable to take contraception regimens because of the side effect profile?
A Absolutely, which I can get into with you about there are women that would want to have tried many others, could not tolerate others because they are highly sensitive to estrogen.
Q Let's turn to the first of the three topics.

Let's talk about how clinicians would decide which oral contraceptive product would be best suited for a patient.

Let's first start off with identifying the types of combination oral contraceptive products that were available as of 2005.

Can we please go to PTX-135?

Dr. Kagan, what is PTX-135.

A Well, this is one of a few pages, I believe, I think three, which is a list of various oral contraceptive regimens that basically have combined oral contraceptives approved in the United States since Loestrin FE 1/20 was approved through 2005, which I guess is the date that this patent was filed.
Q And are you familiar with the oral contraceptive products that are identified on PTX-135?
A Yes. I have been, as I said, prescribing since 1978, so I think I have probably prescribed each and every one of these.

Most of them are different. I saw a few that might be the same, but made by different manufacturers like Ortho

Desogen.
Q Just to be clear, the actual amounts of estrogen and progestin in the regimen they follow for those two products have the same -- are the same?
A Right.
Q Now, Dr. Kagan, except for the ones that are the same, are the rest of the oral contraceptive products on the list interchangeable?
A Absolutely not. Each one of these is completely different for each individual woman.
Q And why do you say that they're different for each individual woman?
A Because they each have different or varying amounts of estrogen, progestin, different types of progestins.

All of these have ethinyl estradiol, which up until recently, was the only estrogen we had in pills.

That new pill that you just talked about, Natazia, has a different estrogen, but that's not on this list because it came later.

But ethinyl estradiol in different amounts, norethindrone, different progestins, we have monophasic, biphasic, triphasic; different lengths, 21 days, 24 days, different numbers of pills.
Q Now, Dr. Kagan, have you reviewed Dr. Barnhart's trial testimony regarding whether a clinician can determine what

oral contraceptive product is best suited for a particular patient?

A Yes, I have.

Q Mr. Brooks, can we go to trial testimony transcript page 143?

Let's look at line six to line 16. In his testimony, Dr. Barnhart was asked, "In your practice, Dr. Barnhart, if a patient comes to you and asks you to prescribe a combination oral contraceptive, are you able to select an oral contraceptive that is best suited for that patient?

"ANSWER: I'm unable to look at somebody and say, based on your personality or your body or your symptoms which oral contraceptive is better for you, other than the fact that if you came in and told me I wanted one, I'll probably give that to you. I would give one of many safe, effective combined oral contraceptive pills to you, if that's what you were -- if that was a good medication for you."

Do you agree with Dr. Barnhart's analysis?

A No, I disagree with his statement.

Q Why is that?

A Because I think that we have been taught from the early days of time that patients are individuals. We -- there are absolutely ways in which one can take a good history and physical and try to come up with maybe not just one and only one birth control pill for that patient, but I believe that

there are signs and symptoms that are given in that history and physical that you have with that patient to try to help them find one of the pills that might work the best for that individual woman.

Q Now, with regard to your academic activities, is teaching the students how to select the best oral contraceptive product for a particular patient something that you do?

A Yes. There are numerous guides and courses and CE courses and lectures are given to teach medical students and house staff, residents, basically contradicting what he is saying here.

Q Okay.

Dr. Kagan, let's go to Kagan slide six, Mr. Brooks.

Dr. Kagan, does Kagan slide six identify in general the types of things you would look to, to determine what particular oral contraceptive product would be best suited for a patient?

A Yes. I think that it's important to obtain a good medical history, with pertinent facts that help one decide which, say progestin might be better for that patient or what dose of estrogen.

Her family history, whether this is a new-start patient or whether this is a patient looking for a new pill so you want to get her history of past usage of oral contraceptives and, of course, always do a physical examination.

Q Mr. Brooks, can we go to Kagan slide seven?

What information about the patient's medical history would be relevant to selecting the oral contraceptive product that's best suited for that patient?

A Well, this is a list that I put together because these are the kinds of things I like to hear about when I take a good history from a patient.

For instance, all birth control pills, all oral contraceptives, whatever you want to call them, are generally or supposedly good for acne because they suppress ovarian production of androgens, but we all know that there are some birth control pills that are better than others, and for each individual woman.

Some of the newer progestins that are lower in their androgenic activity tend to work better for acne. One might try that or it's important to know how bad their acne is.

Many women come, younger adolescents come to me just for acne, not for birth control, they use it for a non-contraceptive reason.

History of headaches or migraines. There are some women are so they get a -- there are some women that are verify hormone sensitive and they even get migraines or headaches or menstrual migraines and small fluctuation in their own circulating endogenous hormones, so I want to know that.

Mood changes, PMS, people who are very -- they live their life by their moods. These are important -- this is important information. Again, that kind of patient I probably would want to give a monophasic pill to, something everyday the same, not to disrupt the hormones.

Someone who smokes -- the teaching has been from early on, of course, anyone over the age of 35, I would not give birth control pills to, and we teach that, combination birth control pills, but for smokers we try to find the lowest dose possible that works for that patient.

History of hypertension, again, we would try to find the lowest dose possible that would work for that patient.

And, of course, anyone who has ever had a stroke or heart disease, we do not give birth control pills to.

Q Now, Dr. Kagan, can we please, Mr. Brooks, go to Kagan slide eight?

You mentioned that you want to know whether a woman had previously taken an oral contraceptive tablet or pill.

Why is that?

A For all of the obvious reasons that are on this list. So when a woman comes in, the first thing I find out is whether she ever tried something or not. Not just me, I think generally we all ask that question to our patients. What have you tried, what has worked for you, what pills haven't worked for you.

And the number one reason why women will change, call, come in, stop unintended pregnancies is because they stopped their pill because they're having abnormal bleeding. Cycle control is probably on the top of the list for everybody who's on a birth control pill because it interferes with your quality of life and functioning. So nobody wants what's called unscheduled bleeding.

I want to know if that patient took a pill that made her acne worse. Some pills make acne worse even though you think they're supposed to get better and that has to do with the progestins and the ratio of estrogen and progestin.

Breast tenderness, there are some women that are so sensitive to estrogen, that when they take even the lowest up to recently the 20 microgram tablets, they still have breast tenderness and they're miserable because women who have breast tenderness, the only thing they can equate that with is breast cancer. This is the reason why most women are anxious about their breast and breast cancer. So breast tenderness.

Headaches and migraines. Again, it's important to know did you have a headache on your pill, were you on a triphasic pill that stimulated a headache? So then you need a monophasic pill and the lowest dose pill. Some women get headaches when they went on a pill and they went on, say, a 21-7 from the day that they were on to off.

Nausea is the biggest. I would say this is one of the

main advantages to this new pill, this lowest dose Lo Loestrin. I have patients in my practice that are so sensitive to estrogen, that even the 20 microgram tablets created within two days, three days, severe nausea.

The patients that I really had success with, and this is why I say it was an unmet need, were women who could not tolerate any birth control pill that are now tolerating Lo Loestrin, because they were so nauseated with every other pill.

Then, of course, bloating and weight gain, which is typical for some birth control pills for individual women, depending upon the combination.

Q I just want to go back up to the top of your list.

Can you just explain more about what consequences -- what the consequences of taking an oral contraceptive pill that has poor cycle control?

A Well, it wreaks personal havoc. Women are taking these pills to be able to exercise, have sex, have a quality of life, to basically function, but have contraception so they can have a choice as to when they get pregnant.

As I said earlier, it's one thing if a woman goes into a pill and you say to them, okay, for the first two to three months you might have what's called break-through bleeding or unscheduled bleeding. It could happen at any time over the pill packet, but by the third month, for the most part, most

people should know when they're going to bleed. Usually people bleed during the time which they're taking the placebos or the dummy pills, as we say.

But, you know, the truth is, is that if a woman persists and has a lot of unscheduled bleeding, break-through bleeding, they're just not going to take it no matter how great that pill is. They're -- that's the reason why they call us, that's the reason why they stop taking it and I read that that's the reason why we have unplanned pregnancy, because people stop taking the pills.

Q Now, Dr. Kagan, can you please provide an example of an oral contraceptive pill that in your experience has poor cycle control?

A Well, the irony is, and I've testified about this I think in my deposition, was that back in the day, we all wanted to give the lowest dose pill. That was the teaching, that is the teaching in all of our textbooks when it comes to hormones.

1/20 was a great pill. I mean, I started in '78. This was out before I even started. We were supposed to give it to smokers, try to give it to whoever you can give it to.

In my personal experience and with Loestrin 1/20 was that it had so much break-through bleeding and unscheduled bleeding, that a lot of patients were calling to change pills to a different pill.

So I -- it is an example of a pill that didn't go so

well.

Q So now, Dr. Kagan, let's shift gears and talk about marketing.

In your opinion, as an expert clinician, what effect does marketing have on a clinician's prescribing decisions?

A I think that marketing plays a role to make people aware that something has been approved by the FDA and now we have it available to start using, writing, prescribing.

I think that over and beyond that, it is not the way that good clinicians learn about products and how to use them. They learn at meetings, they learn by reading the literature and basically from colleagues, peer-to-peer, but that's really -- I think marketing is really just, again, what it sounds like, marketing. Makes you aware it's been approved, now you can start writing for it.

Q Have you ever been approached by a Warner Chilcott sales representative with regard to Lo Loestrin?

A Yes.

Q How many times?

A I don't remember how many times. I just know that when it first came to market, there was a representative that came through our huge practice and I may have met her a few times, but that's the only way I knew that I could start -- I knew, I heard about it at the meeting and I basically -- that's how -- we don't see this person any more. We don't have anybody at

all.

Q And so you prescribe Lo Loestrin because of the performance of the product?

A Well, here's the irony of the situation for me and Lo Loestrin. I told you I did not have a very good experience with the Loestrin and I was very much in favor of the newer progestins, longer acting, better side effect profile as well as less break-through bleeding.

So Loestrin, as much as I wanted to prescribe the 1/20, it generally fell out of favor as far as myself and most of my patients.

So I was at a meeting, I think it was AHOC meeting where I ran into a colleague of mine and I saw Lo Lo and I didn't even really know what it was. I knew it was something in development, but I didn't realize it was ten micrograms and I laughed.

I said to him, are you kidding me? No, seriously. He said, they really have developed a pill that's even lower than 1/20, which shocked me because I never thought that you could go lower than 20 micrograms for contraceptive efficacy.

So he was the one who had some experience with it and basically said to me, you'll see, wait until you see. I mean, it's really different in that not only is it ten micrograms with the norethindrone, which is not long acting, but it performed quite well.

It was one of the newer extended 24 and then two estrogen pills only, two days of placebo and I -- so I started reading up about it and learning more about it and I thought I would give it a chance for some of those hormone sensitive patients, which subsequently worked very well.

Q Now, Dr. Kagan, let's go to Kagan slide nine, please.

We've seen variations of this slide with Dr. Darney and others. I just want to make sure we understand what this is.

This shows Loestrin 1/20 which was approved in the early 1970s, correct, Dr. Kagan?

A Yes.

Q And we see a period of time where there were as many 15 new FDA-approved regimens that all used 30 micrograms or higher of EE, ethinyl estradiol, you understand, correct?

A Yes.

Q And then starting in about 1995, until 2005, we have the new FDA-approved products that came to the market, all of which were 20 micrograms of EE or above, correct?

A Yes.

Q And just so that we make sure everyone is clear, there's a gap in the slide between about 2005, when the patent was filed, and the Lo Loestrin product and in that gap there were a few other additional products that were approved by the FDA as well, right?

A That's correct.

Q And was there estrogen amounts 20 micrograms or greater?
A Yes.
Q Now, Doctor, could you please explain to the Court how the information on this slide played a role in your surprise about the Lo Loestrin product when you first heard about it?
A Well, if you go to the left side of that slide, I'm actually kind of -- I have been -- I feel old, but basically Lo Loestrin was approved before I even -- I was in college I guess. I didn't even -- in medical school.

So when I started training in this field, which is 1978, we were just thrown a lot of different birth control pills that you saw on the chart earlier and there were a lot approved, but they all basically -- I watched birth control pills go down from 80, which had horrible nausea and headache side effects, to 50, and then when I came into training, we still were using some of the 50 micrograms, but we were being urged and taught to go lower.

So we had 35s, primarily, micrograms and really looking at the estrogens because that was the thing that was most risky as far as DVT risk, blood clot risk, et cetera. So 30s, lots of different pills.

And then as the years went on, what came out were all the new progestins and different regimens and different combinations. We'd have to have the guide books at our desk and we still do to try to remember which was in which one, you

know, how many days of this one, how many days of that one.

All of these pills were all the lowest was 20 and, nobody, I don't think any of my colleagues, and I know nobody I know to the teaching of it and looking in all those books, those guide books that guide clinicians in how to practice, would ever think that one could get contraceptive efficacy, meaning that you suppress ovulation or have good contraception to prevent pregnancy with a side effect profile that was tolerable that would be less than 20 micrograms.

All of a sudden Lo Loestrin comes on the market, which is ten micrograms and that's why I laughed. I thought it would have the worse break-through bleeding ever, because I thought Loestrin 1/20 had terrible break-through bleeding and if you have horrible break-through bleeding, patients don't want to take it.

So I think this is a beautiful slide, because it does tell you how, yes, we've changed the regimens. Yes, we've gone to 24 days. Yes, we tried different progestins, but never before in these 30, 40 years did anybody try to go below 20 micrograms.

Q Now, Dr. Kagan -- actually, Mr. Brooks, can we go to Dr. Barnhart's testimony early in the trial at page 140?

Dr. Kagan, I think you mentioned earlier that you reviewed Dr. Barnhart's testimony to the extent it related to the issues that you are concerned with at the trial?

A Yes.
Q And at page 140, starting at line 15, Dr. Barnhart was asked, "In your experience, are there patients for whom a ten microgram dose combined oral contraceptive containing ten micrograms of ethinyl estradiol is particularly suited?
"ANSWER: No, I don't think so. I think there are patients that might want a low dose, but there are multiple low doses available. If the patient is contradicted -- contraindicated to have estrogen or has side effects of estrogen, they shouldn't get estrogen at all, even at ten" micrograms, it says "milligrams."
Dr. Kagan, do you agree with Dr. Barnhart.
A With all due respect, absolutely not. I mean, I am in the trenches, I see lots of women. I have some very hormone-sensitive patients.
I saw one the other day back who never could take a combination birth control pill and she is now successfully taking Lo Loestrin. She herself says to me, I can't believe I can finally find a pill that I can take that works, that doesn't create nausea.
So I would say the main -- the original place where I think this is so new, novel and different was that women with terrible breast tenderness, terrible nausea could now try a new option that would work for contraception with an acceptable and pretty good break-through bleeding rate.

So I disagree with this.

Q Dr. Kagan, have you extended your use of Lo Loestrin beyond just those patients who have nausea or breast tenderness side effects?

A Or headaches, yes. I would say those are the three categories, the headache patient who tried other pills and this is so lovely because it's monophasic. So it is something different.

So Lo Lo dose, so headache patients, breast tenderness patients and patients who had severe nausea basically could never -- they've tried combination birth control pills that didn't work. Because -- originally, I was so skeptical of this pill, not -- they tell me the FDA approved it, it has to work for birth control, so that wasn't my skepticism.

My skepticism was that it would have terrible break-through bleeding. I initially tried it in these types of patients and now I definitely have extended, so have my partners and people I know, to all kinds of women, women who want to be on the lowest dose possible, which is more or less the teaching of hormones these days, is try to be on the lowest dose possible, not just hormones, any drug.

If there's a lower dose available and medical good practice, why not try that drug? So, yes, I do try it on other patients or offer it to other patients.

Q Dr. Kagan, I think you mentioned this, but do your

colleagues also prescribe and like Lo Loestrin?
A Absolutely. I think picking up as one gains experience with the pill and has, again, a good result from it, then, yes, they have.
Q How do you know that?
A Well, I'm in a group of -- I share a practice in this group that has, you know, 18 practitioners in it, we cross cover each other, we're on electronic medical records so I see their patients, they see my patients.

I also, when they're on vacation, I cover what they call their inboxes, which means I have to refill their prescriptions so I see what's going on.
Q Mr. Brooks, can we put up Kagan slide ten, please?

Dr. Kagan, could you just please summarize your experience with prescribing the Lo Loestrin product?
A Yes. I think that, as I said, this was a new, novel surprise to me in my 35 years of practicing or using birth control pills, contraceptives or combination. I think that it really fills a nitch for patients and the proof is in the pudding.

It's been out now, it's starting to be used. I think the surprise to many of us that you can go lower than 20 and you get to ten micrograms, which is very low and have contraceptive efficacy, with a very nice acceptable side effect profile, especially with the break-through bleeding,

and it is especially well suited for those women that could not use a combination birth control pill prior to this time.

So I think it's been really a good addition to what we have to offer our patients.

Q Dr. Kagan, has Lo Loestrin fulfilled an unmet medical need, in your opinion?

A Absolutely. I think, as I said, I was so surprised when I heard about it. I was skeptical, but I'm pleased that I'm able to offer this to those patients.

MR. CONDE: Your Honor, we offer as demonstratives Kagan slides one through ten.

MR. WEZOWSKI: No objection.

MR. CONDE: We have nothing further at this time.

THE COURT: Okay.

Let's take a short break.

THE CLERK: All rise.

(Recess.)

THE CLERK: All rise.

R I S A K A G A N, previously sworn, resumes the stand.

CROSS-EXAMINATION BY MR. WEZOWSKI:

Q Good morning, Dr. Kagan.

A Good morning.

Q If a patient has presented herself to you -- and this is a hypothetical that I'd like to give you.