IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

WENDY B. DOLIN Individually and as Independent Executor of the Estate of STEWART DOLIN, deceased, Plaintiff,	No. 12 CV 6403
vs.	Chicago, Illinois
SMITHKLINE BEECHAM CORPORATION D/B/A GLAXOSMITHKLINE, a Pennsylvania Corporation, Defendant.	March 16, 2017 9:15 o'clock a.m.

VOLUME 3 A
TRANSCRIPT OF PROCEEDINGS
BEFORE THE HONORABLE WILLIAM T. HART

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(The following proceedings were had out of the presence of the jury in open court:)

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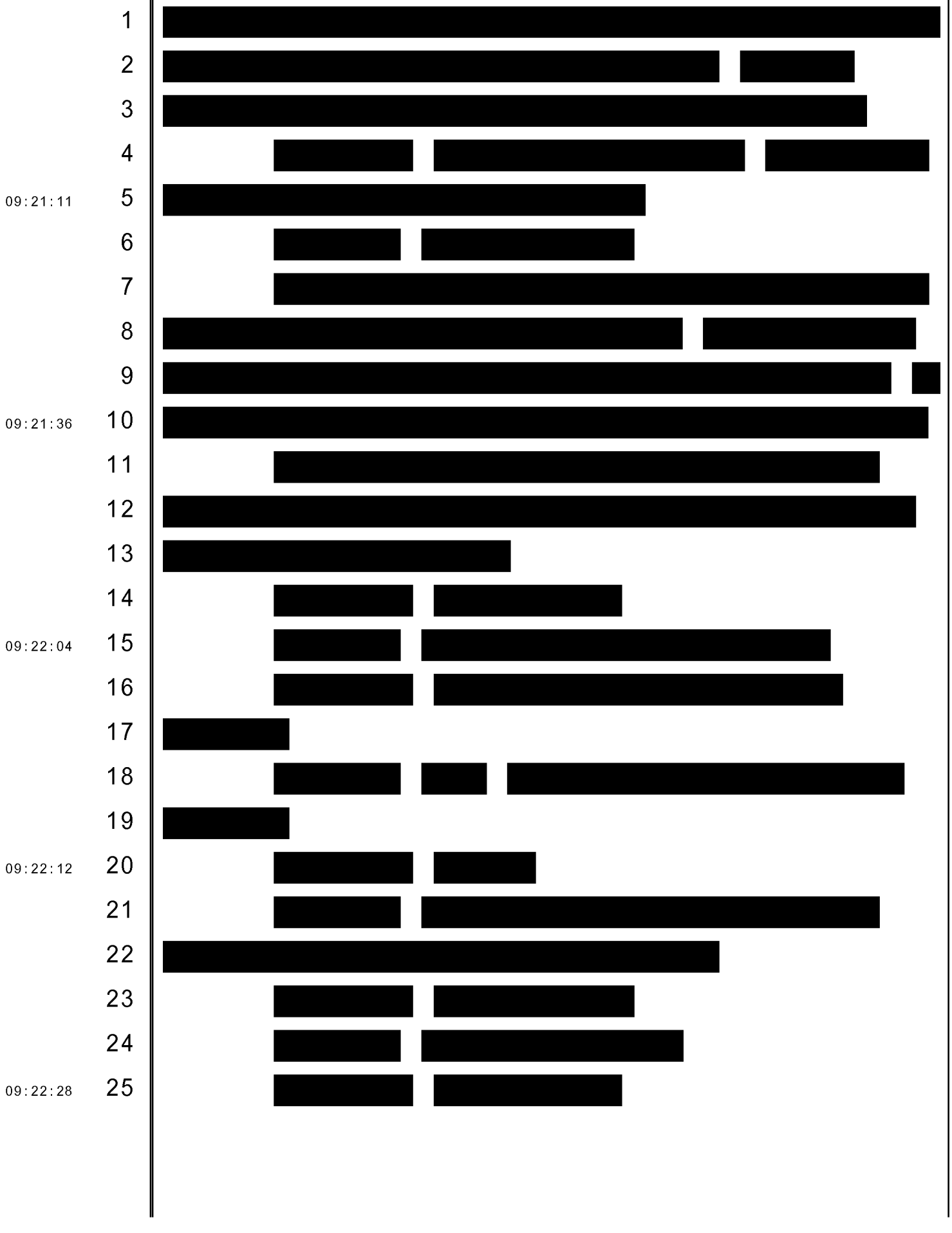


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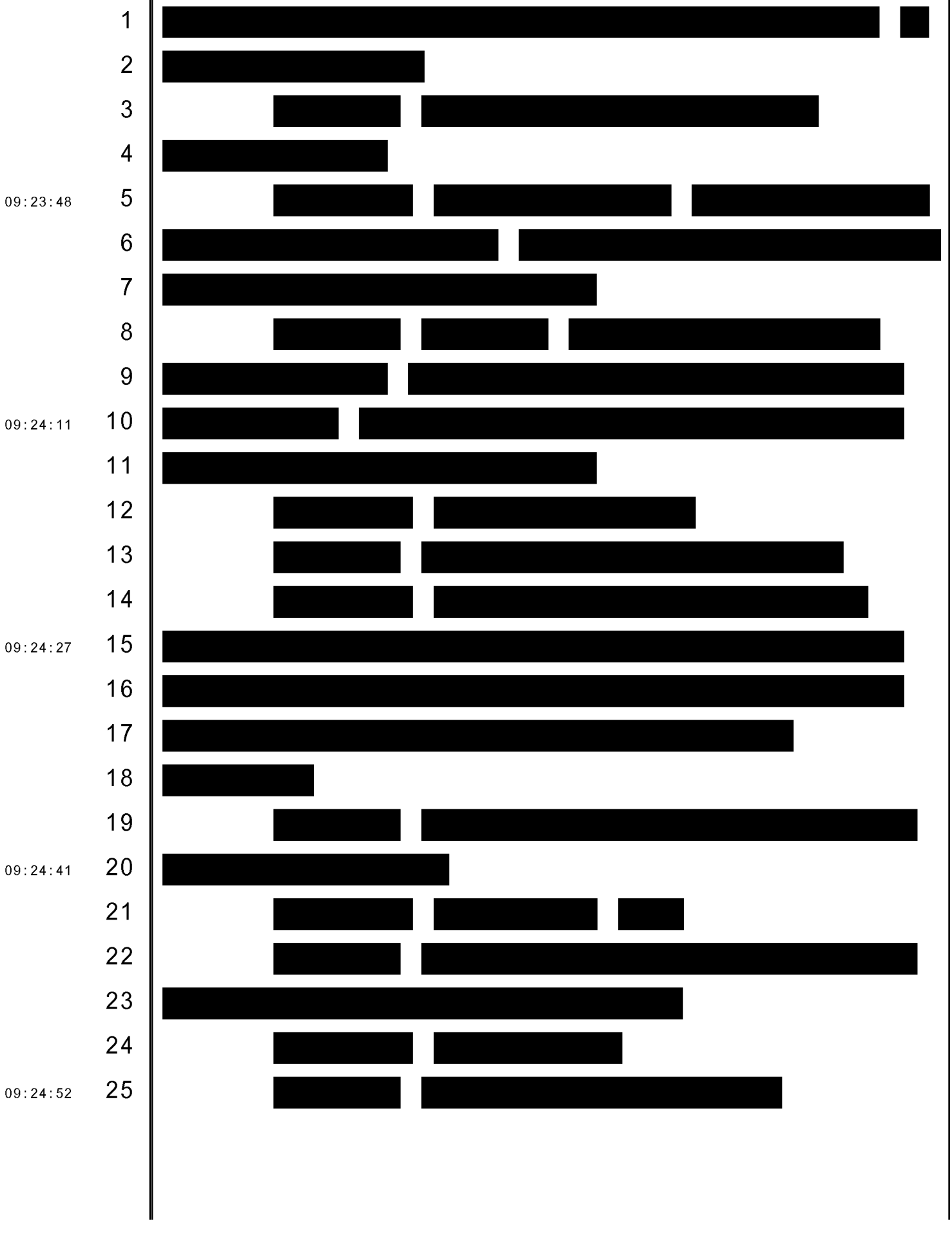
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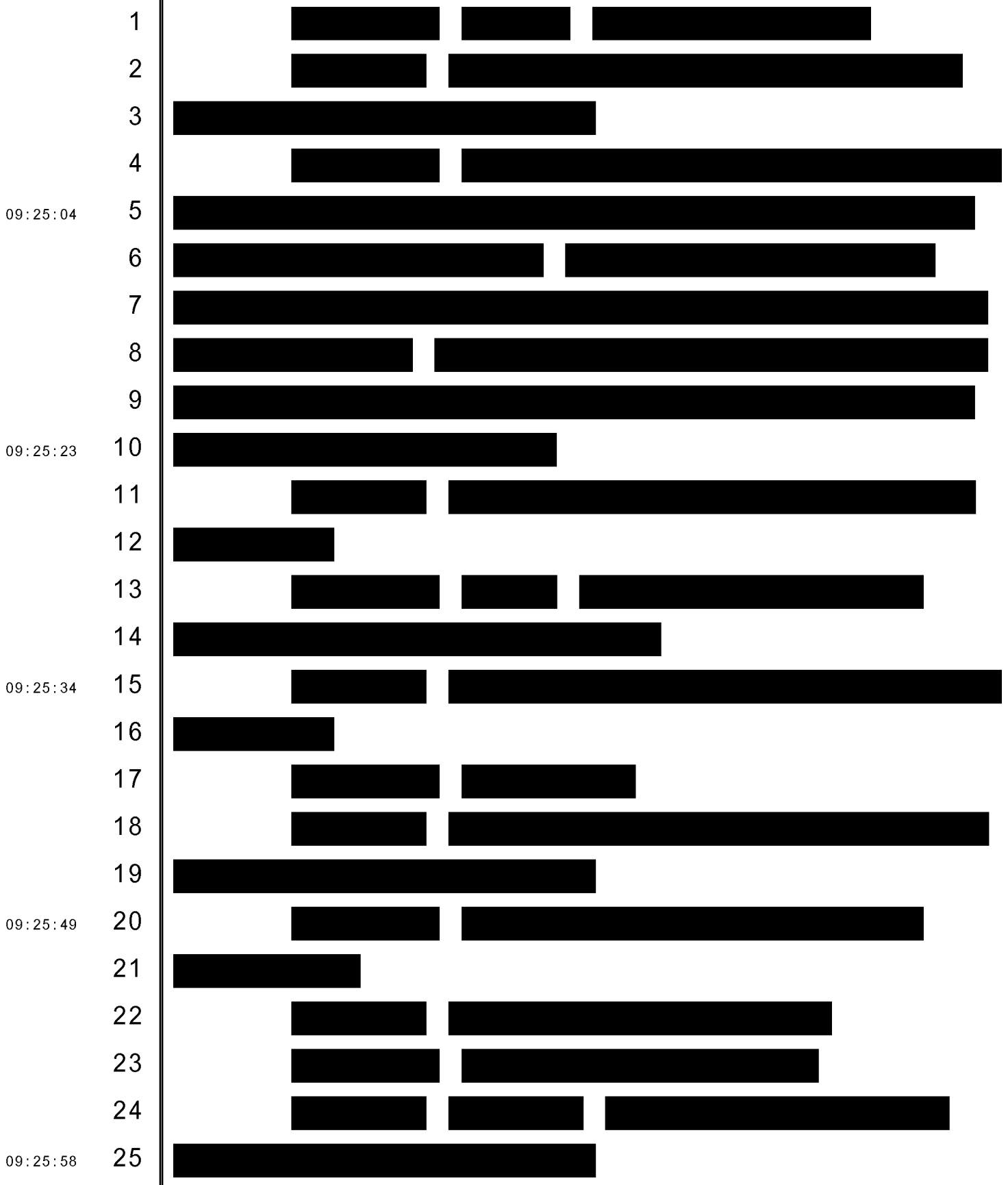
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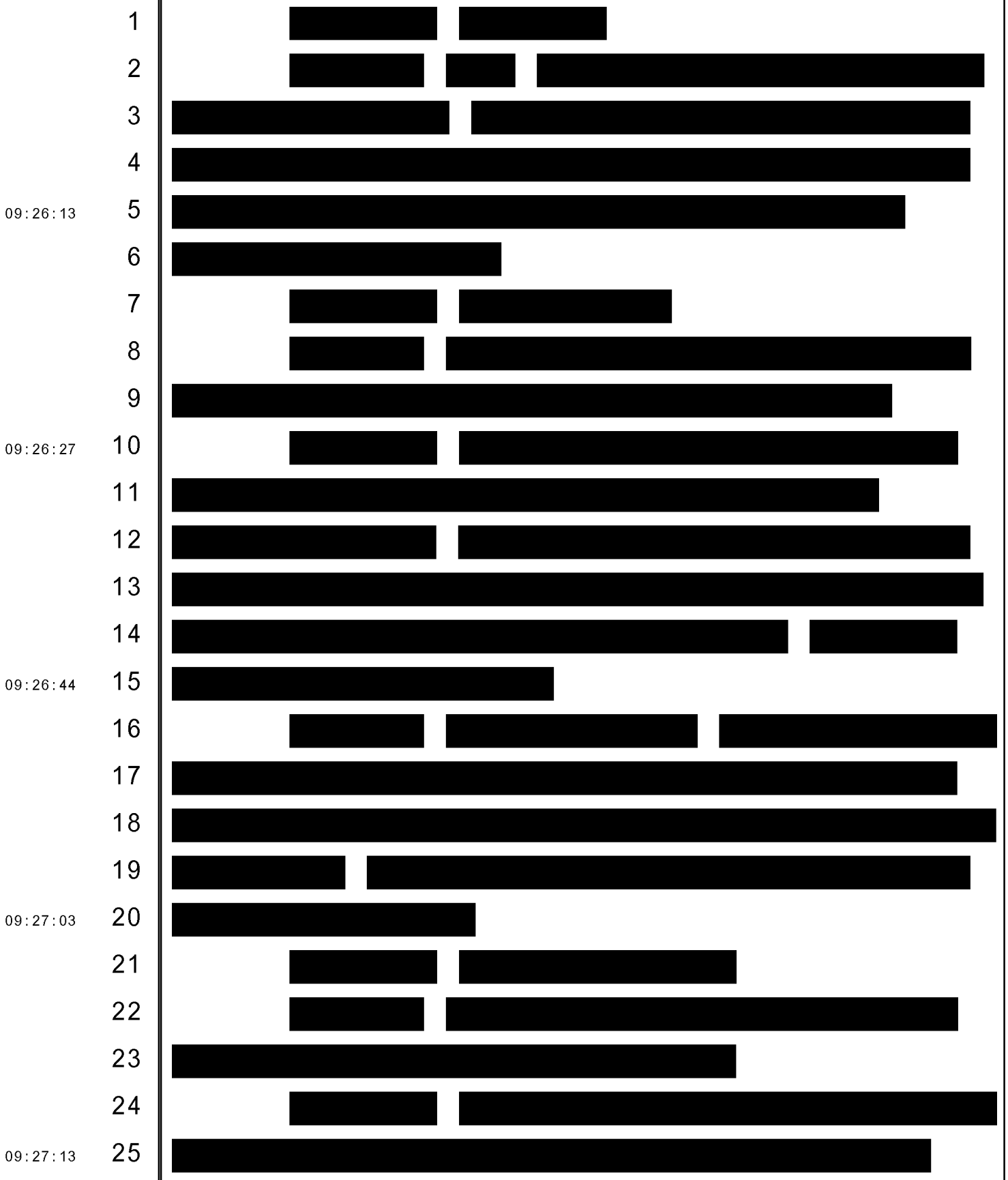
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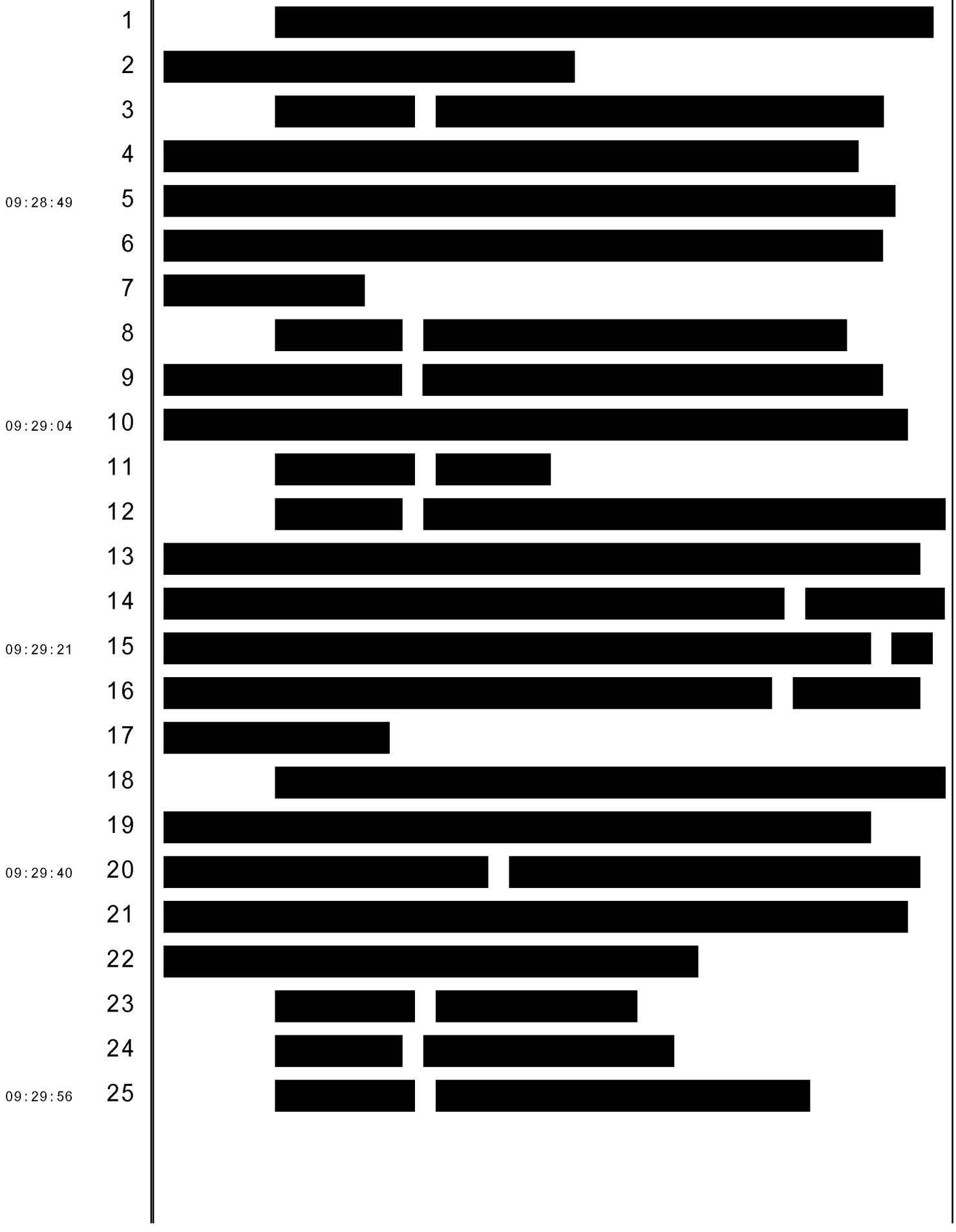
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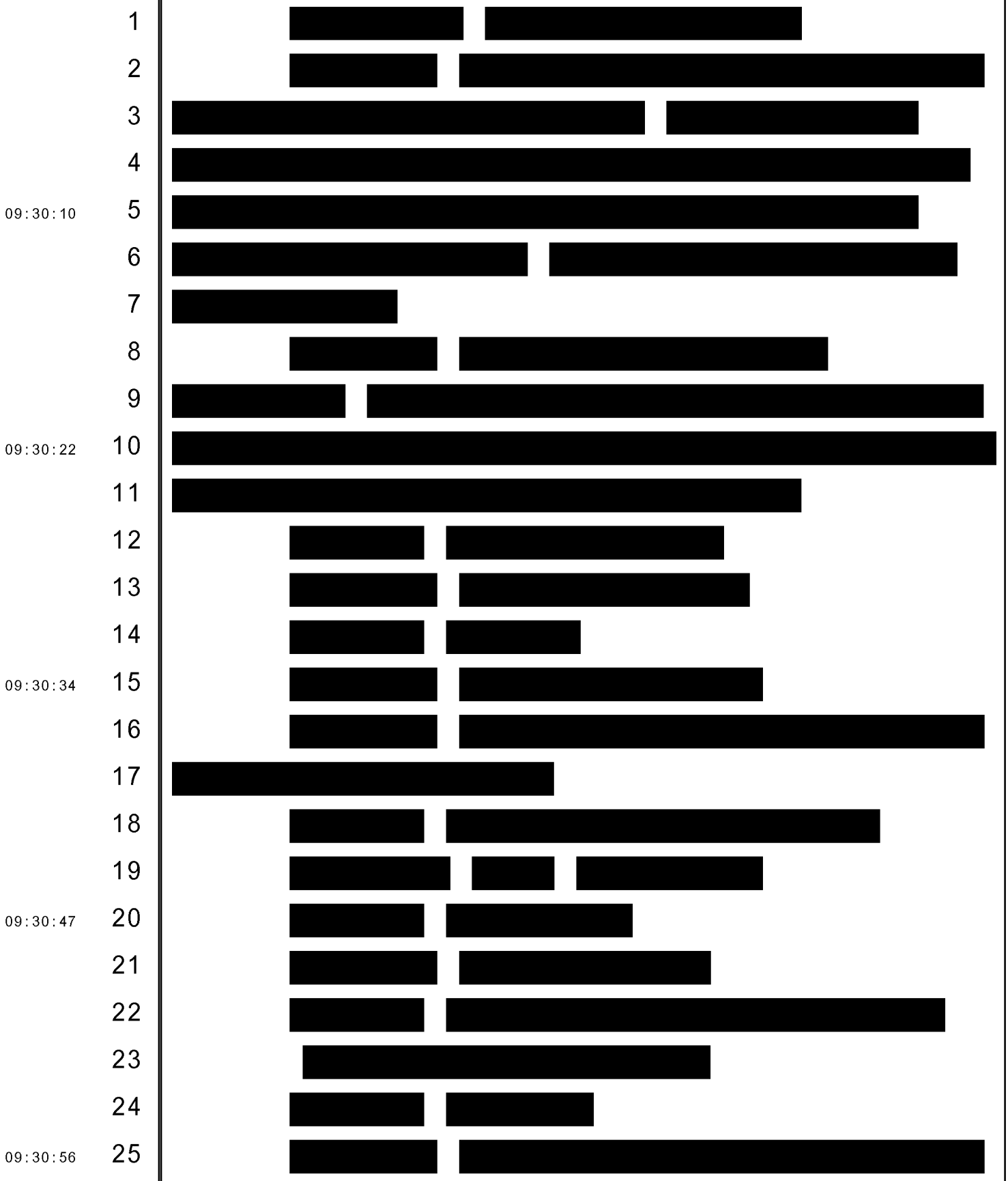
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(The following proceedings were had in the presence of the jury in open court:)

THE COURT: All right. Thank you very much, ladies and gentlemen. We appreciate your presence here. Please be seated.

We will resume. You may proceed, sir.

MR. WISNER: Yes, Your Honor. I have to get this working properly. Two seconds.

(Brief pause).

MR. WISNER: Okay. Great.

DAVID HEALY, PLAINTIFF'S WITNESS, SWORN (resumed)

DIRECT EXAMINATION

BY MR. WISER:

09:34:11 Q. All right, Dr. Healy, good morning.

A. Hi, Mr. Wisner.

Q. Just before we ended yesterday we were talking about an article by Anthony Rothschild, do you remember that?

A. I do, yes.

09:34:28 Q. I believe this was Plaintiff's Exhibit 88.

Let me get it back up here on the screen.

Just to get us oriented, doctor, what is this article about again?

A. Well, it's about the role of akathisia, as at title of the

09:34:44 article says, and its links to people taking SSRIs, like fluoxetine in this case, and going on to commit suicide.

Q. And to be clear, Paxil, is that a SSRI.

A. It is, yes.

Q. Okay. Now, we were in the middle of a passage just before

09:35:02 we ended the day and I want to go back to it. About here (indicating).

Here it said:

".. similar to 3 cases describe in this report, colleagues described two patients who

09:35:15 successfully killed themselves by jumping after

the development of akathisia secondary to depot pot fluphenazine treatment."

I'll stop right there.

What does that sentence mean, doctor?

09:35:28 A. Well, it's actually described here a different group of clinicians reporting that, in their view, two patients that they put on a completely different drug, it's not an SSRI but one that also causes akathisia, that the akathisia led on to these two patients completing suicide.

09:35:55 Q. Thank you, doctor.

How does this article in any way relate to your understanding of the risks associated with SSRI induced akathisia and suicide?

A. It relates in that if we go all the way back to 1955 when 09:36:10 akathisia is first described here in the United States and over in Europe, it was linked then to people going on to complete suicide, not just people making gestures or saying that I think, you know, I may harm myself. These were people who didn't have mental illnesses and who went on to kill themselves 09:36:36 after they became Akathisic.

Through to the late 1950's and into the 1960's a range of senior clinicians said, look, this is one of the serious hazards of any of these drugs, either antidepressants or antipsychotics.

09:37:04 Q. It says right here in the next part:

"... it remains unclear whether there exist a common pharmacological basis for akathisia and suicidal ideation or acts, although it has been postulated that suicidal ideation and suicide occur secondary to the emotional distress of akathisia."

What does that mean, doctor?

A. Well, that goes to the4 issue of do we know what actually happens in the brain of people when they become Akathisic.

Akathisia, as I said, is a very unfortunate word. And it's a word that these days covers a wide range of effects that different drugs can cause.

There's a group of different antidepressants to the SSRIs that can also make people feel bad. And, again, there's a good deal of evidence that the way they feel bad can lead to then go on to commit suicide also, but it's not the same kind of feeling bad that you get with akathisia.

It's not usually the kind of sense that, you know, I'm in a state where death would be a welcome relief, which is the kind of state that's linked to the SSRIs.

But given all these effects that these drugs can cause, there isn't any work where people have come in to try and see where the slightly different state that other drugs can cause, is that to the same way as the akathisia that SSRIs can cause.

And even on the SSRIs, there's no good research to this that has been done to pin down are they all producing just the same effect and how is it.

If we knew just what happened in the brain, we'd be in a better place to design an antidote to try and intervene and make sure that things don't go wrong.

Q. All right. Doctor, so this article, Dr. Rothschild's article, came up in a context of challenge, de-challenge, re-challenge study. What is the fourth type of data that you look at to examine whether or not a drug can cause certain side effects?

A. Well, one of the other things to look at is controlled clinical trials.

Q. Okay. Let's go back to the diagram that we were using yesterday.

A. I don't have them here. It would be up here, but I don't have it actually here with me.

Q. So, doctor, thank you for reminding me. I took the liberty of putting them into a binder with tabs so we could avoid the problem of yesterday.

And I actually have one for Court as well.

(Binder tendered to the Court and witness.)

BY THE WITNESS:

A. Well, we just have to hope, although you try to make things full proof, we have to wait and see (laughing).

BY MR. WISER:
Q. All right, doctor, we are on Plaintiff's Exhibit 35. I have it up on the screen as well.
A. Okay.
09:39:58 THE COURT: It's on your screen, doctor. It should be.
BY THE WITNESS:
A. Yeah.
BY MR. WISER:
09:40:03 Q. All right. Doctor, so we are in the fourth one here, Controlled Clinical Trials.
Now, I want to break this down because I know it can be pretty complicated. Let's start off with the first part of the -- well, let's start out off with what it's about. How are
09:40:18 clinical trials sort of generally organized?
A. Well, the key word here -- well, clinical trials go back a few hundred years, but over the course of doing trials of new treatments, we've learned over time that actually a great deal of bias can come into them.
09:40:38 Bias from people who have been put on a new treatment where they hope it's actually going to work, bias from the point of view of the person putting people on a new treatment, like me, who also hopes that the new treatment is going to work.
09:40:55 So over the course of about a hundred years or more,

there were great efforts to try and control that bias. So the world "controlled" here refers to efforts to control bias. And there's a few different ways you can do it. One is, you can try and match the people that go in the active drug or the
09:41:10 placebo or other drug, and you can match them by age and sex, and things like that. You hope and try to make sure you got two groups who look exactly the same.

But even when you do that, there is still a hunch that some clinical people, like me, were still somehow managing to
09:41:28 get the people whom they thought might respond best to the new treatment into the active treatment group.

So in the late -- well, in the 1950's, the first round devise controlled trial was late 1940's. And that was about -- that's an extra step, again, where rather than let me build two
09:41:47 groups of patients, what happens is, when people come into a clinical trial they agree to be randomized. And so a computer, which generates random numbers, works at if you're going to be on the active treatment or the inactive treatment. And anyone going into the trial hasn't any idea of what they're on, and I
09:42:08 have any idea either. And I've had no influence in trying to ensure that good patients for the treatment are actually getting the treatment or not.

And the other thing we do is, we introduce a placebo, which means we're not just trying to compare the new drug with
09:42:25 an old drug, although we will often do that as well. There may

be three arms to the trial: New drug, old drug, and placebo. But the key issue is trying to make sure that we have some sense of how people would do even if they weren't on any treatment at all; although placebo, strictly speaking, is not no treatment at all.

09:42:44

Q. Now, wait a minute, doctor. You said that these randomized controlled trials emerged so that you could eliminate bias in assessing if a drug works. What about side effects?

A. Well, there's two things here. The first thing is, the first randomized controlled drug was done on a drug called streptomycin, which was an antibiotic discovered here and which was hoped was going to be -- well, it appeared to be the first effective treatment we had for tuberculosis.

09:43:01

The first trials on tuberculosis, the first controlled trials were done here and they involved doctors giving it to two groups of patients matched by age, and sex, and things like that.

09:43:19

And over here, the clinical work over here by doctors giving the drugs, giving streptomycin to patients with tuberculosis picked up all of the problems, all the good things it did and all of the bad things linked to it, including hearing loss, which is one of the big problems.

09:43:36

In the U.K., a few years later, they did the first randomized control trial on this drug. And the randomized trial didn't pick up all of the things that have been picked up

09:43:54

previously. The randomized trial just confirmed the idea that, yes, this drug does work, but it missed the fact that there are things that can go wrong like hearing loss, for instance. So randomized controlled trials can be useful, but they're not the only thing.

09:44:16

A good way to relate to this process is, the person who's responsible in a way for us being here today, the person who put randomized controlled trials into the Food and Drugs Act in 1962 was a man called Louie -- Louie Lasanthia (phonetic). And he was one of the big enthusiasts for randomized controlled trials during the 1950s, but shortly after this, by the late 1060's he was going the place saying to doctors, look, you've heard me talk before and say we need to be doing RCTs for everything, well the natural fact is, I've changed my mind, RCTs are not the only way to the truth.

09:44:27

09:44:51

Q. All right. So let's break down the phases of a randomized control trial.

So we start off here with a cohort of people. I have it here as depressed patients. Do you see that, doctor?

A. I do, yes.

09:45:05

Q. Okay. Great. So then they go through and I have here as the washout. What is that?

A. Well, that's a thing that looked like a very good idea in the 1980's. Washout periods weren't there right from the start partly because when RCTs began to be done first in the 1950's,

09:45:21

1960's, lots of people going into them weren't on prior treatment.

And if you were to do an RCT in some parts of the Third World say when people weren't actually on active treatment, you could skip the washout phase. The washout phase begins to happen more and more during the 1980's when an increasing number of the people who were going into a controlled clinical trial were on prior treatment and you had to wash out the prior treatment that they were on.

09:45:37

09:45:57

You didn't always ask them to stop all of the other treatments they were on, but, for instance, in an antidepressant trial you might want to make sure they weren't on any other antidepressant, because, you know if you try to test out a new drug, it seems clear that you shouldn't have person on an old antidepressant and the new antidepressant at the same time.

09:46:13

This seemed to be an obvious thing to do back then, but it seems that one of the obvious flaws are problems missed by people, which was, if we put you off the other antidepressant you were on or the other pills you were on, you might during this period go into withdrawal from those other pills. That's a thing that didn't seem to be considered all that closely back then when the SSRIs trials were being done.

09:46:28

Q. Well, that's actually my next question. If they're washing out all these drugs, can things happen during that time?

09:46:46

A. Yes, of course. I think we now recognize --

MR. BAYMAN: Your Honor, this case is not about withdrawal and discontinuation. This is getting far afield.

THE COURT: Overruled.

09:46:56 You may proceed.

BY THE WITNESS:

A. We now recognize that at the washout period although it's only one or two weeks, when people go into this period it's usually only for a week or two. It isn't that we keep you off, 09:47:11 you know, the pills you've been on for ages, it's just off a week or two that you're going through this period. And during the washout period, you may be put on a placebo pill. All the people going into the washout period may be given a pill while they're in the washout period but it's a placebo pill.

09:47:30 Q. Okay. Is there other terms used to describe the washout period?

A. Yes, it can be called the run-in period.

Q. Okay. All right. So then we go past the washout period and now we're -- now we have less patients. Do you see that, 09:47:48 doctor?

A. I do, yes.

Q. Why is that?

A. Well, it may be that there are some people who drop out at that point. They come in and they get baseline screening and 09:48:02 they don't come back for to the next screening which happens

before you enter the actual trial.

There's two screenings, at least, that happen before you go into the trial proper. One is when you come along first and you're told about the trial and you agree to get involved, I may do some rating scales on you. Later on, after you've been through the washout period, before we actually randomize you to the new drug or placebo, there would be a further screening, and that's usually taken as the most important baseline screening.

09:48:32 Q. Okay. So now we have fewer patients here. And I marked here -- we've marked here that some of them are red. Do you see that?

A. I do, yes.

Q. What does that reflect, doctor?

09:48:43 A. Well, here in this case, for instance, there may be in the mix of people going into an antidepressant trial, and for most part, these are going to be out-patient primarily care people. They're not going to be severely depressed, they're not going to have melancholia, for instance. These are people who won't

09:49:03 actually be suicidal.

So the blue figures here refer to people who meet the criteria for being depressed, but may not be actually suicidal. And the red people may be in the mix. We've got some people who are more depressed are maybe not obviously more depressed,

09:49:18 but who are somewhat suicidal.

Q. Okay. And then we get to this next phase. So we got a group of people, they get screened, they go through the washout, and now we have less people, and then they go to this next phase of randomization or randomized; what is that?

09:49:36 A. Well, that's the point where the person ends up either on the new treatment, or the placebo, or maybe even one of the older treatments.

Q. Now, when you're talking about side effects or adverse events that might've happened during a placebo controlled

09:49:56 trial, at what point do you start looking at the side effects that might be associated with the drug?

A. Well, there's all kinds of debates about these things. And you can get into angels on the head of a pin debate about this things about where you should begin to check these things out,

09:50:13 but the usual thing is, from the point of randomization, from the point where you go on one or other of the treatments, whether either active treatment or placebo.

Q. Is this also referred to as the baseline?

A. Well, they've been through -- yes, at the points they've

09:50:28 been baseline-screened and, you know, take some pills away with them that day to begin at home maybe that evening or else the following morning.

Q. All right. So let's go back, let's go down to the second part here.

09:50:42 So after they've been randomized, we have these two

groups here, doctor. Do you see that?
A. I do, yes.
Q. And again, I see there's these two red people in each of these groups. What does that reflect?
09:50:51 A. Well, again, prior to the treatment actually beginning, there may be a few people in the group who are on the Hamilton ranking scale will turn up as having some suicidal ideation. That doesn't mean that they're going to kill themselves in the next week or two, it just mean having thoughts -- well,
09:51:13 thoughts like they wished it were all over.
Q. Okay. Now, you have these two groups. One group appears to be given the drug, is that right?
A. Yes.
Q. And the other group is given a drug too, but are they given
09:51:26 a natural drug?
A. No, they've given a drug that looks identical. I mean, you got two drugs that will look totally the same. The active drug and the placebo going to look identical.

So neither I handing the pills over to you nor you,
09:51:42 unless you do things like chop the pill open and check it out in ways. I mean, you know, it would be more than look at it. You'd have to do some chemical tests on it to try and find out if it's got some active drug in it rather than just whatever they put into a placebo, but they'll look both the same.
09:51:59 Q. Now, the placebo pills, what, generally, does go into them?

Is there any sort of medication in them?
A. No, there isn't.
Q. Okay. Have you ever heard of the phrase sugar pill?
A. Yes.
09:52:13 Q. Where does that come from?
A. Well, I'm not sure of the actual -- oh, where that word came from first, although the placebo was invented over here in the United States and was first used in trials of Coca-Cola, so it may be linked to that.
09:52:31 Q. Okay. All right, so then we observe the effects. And so this is one of the things, in these depression trials that we're talking about or just clinical trials for Paxil, how long do they observe the effect for?
A. It can be anything from 4 weeks. Some of the early SSRI
09:52:51 trials only lasted for 4 weeks. Most of them lasted 6 weeks. Some of them went on a bit longer, went on to 8 weeks. And a very, very few of them went on longer than that.
Q. Why are they so short?
A. Well, what the -- what's -- what the trial is aiming to do
09:53:08 is not to check and -- not to find out everything there is to be known about the drug. And in particular, it's not aimed at trying to work out what the adverse effect profile of the drug is. It's really aimed at trying to say can we see if this drug works or not.
09:53:28 And from that point of view, it had seemed

particularly based on the older antidepressants, which were very effective for severe mood disorders and often got people well within 2 or 3 weeks. It seemed that 6 weeks was a safe bet for us to be able to tell if the kinds of changes linked to
09:53:46 people getting better were happening or not.

Now, those changes aren't conclusive evidence the drug works. You know, we're not finding out that you actually go back to work or not, we're not finding out that you became more functional or not, we're not actually even finding out that you
09:54:02 just stayed alive or not, we're finding a signal that the drug probably does useful things.

Q. Now, you mentioned earlier in the context of the hand rating scale. How does this fit here in the clinical trial?

A. Well, in the course of a clinical trial, the major focus
09:54:22 for a person like me will be completing a few different rating scales which point to the question of does the drug work or not.

And the most famous of those is a thing called the Hamilton Rating Scale for depression. And that was, first of
09:54:43 all, discovered by a man called Max Hamilton, and he was based over in the U.K. One of the other ones is called the Montgomery Asberg Scale.

But a person like me taking anyone from the jury, say, into a clinical trial would be asking you a bunch of questions
09:54:57 from those rating scales and also getting --

Q. Please continue, doctor. I'm sorry.
A. Also getting you to fill out some forms and getting a sense. I mean, part of what I have to do is to talk to you as well and chat about various different things to get a sense of
09:55:18 whether you're actually improving in ways that the rating scale may not pick up. So I'm being asked for my overall clinical view about whether things are moving forward or not.
Q. Now, are there other types of rating scales?
A. There are. There's a whole bunch of rating scales to check
09:55:37 out -- if, for instance, we were looking at the question of whether you were able to function sexually or not, there are rating scales to check that out. If we're interested in the issue about whether you are becoming suicidal, well the Hamilton has one item on it to emphasize to a person like me
09:55:58 that, you know, it's not just whether the drug is doing good things that's of interest to the person running the actual trial, but also we want to know more about this particular problem, then you'd include a suicidal ideation rating scale too. And there will be a bunch of questions on that, perhaps
09:56:14 20 odd questions or so, and the idea is for me to go through these with you.
Q. Is using a suicidal ideation scale an effective way to see if there is suicidal ideation?
A. Well, if you're interested in this aspect of what happens,
09:56:33 then you can't really explore it using the Hamilton scale or

the Montgomery Asberg scale, you have to introduce a new scale, both because it has far more questions, but it also gives me the message that this is an important thing that we need to be keeping an eye on.

09:56:49 The message usually is, does the drug work, keep an eye on that. And while I'm keeping an eye on that, I can miss the fact that most people taking an SSRI, well, you know, they're not functioning sexually in the same way as they were before they went on the SSRI. That can be missed completely.

09:57:09 In the course of these clinical trials, the data that came out was that these drugs have an intact on how you perform from a sexual point of view 5 percent of --

MR. BAYMAN: Your Honor, objection to sexual side effects. Again, this is far afield of what this case is about.

09:57:24 THE COURT: Overruled.

Proceed.

BY THE WITNESS:

A. No, it's just I'm simply trying to bring out things that are happening to everybody that goes on the pill that maybe 09:57:34 were missed completely, that someone like me may only pick up 1 in 20 of the problem happening even though there's a question on the Hamilton rating scale that would direct me to check these things out with you.

BY MR. WISER:

09:57:47 Q. Now, you mentioned the suicidal ideation scale that

could've been used. Was there ever one of those used in a GlaxoSmithKline trial?
A. Not that I'm aware of.
Q. Okay. Do you know why that it is?
09:58:03 A. I'm not really here to offer a view on that.
MR. BAYMAN: Your Honor, objection. That calls for speculation.
THE COURT: All right. Sustained.
Proceed.
09:58:11 BY MR. WISER:
Q. Were these clinical trials meant to look for suicidal ideation?
A. No, they weren't.
Q. So I guess my question, doctor, then is, considering that
09:58:21 the trials weren't meant to locate this risk, are they the best source of data to determine that there is a risk?
A. No, they aren't.
Q. All right. Now, let's say during these clinical trials, and we have this in front of us, a patient makes a suicide
09:58:39 attempt or even commits suicide, what is the investigator supposed to do?
A. Well, I mean, sort of yes, you're actually supposed -- if the patient is actually alive still, you can interview the person and ask what's actually going on, tell me more. If the
09:58:56 person is death, clearly you can't do that. But in either

case, you got to try and come up with a view as to has there been any link between the treatment that you were taking and the outcome, the fact that they have tried to harm themselves or not.

09:59:11 Q. And when you say they have to interview the patient, for example, with a suicide attempt. Well, is a suicide attempt or suicide an important event during a clinical trial?

A. Yes, it is, clearly. It's a major event. And it's one that the companies have to report to at the regulators, for

09:59:28 instance.

Q. And the severity of the event, how does it scale relative, for example, sexual dysfunction?

A. This would be called a serious adverse event where sexual dysfunction wouldn't.

09:59:42 Q. You said one of the jobs of the investigator is to see if it was related to the treatment that they were getting. What is that called?

A. Well, the investigator, and company personnel also, are asked to do a causality assessment.

10:00:00 Now, having asked to do this, often it's done very poorly. In that, for instance, if a person has killed themselves or if they've tried to kill themselves and end up in the hospital and out of the clinical trial, often the investigator may have very little contact with them afterwards.

10:00:18 So when I say the optimal thing is for me, the

investigator, to interview the person to whom this has happened, that doesn't always happen.

Q. All right. Have you, in the context of your investigation, review of the Paxil data specifically, looked at these causality assessment?

A. Yes, I have.

Q. Why did you do that?

A. Well, it's of interest to look at the adverse events that happened through the clinical trials and see what the doctor said, and also see what company personnel also said.

Q. Do you have any opinion about whether or not the investigator who is interviewing the patient at the time of the event has any special insight into whether or not it was caused by the drug?

A. That's a totally complex question, Mr. Wisner. And to give you and the jury a feel for what can happened: Sometimes the investigator is asked of you after the blind has been broken, for instance. And you see cases where the person has been on placebo and the investigator knows this and is then asked whether the placebo has caused the problem or not, and he or she says yes, it has.

So this can be often complicated. It may be the investigator's thinking, well, they weren't on active treatment, and the fact that they weren't on active treatment played a part in the whole thing. So trying to work out what

was in the investigator's mind can be tricky.
Q. But you can see what they wrote down, right?
A. Yes, you can.
Q. These investigators, who hires them?
10:01:54 A. Well, in the course of a clinical trial that's been run by one of the pharmaceutical companies, it will be the pharmaceutical company. Although, these days there are specialist companies that run trials for all the pharmaceutical companies. So there are clinical trial companies and they're
10:02:14 the ones who would usually hire people now.
Q. For example, in the Paxil clinical trials, did GSK have a right to make sure that the investigators that were working on these trials were qualified?
A. Well, yes. And I think it would be assumed that they were.
10:02:29 And certainly having been involved in SmithKline Beecham clinical trials, it was at a point when SmithKline Beecham weren't running the long trials. They didn't have this contracted out to any other companies and they would check them. And presumably, be happy that a person like me had the
10:02:48 qualifications that I needed to have to be involved in one of their trials.
Q. And so you actually worked as an investigator for the defendant?
A. Yes. So I'm not actually just talking about things in the
10:03:02 abstract, I'm giving you a feel for what I've seen actually

happen.
Q. And when you were working as an investigator, did you work on Paxil?
A. Yes.
10:03:10 Q. And as part of your work, did you receive training from the defendant?
A. Well, as part of the work, one of the things that needs to be done is to convene all of the investigators together and check and ensure that the way they're rating, say, a rating
10:03:29 scale, like the Hamilton scale, is much the same for each of them.
You don't want a person like me and most of the group to be interviewing the patient and coming up with one score and a completely different person coming up with a totally
10:03:44 different score. You want to try and ensure that the group, as a whole, is reading things the same way.
Q. And based on your experience in that, I mean you were there, were these investigators pretty qualified?
A. Based on my experience, I would say that they weren't
10:03:58 always wonderfully qualified.
Q. Okay (laughing.) Well, that said, I'd like to turn your attention to Exhibit 263 A in your binder there.
(Brief pause).
BY MR. WISNER:
10:04:28 Q. Do you recognize this?

A. Yes, this was the kind of document that would have been in the package. I mean, during the course of doing a trial for GSK, I might have a big folder, a little bit like this one (indicating), one with a bunch of tabs, and one of the tabs would point to a page like this (indicating).

10:04:41

Q. All right. Now, before we show it to the jury I just wanted you to look through it.

Now, we have in here, if you look through the pages, doctor, it's a compilation. It's a subset of a larger exhibit.

10:04:58

And as you see here, do you see there's some causality assessments?

A. Yes, I do.

Q. And these were documents produced by the defendant, is that right?

10:05:02

A. Yes.

Q. And these are documents that you have reviewed?

A. Yes.

Q. And you considered them in part of your analysis?

A. Yes, I did.

10:05:07

Q. And these specifically relate to Paxil?

A. They do.

MR. WISNER: All right. At this time, Your Honor, permission to publish portions of Plaintiff's Exhibit 263 A to the jury.

10:05:17

THE COURT: You may proceed.

(Exhibit published to the jury.)

BY MR. WISNER:

Q. Doctor, when we talk about causality assessments, I want to talk about what they first mean.

10:05:24 So we have here four terms. Do you see that, doctor?

A. Yes, I do.

Q. And to be clear, this is a document that GSK created, is that right?

A. Yes.

10:05:30 Q. All right. So we have the first term here, "related."

A. Yes.

Q. It says:

"There is a direct cause-and-effect relationship between the adverse experience and the study

10:05:41 drug."

Do you see that?

A. Yes.

Q. What is your understanding of that?

A. Well, that's where GSK, either the investigator in the

10:05:53 clinical trial but also with the GSK person agreeing, or else the GSK person, will have looked at what happened in the course of -- at the trial, and based on things like challenge, de-challenge, re-challenge, dose responsiveness, antidote use, and things like that, will have come to the view that the only

10:06:13 way to explain this, perhaps, is that the drug has triggered

the problem.

Q. You mentioned this in the context of the blue feathers example; do you remember that, doctor?

A. Yes.

10:06:21 Q. Can you explain how that would be done for the related assessment for the blue feathers.

A. Well, if you turn blue and produced feathers shortly after you go on a new drug, the fact that it happens after you go on the drug is important.

10:06:37 If it was there before, if it was there before you were on the drug, well, then, hey, things are a little more complex. I mean, there are other reasons you could turn blue. I mean, there are real reasons why people can turn a shade blue, which may make it hard to judge whether the pill is

10:06:53 actually causing the problem or not.

But if it then clears up when the pill is stopped, that's very strong evidence that the pill is linked to the problem, particularly, particularly if it's an unusual problem.

In the case of some drugs used for multiple sclerosis,

10:07:15 for instance, FDA have decided, simply on the cases of 3 case reports, that the drug has caused the problem.

Clinical trials are anything. They have said this drug causes that problem. Because it would be so unusual for it to happen without the drug being there.

But in this case, and in your case, turning blue is a

bit unusual. So it would take very few cases for people, you know, to make a tight link. But the kinds of things we have been looking at is, does it happen after you go on the drug, does it clear up when we stop and drug, and is there any real exposure, did it come back again, did it happen on a high dose of the drug as opposed to a low dose or was there any evidence as we build the dose up that the thing got worse, you turned a deeper shade of blue, for instance.

Q. Okay. Well, the next sort of possibility here says, "possibly related." It says:

> "A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but is possible or likely."

Well, what does that mean, doctor?

A. Well, again, this is a step down from the idea that we're pretty certain that the drug has caused the problem, to it looks highly likely that it did.

Q. And then the next one is "probably unrelated," do you see that, doctor?

A. Yes, this is where it's not being out-ruled, but would think that it may not be our drug.

There's a few other -- well, one of the things that a few of the companies, or a few people generally do, is they try and score these things. So that if you've got a score over 10, say, then it's definitely related. Between 10 and 7 probably

related. Between 7 and 4, say, possibly related. And less than 4 we'd say unrelated. And that's a thing called the -- the Naranjo algorithm.

Q. Okay. Without getting into too much detail about those things, the general gist of it is, the assessor makes a decision of whether or not it was related to the drug, is that right?

A. Yes. And in the processes you often have, you know, the company looking at things also and either agreeing or perhaps even overruling.

Q. What do you mean overruling?

A. Well, there can be instances where you have the doctor, for instance, say the blinds been broken and he or she, let's say it's me, thinks that the suicidal act was definitely caused by the placebo, the company might overrule that on the basis of, well, look, placebos don't cause you to commit suicide.

Q. Okay. All right. Let's go down. This is a chart that was produced in this case. It has a listing of -- well, let's go through this.

The first is patients ID numbers, do you see that, doctor?

A. Yes.

Q. What does that refer to?

A. That refers to -- that gives whoever is reviewing the data the code of where to go and find out more about this patient if

they need to. You know, the patients come from a particular clinical trial, like trial 09, or 05, or whatever, and what patient number they were in that trial.

Q. All right. So going through this there is a couple here I just want to give some context for.

10:10:31

Here we have one, a patient, January 14th, 1986, do you see that?

A. Yes.

Q. And this is attempted overdose, do you see that?

10:10:40

A. Yes.

Q. So this is a patient --

A. Yes.

Q. So this is a patient who's on drugs -- on Paxil, sorry.

A. Yes, that's what it looks like.

10:10:48

Q. And there's a causality assessment here, do you see that? It says "definitely"?

A. Yes.

Q. What does that mean?

A. Well, you note that that's not on the previous page. That

10:10:58

means that it's definitely caused by, but it's not one of the codes that was on the previous page.

So, you know, you've got to, in a sense, to be absolutely sure about these things. We'd have to have the patient record to be -- you know, to be clear what we think has

10:11:13

actually happened here. But it seems to be saying definitely

caused by.
Q. Doctor, I looked for the patient record and I couldn't find it, but let's look what we do have.
And we have this listing right here (indicating).
10:11:29 It appears to be the same entry, is that right, doctor?
A. Well, yes, between two different --
Q. You look at the page number.
A. Yes. Yes. Yes.
10:11:46 Q. Same page number.
A. Yes, it appears to be.
THE COURT: Is that page?
BY THE WITNESS:
A. The previous page, Your Honor, it's pulled out from here
10:11:56 (indicating).
THE COURT: From the previous page?
THE WITNESS: Yes.
THE COURT: I got it.
BY MR. WISER:
10:11:59 Q. Okay. And here it says that the patient started January 8, 198- -- I'm sorry. December 20th, 1985, is that right?
A. That's what it appears to be, yes.
And I may have to get my glasses, Mr. Wisner, but let's keep going for a moment.
10:12:18 Q. Okay. Let me see if I can blow it up a little bit bigger.

THE COURT: Go get your glasses, doctor. Looks like trouble here.

THE WITNESS: Okay.

BY MR. WISER:

10:12:25 Q. Is that better (indicating)?

A. That's fine. Yes.

Q. Okay. All right. So it says that it started December 20, 1985, and then they stopped January 14, 1986; do you see that?

A. Yes, I do.

10:12:37 Q. So the patient was on the drug for what, 20, 24 days?

A. Yes, it would appear to be.

Q. Okay. It says, "overdose, attempted overdose," and then it has this causality statement over here on the right, do you see "definitely related"?

10:12:51 A. Yes.

Q. Okay. So who made that "definitely related" statement? Whose decision was that?

A. Well, it may have been the doctor who had put the patient in the actual trial, but it wouldn't get to this stage without

10:13:08 GSK endorsing it.

So whether it's the doctor putting the patient in the trial or the GSK person who was over-viewing what was happening at the actual trial, you know, it would go through those two filters.

10:13:25 Q. So GSK signed off on this, is what you're saying?

A. Yes.
Q. Okay. Let's look at a few more of these because I think I think we have some more better narratives to help illustrate.
Let's look at patient 059-005-003. I'll called it out here.
Do you see that one, doctor?
A. Yes, I do.
Q. This event occurred March 20, 1989?
A. Yes.
Q. And this is suicidal tendency, do you see that?
A. Yes.
Q. What is a suicidal tendency?
A. Well, this is where a person might have suicidal ideation. And the words move around the place a bit. There wasn't -- just like akathisia doesn't always get coded as akathisia, it may be coded as being anxious, agitated, or whatsoever. Suicidal ideation may at times be referred to as suicidal tendency, or perhaps the person has made minor attempts at trying to harm themselves and this might be coded as a suicidal tendency rather than a clear suicidal act.
Q. You mentioned this word "coding," what are you talking about?
A. Well, when people are in clinical trials things happen to them and they report what happens to them. And the doctor, in the first instance, has to report that back. And they'll try

and keep somewhat close to what the patient said to them, but ultimately then things get coded by the company.

There's a whole range difference in like akathisia. This is a tricky state where a bunch of things happened to the patient and the coder is faced with the doctor having reported a string of things happening and might just pick out anxiety, and a different coder might pick out agitation as the best code for this state, or a different coder might pick out hypokinesis as the best coding for this state, or a different coder might say restless.

10:15:03
10:15:23

So ultimately, for the computer to handle these things, it has to sort of be boiled down to one word, and it's not clear that the one word is going to be akathisia. So the same problem may be spread across a range -- or maybe dumped into a bunch of different buckets.

10:15:40

Q. Couldn't that obscure the risk of the event?

A. Yes, it could.

Q. All right. Well, this one is patient 059013. Let me see if I can keep it on the screen while I go to the narrative.

All right. You see here, we have the narrative for patient 059? Do you see that, doctor?

10:15:56

A. Yes.

Q. Okay. Let me use this one (indicating).

All right, so this is a 50-year old female, had incipient signs of -- what is that word?

10:16:09

A. That is respiratory condition where you're left short of breath. It is much more serious problem than asthma, for instance.

Q. Okay. Let's go down here. It says she received Paroxetine 20 milligrams on days zero and 3 and Paroxetine 30 milligrams on days 4 and 6, do you see that?

10:16:34

A. Yes.

Q. What is it called when you increase your dosage like that?

A. Well, that's called an increase of dose. And the dose is titrated up.

10:16:48

Q. Is that a common practice in medicine?

A. Reasonably common. And in the course of a clinical trial, the company may be trying to find out what's the optimal dose for our drug.

10:17:00

There was a lot of indications that a 20 milligrams dose was a pretty high dose to begin with, that is lots of people who do awfully well on an even lower dose than that, but here the dose is getting stepped up from what I would say is a high dose to an even higher dose.

10:17:17

Q. What would prompt a doctor to increase the dose like that? What's the reasoning behind that?

A. Well, this is a clinical trial and it's, as I say, one of the things that's being looked at is what the different dosages do.

10:17:34

So this isn't being done for clinical reasons, this

has been done by computer. This lady might have been on placebo, in which case there would have been no increase in dose at all. I mean, she may have ended up taking more pills, but in actual fact she wouldn't be getting an increase in dose.

10:17:52 So in clinical practice, it's if you think the patient is not improving or maybe even getting worse -- and one of the tricky things bout the SSRIs can be, if on a dose you're looking more agitated a week later, the doctor might think you're getting worse, clinically, and might increase the dose,

10:18:08 which is exactly the wrong thing to do if the drug is causing the problem.

Q. All right. Let's go down. It says, on this narrative down here:

> "... the patient displayed severe suicidal
10:18:22 tendencies preferred term, emotional lability, paranoid reaction and insomnia from day 5 which the investigator considered to be probably related to treatment."

I'll stop right there. What does that sentence mean,

10:18:38 doctor?

A. Well, I think one of the -- there is a whole bunch of things in here, and one of the things is the coding issue that you raised earlier.

Q. Let's put that aside for now. Let's just focus on --

10:18:50 ignore the emotional lability, we'll get back to that later.

A. Okay.
Q. What does the rest of it say.
A. Well, it appears that the patient became severely suicidal from early on in the course of treatment. And the investigator
10:19:04 considered it to be probably related.
Now, on the previous -- I mean, this is where sort of the jury could get misled a bit in that in the previous page, probably it's linked to unrelated, but here it's been linked to related, and the investigator is saying that it's probably
10:19:25 related to treatment.
Q. Okay. Well, "paranoid reaction insomnia," what does that tell you, doctor?
A. Well, these are among the things that I indicated to you earlier can be caused by the SSRIs. They're an interesting
10:19:43 group of drugs. And as I said, it's like putting ink into water. Some people will find they can't sleep on them, so they take them first thing in the morning, other people will find if they take them first thing in the morning, they get drowsy on them, so they take them last thing at night. These drugs can
10:20:01 have a big effect on whether you're able to sleep or not.
In randomized controlled trials, one of the problems can be, the company can end up concluding these drugs do nothing to your sleep because they average out the effects. You know, you're eyes are unable to sleep, or you're
10:20:15 over-sleepy, and if we average them out, well, these drugs are

doing nothing to your sleep, and that's clearly wrong.

In a sense, randomized controlled trials are slightly dumb. They can do great things, but they can come up with terribly bad answers also.

10:20:29 And in this case, we have a lady who is having some of the classic reactions that can happen when an SSRI goes wrong, which include being unable to sleep because she's agitated, and as I said, it can also cause decompensation and people can become psychotic. Well, this is a good instance of this, this

10:20:48 lady is becoming paranoid.

Q. Now, the fact that she's 50 years old, does that have any bearing on your assessment of whether or not it was drug induced?

A. No. And it wouldn't have any bearing on anyone's actual

10:20:59 assessment of it at this point in time when this trial was being done.

Q. And the fact that she had only been taking it for about 5 or 6 days, does that have any bearing on whether or not it was drug induced?

10:21:13 A. No. That fits in -- I mean if she's been doing awfully well for weeks and weeks and weeks and then the problem appears and there's no change of dose or anything like that, then I'd be inclined to think it's not linked to the pill, but this is a point closely related to the point when she took the drug.

10:21:27 Now, there are other things in her case which makes

this a little more -- more -- more complicated, but there's a good case, you know, for saying that the drug may be linked here.

Q. All right. And then the last sentence part here, it says:

10:21:47 "... the emotional lability was considered to be serious as it was incapacitating, life threatening, and long hospitalization."

Let's take a stop right there. What is emotional lability?

10:21:58 A. Well, first of all, in this context, it's a coding term. In real life it's something different. When a person becomes emotionally labile, it would mean to the average person who reads books and things like that are, to the average doctor, we actually describe people as becoming emotionally labile, which

10:22:26 would mean their emotions are all over the place. Are they swinging from being happy one minute to being sad the next, you know. There may be a little bit Mediterranean use is what the English would say, okay.

Q. (Laughing).

10:22:38 A. I mean, the English don their feelings. So anyone else, you know, when they swing a little bit upward, swing a little bit down and they're emotionally labile.

But here it's been used as a coding term, which is quite different. It doesn't mean that you're -- that your

10:22:54 moods are going a bit high or a bit low. That's your -- that's

your expressive. It's a coding term under which suicidal reactions are being put. So the coding -- the people who are doing the coding have an option to code this as suicidal, whether it's been coded as emotionally labile.

10:23:18 Q. Let me ask it this way, if a doctor were to say, oh, I have an emotionally label -- label --

THE COURT: Labile.

MR. WISNER: Labile. Thank you.

BY MR. WISER:

10:23:29 Q. -- labile patient, would that indicate to you that they had incapacitating, life threatening suicidal tendencies?

A. No, I would think a person who was possibly likely to be pretty expressive and might storm out of the office, and things like that, but it wouldn't -- but, you know, I think that,

10:23:50 well, this is the kind of person that often, you know, will make gestures but they won't do anything serious.

Q. Okay. Let's look at a few more of these. I don't want to spend too much time on this. This is another patient here.

We have patient number 059 -- by the way, doctor, I

10:24:07 have some reading glasses. Do you want them?

A. No, that's okay. That's fine. I have my own reading.

Q. Okay. This 55 year old male patient had -- what is that?

A. That's an unusual condition. That's where you've got pain down in the testicular area.

10:24:28 Q. Okay. How did you say the word?

A. Didymodynia.
Q. Okay.
A. I'm sure there are different ways to actually pronounce it.
Q. All right. So we have a patient that's 55 years old with
10:24:43 these various conditions. I don't want to get into that.
Let's look at the part that's relevant here. He received
Paroxetine, 20 milligrams on days 1 to 3, and Paroxetine 30
milligrams for further 10 days; do you see that?
A. Yes.
10:24:53 Q. Again, what does this convey to you?
A. Well, just that he's gone on Paxil and that the dose has
been put up.
Q. And how long has he bee on it for here?
A. Well, he's ultimately been on it for 2 weeks, roughly.
10:25:07 Q. Okay. All right. So let's go down to the bad part. It
said:

> "The patient developed moderate moderate agitation from day 2 for 4 days. This had become severe by day 7 and continued for a
10:25:23 further 7 days. By day 12 the patient had developed severe suicidal tendencies. Preferred term, emotional lability. The patient was withdrawn on day 13 because of these adverse events and lack of effect. All events were
10:25:40 considered by the investigator to be possibly

related to study the treatment."

Do you see that, doctor?

A. I do, yes.

Q. What does this narrative show you?

10:25:47 A. Well, that's again showing what a lot of people would say, would have said is the classic picture of an SSRI induced problem, that you can become agitated after you go on the drug, and it can happened within 3 or 4 days of going on drug. And as the dose goes up, it becomes more severe. This is all

10:26:09 happening in the classic timeframe that people have thought these reactions are most likely to happen in.

Q. Now, this idea that day 2 you have agitation, day 4 it gets more severe, and then finally it develops, day 12 into severe suicidal tendencies. Is that sort of progression, declining

10:26:34 progression something you would expect to see in an SSRI -- forget SSRIs, a Paxil induced suicidal event?

A. Yes, it is. A person can become acutely suicidal right from the start or you can see the kind of picture you see here where it's building pressure-cooker-like to the point where

10:26:53 unless something is done, you figure that the -- that the situation is going go very badly wrong.

Q. Now, as that pressure cooker is building, would you expect to see a physical manifestation of akathisia or an agitation all the time or would it come and go?

10:27:11 A. It may come and go. And the other thing is, it may be more

obvious retrospectively than at the actual time. And that the doctor may not be focused on it and the patient may still be hoping it goes away, so they don't verbalize it quite as much as they might afterwards and said, look, I should've told you about this earlier.

Q. Okay. All right. Well, let's move on to something else I want to get at.

You mentioned earlier that there can be problems by missing stuff that, in your opinion, was akathisia but was coded as something else; do you remember that?

A. Yes.

Q. All right. Let's look at we're on to the 9th page in your document. They're not numbered. It has the Bates Stamp 481 at the bottom.

A. Okay.

Q. Are you there, doctor?

A. Yes, I am.

Q. Okay. So this appears to be an individual patient summary of signal safety data, do you see that?

A. I do.

Q. What does that title mean?

A. Well this is, again, it's referring to a single case, and it's talking about issues where there appears to be a safety signal.

Q. Now, it says right here the adverse event and it's all

capitalized, "unrest agitation," do you see that?
A. Yes.
Q. Are those the codes?
A. Well, they are two of the codes that will be often used for
10:28:40 akathisia. As I say, the coders -- I mean, it a tricky thing.
You know, you don't want to -- I mean, I'm not saying the
coders are doing this deliberately. It's simply that faced
with text, and they're often asked not to think too much, just
to code every little bit of what they see with what seems to be
10:29:01 the best word. The problem is, they don't always come up.
If they're not thinking akathisia, and they're not
trained to think akathisia, they aren't all going to put the
same word on what they're seeing.
Q. All right. So then we have some facts in here. We have
10:29:17 the start date was October 27th, 1992; do you see that?
A. Yes, I do.
Q. The stop date was November 7th, 1992.
A. Yes.
Q. And then we have the onset date was the 30th of October
10:29:29 1992; do you see that?
A. Yes.
Q. What does that tell you for how long the patient was on the
drug?
A. The patient was on the drug for 3 days when the problem
10:29:37 begins.

Q. Okay. And then it says "related," do you see that?
A. Yes.
Q. Again, is that a causality assessment?
A. Well, this is one where if you go back to the page you put
10:29:49 up first where they said "related" means "definitely linked to," yes.
Q. Okay. And if we go to the next page, it actually has a narrative of this event. We have some more information, it says:

> "... patient developed unrest agitation. The patient recovered. She received Paroxetine 20 milligrams daily for 12 days. Physician relationship related, manufacturer's relationship possibly related."

10:30:19 So I want to sort of unpack what's happening here. First, it says that the patient recovered. Does that have any significance to you?
A. Yes, it does. Clearly, if the problem begins happening after you go on the pill, it's a strong case for saying that
10:30:34 it's linked to the pill. And both the doctor and the patient are usually agreed on this.
If, for instance, you go on the pill and you get nauseated, no one has ever argued that the patient is wrong when they say they're feeling nauseated. No one has ever
10:30:51 argued when the doctor says that, you know, I think the nausea

is linked to the pill. The arguments come when it's a trickier area like this. And, you know, where -- and it is the case that people who are depressed can be suicidal, but, you know, you're in the business of being doubtful about the patient, which isn't a great thing to be doing. It's -- it's -- you know, if you're concerned about patient safety, it's not actually the best approach to be taking.

Q. Well, no, but the fact that it cleared up after she stopped the drug, what does that tell you?

A. Well, yes, the point I'm making is that it was a very strong case simply when the doctor reports that it's related, it becomes even stronger when she holds the pill and the problem clears up. This is what appears to have the doctor to make quotes quite a strong statement that it's related.

Q. How does this relate to a challenge, re-challenge, de-challenge approach?

A. Well, you just seen the challenge de -- the challenge, de-challenge bit, we don't have the re-challenge bit here at all, but, you know, you don't really need it.

Q. All right. Then it goes down here and it says:

"The physician who is treating the patient stated it was related but the manufacturer ... "

and who is the manufacturer here?

A. This is GSK.

Q. Okay. They determined it's possibly related. Are these

divergent views about the cause and effect of this particular side effect?

A. No. If you recall the first page that was put up, "possibly related" is actually quite a strong link also.

10:32:30 Q. Now, why does the manufacturer have the right to come in and say to the doctor who is on the ground, well we don't think it's that related, it's only possibly related? How does that work?

A. Well, again, you'd have to go back and check the details of

10:32:45 the actual case and interview the person and, you know, the company who thought there were reasons why this isn't absolutely related.

I mean, there's a few different things here, but it isn't always the case that it goes like this. It can go the

10:33:02 other way around. The doctor may say possibly related and the company person can say definitely related.

Q. All right. Here's another one. We'll do this one quickly. This is another patient:

> "... restlessness, tiredness, obstipation,
>
> 10:33:25 visual disturbance."

Do you see that, doctor?

A. I do, yes.

Q. And again the relationship to the study drug, pretty clear it's related, do you see that?

10:33:31 A. Yes.

Q. All right. Let's go to the narrative which is on the next page. Let's see if there's any new information.

It's a 59 year old man participating in drug monitoring while under treatment with seroxat, 20 milligrams. What's seroxat?

10:33:45

A. That's the U.K. tradename. So this is happening over in the U.K.

Q. And tradename for Paxil?

A. Yes.

10:33:53

Q. Okay:

"... experienced restlessness, tiredness in the evening obstipation."

What is obstipation?

A. Constipation. People who may be too polite to use the word constipation.

10:34:07

Q. Okay. Forgot, this is in the U.K. Okay:

A"... and visual disturbances on set date, not specified. He is reported to have recovered. Relationship per investigator probable, per manufacturer possible. "

10:34:15

Now, I'll step back for a second and ask you, visual disturbances, what is that?

A. Well, this is one of the things that SSRIs can do. It's one of the under-recognized things that there's a significant number of people who get an SSRI who report visual problems

10:34:30

when they're on the drug. It can be a thing that's most obvious when you're trying to drive your car at night. It's almost a night blindness type thing.

Q. And again, these other restlessness, tiredness in the evening, do these indicate anything to you?

A. Well, no, this is, again, part of the classic profile, that the person is restless, at the same time they're tired, fatigued. They may not be able to sleep all that well, and if they do sleep they don't get refreshed by it.

Q. And says right here he's reported to have recovered. Again, is that helpful to establishing causality?

A. Absolutely. If the problem happens soon after you go on the pills and it clears up when the drug is removed, that's a very strong case that the drug has caused the problem.

Q. All right. Now, here's another one that wasn't on the list that we talked about earlier as related things, but this is a patient 1160070198, and it says up here:

> "Adverse experiences leading to withdrawal, insomnia, constipation, delayed or absent organism."

Do you see that?

A. Yes, I do.

Q. Now, just reading that right there, would you have any idea this person experienced akathisia?

A. Not necessarily. The insomnia might led me to the fact

that this is a person also having akathisia in that one of the ways the patient can express the problems is that they're just not able to sleep at night, but, you know, without having more detail, it will be hard to know.

10:36:25 Q. All right.

A. Just -- just quickly put it this way: People often talk about an activation syndrome, and that's one of the other ways akathisia gets referred to. And part of the activation syndrome that we look for is, well, what's the person's sleep

10:36:41 like. And if it's poor, then, you know, we be on the lookout for the fact that they might have a possible activation syndrome.

Q. Okay. But insomnia doesn't necessarily mean akathisia, although it is a symptom of it?

10:36:56 A. It can be linked to it, yes.

Q. Okay. All right. Now, if it said right "here akathisia," that would be clear that it was akathisia, right?

A. Yes.

Q. Okay. Let's go into some of the specifics here. This is a

10:37:12 37 year old Caucasian male with a 3 year history of obsessive compulsive disorder, do you see that?

A. Yes.

Q. It says that he'd been hospitalized once and even received psychotherapy, do you see that?

10:37:23 A. Yes.

Q. All right. Let's go down to the bottom part. It says:
"... on day 1 of Paroxetine 20 milligrams dose, patient developed severe akathisia. This event continued throughout the study. After 1 week, the study medication was increased to 40 milligrams daily per protocol."
I'll stop right there.
This statement that he was having severe akathisia, is that reflected in the terms that we looked at the top?
10:37:54 A. No, it's not.
Q. Is this an example of the terms not capturing a symptom or side effect that might be happening in the study?
A. Well, I think people who train coders would be worried that the coder hadn't coded this, that it had gone missing. Maybe
10:38:15 it was coded but it just -- you see, one of things that we may be seeing here, up at the top is you've got adverse experiences leading to withdrawal, which isn't quite the same thing as telling you all the adverse experiences the person had.
It may be that the doctor or the company at the end of
10:38:34 the day said, look, the things that we're going to withdraw the patient on the trial for is because of these. That's not quite the same thing as saying akathisia.
But in the course of this the akathisia is gone missing, and if I'm trying to look at what caused the patient
10:38:50 to drop, or all patients to drop out of the clinical trials

say, I may miss the fact completely that this patient had akathisia.

Q. Well, let's read through this narrative. It says:

"... after 1 week the study medication was increased 20 milligrams daily."

10:39:05

Now, just as a practitioner, if you had a patient who started immediately having akathisia, actually severe akathisia at the beginning of the dose, would you double the dose?

A. Well, again, this is a clinical trial, I think. So we're not looking at the usually thing that would happen, but in clinical practice, if I gave an SSRI to anyone here in the court and they had a reaction like this, this will be the kind of state where I would be saying to them, look, we really should have you on a completely different kind of drug.

10:39:20

Q. All right:

"... that day the patient developed severe constipation which resolved 2 months later after corrective therapy. The investigator gave a report the adverse event was probably related to the study medication."

10:39:37

10:39:50

So it appears the investigator has made an related assessment, is that right?

A. Yes.

Q. Okay:

"..also on day 1 the patient began experiencing

10:39:56

moderately delayed or absent orgasm and moderate anxiety."

Now, you know, this patient has obsessive compulsive disorder, is that the same thing as anxiety?

10:40:10 A. Not quite, no. OCD, there's a lot of people who think it's a form of anxiety, there's a lot of other people who say, no, it's a different disorder. It's one of the conditions that SSRIs can be quite helpful for, and, arguably, they're better for this condition than they are for treating people who are

10:40:29 depressed.

Q. I don't understand, doctor. How can a drug which treats anxiety precipitate anxiety?

A. Well, it's not -- I mean, as I said to you, you can potentially treat the sleep problems that some people have by

10:40:44 putting them on an SSRI because some people feel very sleepy on them last thing at night, but others aren't able to take them at night, they have to take them in the morning because they aren't able to get to sleep with them.

So we come back to the point that, you know, we're

10:41:00 giving a drug that acts on the serotonin system, it's not necessarily going to be angiolytic. If we do things right, we may get the antianxiety effect that we want to get out of it, but there's going to be lots of people who will react almost just the opposite way.

10:41:15 Q. Okay. It goes on:

A"... the anxiety results spontaneously after 1 week; however, the difficulties with orgasm did not resolve until study medication was discontinued for about 3 weeks due to the ongoing akathisia ..."

I don't have the rest of the document, so I don't know what the rest of that sentence says, but this idea of the anxiety spontaneously disappearing after a week, is that consistent with your understanding of habituation?

10:41:44 A. It can be, yes. And we need to know more about what's actually going on here. You know, the patient may be given other drugs, but it is consistent with that, yes. There are people who will become very akathisic, and if you stay in there, the thing will clear up.

10:42:05 Q. Okay. All right. Doctor, we just spent some time going through some very specific examples of patients in clinical trials. Have you actually had a chance to look at the overall results of clinical trials conducted by GSK on Paxil?

A. Yes, I have.

10:42:21 Q. And why have you looked at all that information?

A. Well, in part because it seemed to be awfully obvious through to the end of the 1990s that cases like this and clinical views and company views about what was going on was the best way to determine cause and effect.

10:42:43 But as of the end of the 1990s, the companies making

SSRIs said, oh, the clinical trial data is really important, and that's really what the court needs to pay heed to and not to anything else. So it was that that led me to say, well, okay, let's see if I can find out about the clinical trial data.

Q. Are you aware whether or not GSK conducted an analysis of their clinical trial data in 2006?

A. Yes, I have.

Q. Have you reviewed that analysis?

A. I have, yes.

Q. And why did you review that analysis in 2006?

A. Well, I reviewed a lot of GSK's efforts to look at their clinical trials from 1989 through to -- to 2006. And it's been of interest to just see how they've been handling the issues the whole way through.

And the -- the -- the -- hang on a second. The 2006 one was of interest because it became linked to a document in which the company seemed to be conceding that the drug can cause people to become suicidal.

And a lot of people were interested in that. And a lot of different authors went and looked at the data, just at the same time that I did, and came to the same conclusion. And we saw the articles and this was all about that. That group took this data and came to the conclusion that this points to a strong link between Paxil and people going on to a suicidal

act.
Q. All right. Doctor, let's take a look at that 2006 analysis by GSK as it relates to Paxil?
MR. WISNER: Your Honor, permission to publish Exhibit 9 to the jury which I believe has been admitted into evidence already.
10:44:38
THE COURT: All right. You may proceed.
MR. BAYMAN: Your Honor, I don't think it's been admitted into evidence yet.
10:44:48
MR. WISNER: Well, at this time, Your Honor, I move Exhibit 9 into evidence as Plaintiff's Exhibit 9.
THE COURT: You may proceed.
MR. BAYMAN: I just don't think that's a complete exhibit, Your Honor. I mean, obviously this is our analysis,
10:45:00
so I would just ask that if it's going to be moved into evidence, it be the entire document.
MR. WISNER: This is what we discussed in pretrial conference, Your Honor --
THE COURT: No, you can bring that up later if you
10:45:10
wish, sir.
MR. BAYMAN: Okay.
THE COURT: But, as you know we're burying the jury with a lot of material and I'm trying to eliminate as much as I can so that we can deal with it. But I do understand your
10:45:21
objection and you can raise it later and you can bring it in

later if you find something that ought to be considered.

MR. BAYMAN: Thank you, Your Honor.

THE COURT: All right. Proceed, please.

(Plaintiff's Exhibit No. 9 was received in evidence.)

BY MR. WISER:

Q. All right, doctor, we're looking at Exhibit 9, Plaintiff's Exhibit 9. I'll let you know this has 58 pages in it.

A. Yes.

Q. How big is this document in actuality?

A. Oh, it's huge. It's a folder that isn't quite as big as this, but nearly (indicating).

THE COURT: I think that's why we have this --

MR. WISNER: Yes.

BY MR. WISER:

Q. All right. Let's go through this little bit. The front here is, we have something that I think we'll come to recognize, we have on the right here the GlaxoSmithKline logo; do you see that, doctor?

A. I do.

Q. And this indicates that this document is coming from who?

A. From GSK.

Q. All right. And it's addressed to, it looks like, Thomas Laughren, do you see that?

A. I do, yes.

Q. Who is Dr. Laughren?
A. Dr. Laughren was one of the key people within FDA who was responsible for drugs acting on the central nervous system, so that includes drugs used for mental health purposes, and some other drugs used for neurourological purposes.
10:46:27
Q. Are you familiar with Dr. Laughren's work?
A. What do you mean by Dr. Laughren's work?
Q. Well, are you familiar with his time at the FDA?
A. Yes, I am. He is a -- now that I've got introduced to probably 15 years before this and I've seen him at FDA on a few occasions.
10:46:48
Q. Now, because Dr. Laughren is working at this division of psychiatry products, is he overseeing the approval and the review of other drugs besides Paxil?
A. Yes, he is.
10:47:11
Q. What about other SSRIs, is he overseeing those?
A. Yes; he was actually involved in those also. I think he may not have been overseeing Prozac, for instance, and he may not have been the senior overseer for all of these drugs, but he was reasonably high up the food chain within the FDA.
10:47:31
Q. We've heard that Dr. Laughren has played a role in the approval and review of every single SSRIs that's on the market in the United States today.
A. That's probably the case.
Q. All right. This is dated April 5th, 2006, doctor, do you
10:47:43

see that?
A. I do.
Q. And you've reviewed this document, obviously, as part of your analysis. I want to just look at a couple of things here so the jury knows what we're looking at if they ever have a chance to look at this later.
What are all these things written here (indicating)?
A. Well, NDA refers to New Drug Application. So this is covering the new drug applications That have been made for Paxil for treating people who are depressed principally, and the fact that the pills are made up in different formulations. It comes in controlled release formulations, so that's Paxil CR. And you'll see, if you look through it, that it comes in capsules and it comes in a liquid form also.
So they're referring to all of the applications that have been submitted to FDA over the years covering these various different forms of Paxil.
Q. And if you see in all of them, they say Paroxetine; do you see that?
A. Yes.
Q. Hydrochloride. Is Paroxetine hydrochloride something different than just Paroxetine?
A. No, it's not.
Q. Okay. And also we see here that -- you said it's a new drug application. I want to be clear, does this mean that the

drug has not yet been approved or that it has been approved way before, this is just the same file?
A. Yes, so just referring back to the applications for approval that go all the way back to the late 1980s.
10:49:17 Q. Okay. All right. Let me go to the second -- sorry, the last page of the letter and just call out who this person is. This is Barbara E. Arning, do you see that?
A. Yes, I do.
Q. It states that she's -- who was she at the defendant's --
10:49:36 A. Well, as you see, now I'm not sure I've got quite the same last page as you have--

Well, yeah, it's on the screen --

Q. Doctor, it's on page 4.
A. Ah, good.
10:49:51 Q. It's an attachment after the letter.
A. Yes. Yes. Yes. Okay.

Well, she's build here as being the senior director for U.S. regulatory affairs, U.S. regulatory affairs psychiatry, and that's within GSK. So she's part of the
10:50:12 regulatory apparatus within GSK.
Q. Okay. Let's go into this letter -- well, before that, what was the context of this letter sent in 2006? What's happening before that with the FDA and GSK?
A. Well, it isn't just FDA and GSK. The FDA 2 years
10:50:28 beforehand have reviewed the pediatric trials and based on that

have said there's a safety issue here that these drugs can make children suicidal --

MR. BAYMAN: Your Honor, now we're getting into the pediatrics again.

10:50:45 THE COURT: Well, yeah. Summarizing it is not the best way to proceed here. Sustained.

MR. BAYMAN: Thank you.

THE COURT: Just go to the point in the letter that you want the doctor to talk about.

10:50:54 MR. WISNER: Yes, Your Honor, I just --

THE COURT: Not summarized in a way that it would be found objectionable.

MR. WISNER: Okay. Yes, Your Honor.

BY MR. WISER:

10:51:07 Q. Putting aside the pediatric issue, that led to what?

A. FDA are asking all companies, including GSK, to submit their adult data so that that can be reviewed from the point of view of whether there is a safety issue: Do SSRIs, do antidepressants, does Paxil cause people to become suicidal and

10:51:36 potentially commit suicide.

Q. And when you say "people" you are referring to adults, is that right?

A. Yes.

Q. And at this point it's defined as what?

10:51:44 A. That's from -- from the age of 18 up.

Q. Okay. Now, the point that this letter has been sent, has GSK already submitted all their data to the FDA?
A. Yes. There's been a process that's been ongoing for a period of time. It's been over a year before this since FDA made the call. They got in touch with all of the companies and said, look, we would like you to send your clinical trial data in to us. And there's been a back and forth between the FDA and companies. In this case, this is part of the back and forth between FDA and GSK.

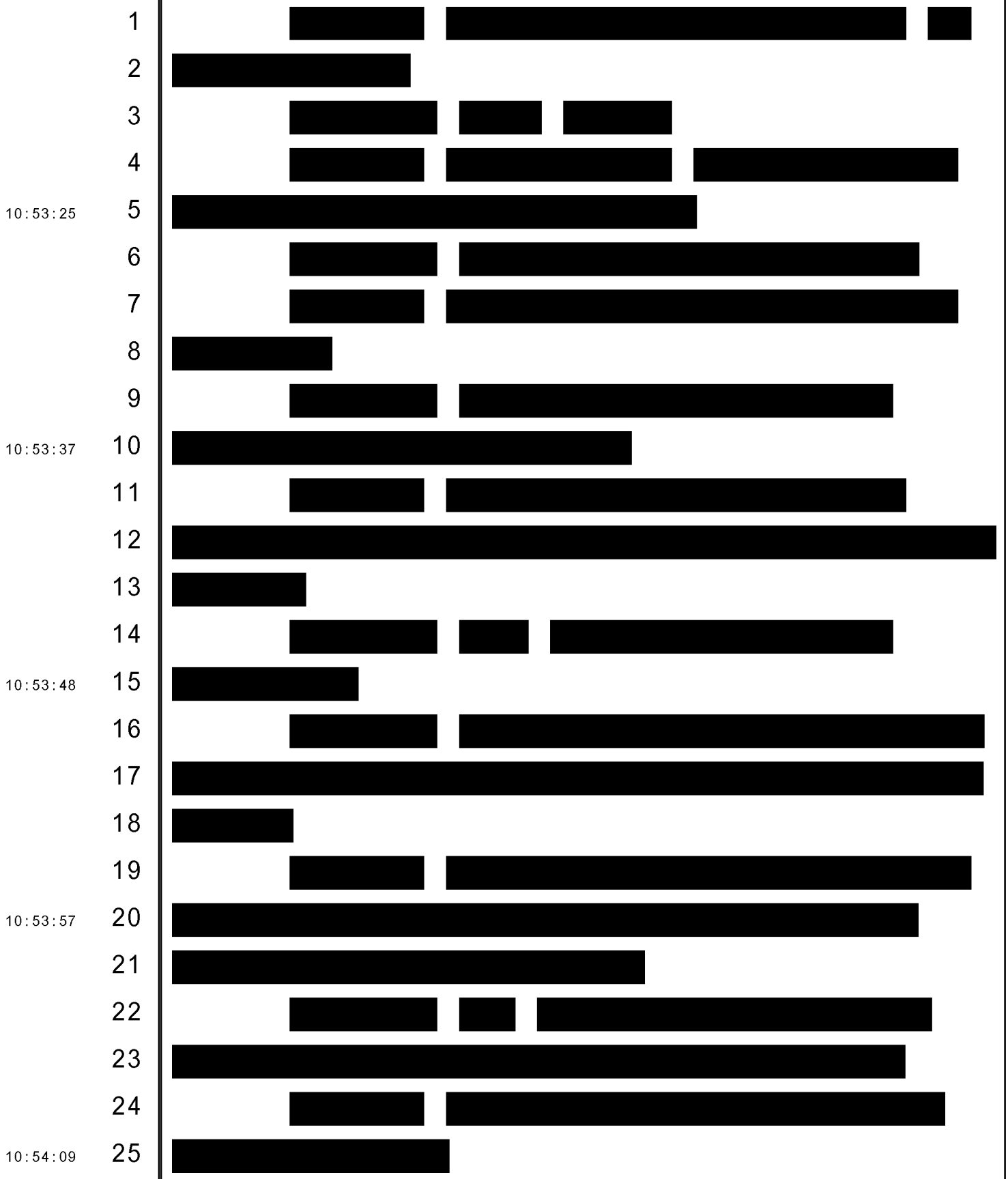
10:52:26 THE COURT: I'm going to interrupt you now. I'm going to take about a fifteen-minute break, ladies and gentlemen. You may step out of the jury box and into the jury room.

(The following proceedings were had out of the presence of the jury in open court:)

10:52:49 [redacted]

10:52:58 [redacted]

10:53:16 [redacted]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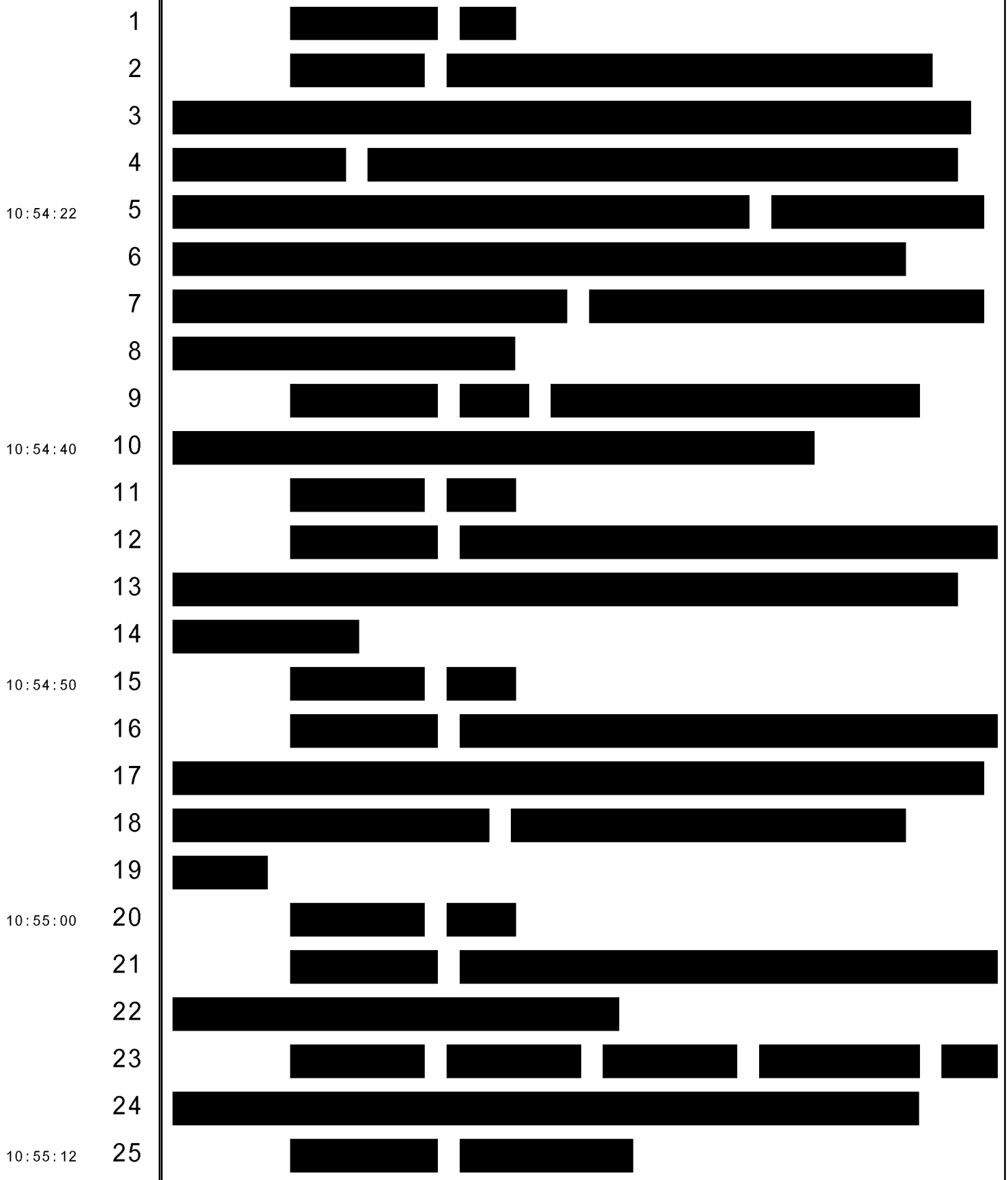
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[redacted]

(The following proceedings were had in the presence of the jury in open court:)

THE COURT: Thank you very much, ladies and gentlemen. Please be seated. We will resume.

You may proceed, sir.

BY MR. WISER:

Q. Doctor, we were talking about Plaintiff's Exhibit 9 just before the break. This is the letter that was sent by GlaxoSmithKline to Dr. Laughren. Just before the break I was

trying to get the context of where we were in this submission and when it was submitted. So it was submitted in 2006. Prior to that, had GSK submitted its adult suicide data to the FDA?

A. On multiple occasions.

11:14:29 Q. You said there was a back and forth with the FDA, is that right, before that?

A. Yes.

Q. And was that about which data would be submitted and which data would not be submitted as part --

11:14:38 A. Yes.

Q. Okay. So at this point, in 2006, this is GSK's submission to the FDA, is that right?

A. Yes.

Q. Okay. Let's look at the letter. There are some -- some

11:15:02 conclusions that are summarized. It says:

> "... the general conclusions of the comprehensive analysis revealed the following ...."

Do you see that, doctor?

11:15:15 A. I do, yes.

Q. And it goes on to talk about that paragraph. What is it talking about?

A. It's saying that patients with major depressive disorder, that's MDD, may be at increased risk for suicidal behavior

11:15:30 during treatment with Paxil.

Q. Now, it says here, "young adults," do you see that?
A. I do, yes.
Q. And it says:
"... an analysis of placebo-controlled trials of adults with psychiatric disorders showed a higher frequency of suicidal behavior in young adult adults, prospectively defined as aged 18 to 24."
A. Yes.
11:15:55 Q. What does this telling us about the risk of suicide between the ages of 18 to 24?
A. Well, what GSK is saying here is that this increased risk in people who are depressed and they're trying to tie it down to the 18 to 24 age group.
11:16:09 Q. Let's look at the next paragraph.
This next paragraph reads:
"... in adults with MDD, all ages, there was a statistically significant increase in the frequency of suicidal behavior in patients 11:16:27 treated with Paroxetine compared with placebo."
What does that mean, doctor?
A. Well, that means that Paxil causes people to commit suicide. Now, I have to tell you, and I explained I'm a bit of geek maybe, and it's not the kind of reaction the jury is going 11:16:50 to have, but I can remember where I was when I first saw this.

And I can remember turning to the people who were in the car with me and saying --

MR. BAYMAN: Your Honor, this is not part of the question.

11:16:57 THE COURT: Yeah. Sustained.

Just give us your analysis, please.

BY THE WITNESS:

A. Well, it appears to be GSK saying "our drug causes people to commit suicide," which was of huge interest to me because I 11:17:13 believe they had thought this from even before I thought it, but only now they appear to be conceding the kinds of points that I had been making for a long time before that.

Q. Now, doctor, to be clear --

MR. BAYMAN: Your Honor, we object to that comment; 11:17:28 nonresponsive.

THE COURT: It may stand.

Proceed.

BY MR. WISER:

Q. Now, doctor, in your opinion as a psychiatrist and 11:17:35 psychopharmacologist, does Paxil induce adult suicidal behavior?

A. Yes, it does.

Q. And what does this sentence that we're staring at say about your conclusion?

11:17:47 A. Well, it said to me at the time, and that's why I can

recall it so vividly, I have been saying this for ages and GSK now seemed to be saying the same thing.

Q. Now, it goes on to read:

"... however, the majority of these attempts for Paroxetine, 8 of 11 were in younger adults aged 18 through 30."

I'm going to pause right there. I thought younger. Adults were 18 to 24. What happened here?

A. Well, that's what it said earlier. And in fact, the majority of attempts, 8 of 11, were over the age of 24.

Q. So even under the 24 cutoff line, 8 out of 11 were above that line, is that right?

A. Yes. Correct.

Q. Does that indicate anything to you about the age relationship to suicide and patients taking Paxil?

A. Well, that supports what I believe, and a lot of other people believe, and was borne out by the Juurlink article, for instance, that people who are over the age of 65, for instance, are at high risk when they go on treatment with a drug like Paxil.

Q. It goes on to state:

"These MDD data suggest that the frequency observed in younger adult population across psychiatric disorders may extend beyond the age of 24."

Prior to this concession by the defendant, had GSK ever told anybody that this drug could cause suicidal behavior after the age of 24?

MR. BAYMAN: Objection, your Honor. He used the word "concession." It's not a concession.

11:19:18

THE COURT: Overruled.

BY THE WITNESS:

A. Quite the opposite. GSK had spent the time saying Paxil protects against suicide. They had not been prepared to accept that there was even a small group of people in the mix who might become suicidal on it.

11:19:28

BY MR. WISER:

Q. Now, lots yesterday we discussed this idea of odd ratios, right?

A. Yes.

11:19:40

Q. Can you explain to the jury again what that is.

A. An odds ratio is where you're looking at the likelihood of a particular problem happening on a drug, say, compared to a placebo or to a different drug. So you're looking at the rate in which it happens on the two different drugs and seeing is it more likely to happen on one drug than the other.

11:19:56

Q. Now yesterday we reviewed one of the studies that you conducted, and there was an odds ratio around 2 and a quarter, and 2 and a half; do you recall that?

A. I do.

11:20:10

Q. What did that odds ratio tell you?
A. Well, for me that was very conclusive evidence that the SSRIs can cause people to engage in suicidal acts and to complete suicides.

11:20:23 And, you know, the fact that it's 2.24, as it was, may not sound huge, but drugs that cause suicide can even in clinical trials show up with an odds ratio of 0.5. So His is way over what the point, the neutral point where people think the odds ratio is, you know, that it's -- it's at -- that the

11:20:51 risk from the treatment is no greater than the benefit from the treatment. In which case, you know, you may still have people going out to commit suicide, but you've also got people who are not likely to commit suicide because the drug has helped them.

Once you get over 2.2, a lot of people think that,

11:21:13 well, that's the point where things become causal, but in fact, it's been conceded, we now accept that actually you can have a strong causal relationship from clinical trials with an odds ratio of much less than 2.24, which is one that I had.
Q. Now, yours was only 2.24, Juurlink's was what?

11:21:34 A. Juurlink was 4.8, as I remember it.
Q. So that's 4 times greater increase that this drug is going to induce suicidal behavior -- or actually suicides in Juurlink, is that right?

MR. BAYMAN: Objection ---

11:21:43 BY THE WITNESS:

A. That's correct.

MR. BAYMAN: Object to the leading, Your Honor.

MR. WISNER: I'll rephrase.

THE COURT: Proceed.

11:21:47 MR. WISNER: Okay.

BY MR. WISER:

Q. All right, I want to go in deeper into this document. It goes to the methods. And there's actually a submission here by GSK and there's a section called Clinical Summary, do you see

11:22:01 that, doctor?

A. I do.

Let me make sure I'm on the same page as you.

Q. It's the page ending in 013.

A. Yeah.

11:22:15 Q. All right. Now, on the bullet points here on the clinical summary there's a discussion that I think -- it goes:

"... the results provide evidence of an increase in suicidal attempts in adults with MDD treated with Paroxetine compared to placebo; however, as

11:22:31 the absolute number of incidents are very small for Paroxetine versus placebo the data should be interpreted with caution."

But right in between, it's stated very small, it says:

11:22:42 "... odds ratio equals 6.7."

Do you see that?
A. Yes.
Q. 6.7 odds ratio, what does that tell us?
A. Well, that's the best estimate that we have from these data as to how big the likely risk is on Paxil compared to placebo.
Q. I want to make sure I get this straight, doctor.
You found 2.28, Juurlink found 4.8, who's spotting the 6.7 here?
MR. BAYMAN: Your Honor, objection. He's now mischaracterizing that as Juurlink was all SSRIs. This is a Paxil document. That mischaracterizes the testimony and the evidence.
THE COURT: You may ask the question without reference to the other study.
MR. WISNER: Sure. I'll re-ask the question, Your Honor.
BY MR. WISER:
Q. Doctor, whose 6.7 number is this?
A. GSK's.
Q. And how does this in any way impact your understanding of what you've been talking about for 20 years?
A. Well, just to give you a feel, when I saw this first, I told you I was in a car and turned to the other people in the car and I --
MR. BAYMAN: Objection, Your Honor. You told him not

to answer that and he's giving the same speech.

THE COURT: Yeah, we don't want your emotional reaction, doctor.

BY THE WITNESS:

11:23:59 A. Okay. Well, it was a very emotional reaction, I said, "Gosh, this is quite a figure."

Q. Thank you (laughing).

Now, this figure by itself, this 6 -- let me put it back up there so we don't lose track of it.

11:24:19 This figure of a 6.7 by itself, is it the only piece of evidence that shows that Paxil can induce suicide?

A. No, it's not. And we've been through a wide range of evidence before in terms of what we know goes on in the brain in terms of the case reports, in terms of other data from all

11:24:37 trials that were done with Paxil, but this is very convincing evidence in terms of people who were depressed that the drug can cause them to go on to suicide.

There's a lot of other evidence in terms of the way -- which you can deduce which show, and the jury can also deduce

11:24:58 if they don't quite understand the figures here, in terms of the way the company has been handling the issues that would lead you to think they knew there was a problem even before this figure.

Q. Now, have you heard the argument that you should only look

11:25:14 at placebo controlled trial data in assessing the risk of a

drug?
A. No, I think most people would say quite the opposite. You are looking at the adverse effects of a drug, the placebo controlled trials can be a way to hide the problem.
11:25:29 Q. I'm sorry, doctor, I don't think you heard my question. Have you heard the argument that you should only look at placebo controlled trial data?
A. And with most people -- there may be some people who may say you should only look at placebo controlled trial data, I
11:25:41 heard people say that. It's not a valid argument, in my opinion.
Q. But even if we were to do that, just look at that little subset of data, what does this 6.7 tell us?
A. This says that there is a high risk of people who were
11:25:59 depressed, if put on this drug, of going on to try to kill themselves.
Q. All right, doctor. Well, I actually want to explore one thing that's in this paragraph just so we don't lose sight of it.
11:26:19 Now, it says in the earlier thing that this 6.7, I don't know if it's in here, that 8 of the 11 occurred in patients under 30. And then you said that, well, actually 8 and 11 occurred in patients over 25.
A. Yes.
11:26:42 Q. Does that mean anything interpreting this data?

A. Well, one of the ways that, you know, the company can try to handle things is to try and say that the problems were restricted to a certain age group. That hasn't never been my view.

11:26:59 The view in the field, the view of anyone looking at these issues -- and when I did the first trials that produced estimates like 2.24, that was before any issue had come up about age groups at all. This was looking at adult trials. And in the original signals had come from adult patients, but

11:27:21 there's been an effort to say actually adults aren't where the problem lies, it's really just an issue among minors; it's not.

Q. Now, a 24 year old who has depression versus a 30 year old who has depression, is there any significant difference between those people?

11:27:38 A. Well, there isn't, no. Except, I mean, one of the issue is, and this relates to what I outlined before, we used to once at times think that young people could not get melancholic, you had to be quite a bit older to get this severe form of the illness, but as I said to you, that's not an issue so much

11:27:59 anymore when most people who have been put on these pills do not have a severe form of the illness to begin with whether the children are adults.

Q. All right. Are you aware that following the submission of this report to GSK, that the FDA conducted an analysis?

11:28:19 A. Yes.

Q. And what was the context of that FDA analysis relative to this submission?
A. Well, that happened a little over a half year later. It was at the end of that year the FDA convened a meeting to look
11:28:35 at the data that they got from all companies, including GSK, bearing on the issue of what do the antidepressants do in terms of this risk.
Q. Can you please turn in your binders to Joint Exhibit 13.
A. Well, I have 14 is what comes after 9. I don't appear to
11:29:00 have a 13 tab.
Q. It might be after the plaintiff's, in a separate area. It's joint, not plaintiff's.
A. Oh, right. Okay.
I may need a little help from either His Honor or from
11:29:16 you.
Oh, yes I found it.
Q. You found it, doctor?
A. Yes.
Q. All right. Okay.
11:29:28 MR. WISNER: Your Honor, do you have it as well?
THE COURT: Yes, I do.
MR. WISNER: At this time, Your Honor, I move Joint Exhibit 13 into evidence.
THE COURT: It's a Joint Exhibit, sir. You don't have
11:29:40 to move it. It's already in evidence.

MR. WISNER: Okay. Great.

Permission to publish.

THE COURT: Yes, you may proceed.

(Exhibit published to the jury.)

11:29:58 BY MR. WISER:

Q. Suicidality in adults.

A. Yes.

Q. What is suicidality?

A. This is a word that didn't exist until quite recently. If

11:30:07 you put it into any dictionaries and things like that, dictionaries didn't have it. It really gets created in the course of the controversies about what the risks are to do with these pills.

We have -- we've always had the word suicide, we've

11:30:27 always had the word suicidal ideation, but generally when people are talking about this issue they put them all under the broad term suicidality, which oddly enough, it's a very recent word. It's only been coined in the last few years.

Q. This suicidality, what does that encapsulate?

11:30:42 A. Well, it would include completed suicides, it will include suicide acts, and it will include ideation also.

Q. Okay. And it says here, and it has a bunch of NDA numbers, do you see that, doctor?

A. I do.

11:30:55 Q. So what does that mean?

A. That's the -- it's a new drug application, is what NDA stands for.
Q. And I see all these different drugs here, doctor. What are these drugs?
11:31:06 A. Well, these are the leading antidepressants that were on the market in 2006. It's not all of the antidepressants. It doesn't include the older drugs. All told, as I indicated to you, we had 30 to 40 odd drugs or so. This include the SSRI and non-SSRI newer drugs. There must have been some even newer
11:31:30 drugs that have come on the market since then that some members of the court may know about which you won't see here.
Q. All right. So we have there's Paroxetine, that's Paxil, right?
A. Yes.
11:31:41 Q. Okay. And what's this one (indicating)?
A. That's Prozac.
Q. And what's that one (indicating)?
A. That's Lexapro.
Q. I'm just calling the ones people might be familiar with.
11:31:59 What's that one (indicating)?
A. That's Zoloft.
Q. And is that sertraline, is that right?
A. Yes.
Q. Okay. And then we have, for example, escitalopram, do you
11:32:12 see that?

A. Yes.
Q. What's that?
A. That's Celexa.
Q. Okay. Now, another one that is highlighted here, what types of antidepressants are they?
11:32:18
A. These are SSRIs.
Q. Okay. And that's different than, for example, and I'll just use a pen for this, that one (indicating), what's that?
A. Ah, that's duloxetine, and that's marketed as an SNRI, but it's also a very strong serotonin reuptake inhibitor and arguably comes with many of the problems linked to the SSRI drugs.
11:32:33
Q. What is that known amongst regular people?
A. Cymbalta.
Q. All right. And maybe there's one more people might've heard of. Have you heard of this one on the bottom, doctor?
11:32:45
A. That's Effexor.
Q. Okay. And is that also a drug similar to Cymbalta?
A. Yes.
Q. Okay. Let's get into the study. What was the purpose of the study, based on your understanding?
11:33:00
A. Well, the FDA had called for a lot of the clinical trials companies had done and wanted to look at the issue of completed suicides and suicidal acts and ideation to see what could be said about what was happening in the adult trials.
11:33:19

Q. Was there any concern about stratifying the age groups?
A. There was a lot of ways in which the FDA constrained the issues. Although they asked the companies for all trials, they didn't, in the end, get -- I mean, they said we want all
11:33:43 trials, but we want you to exclude a range of different kinds of trials. So they didn't get all trials --
MR. BAYMAN: Objection; outside the scope of his report now, Your Honor. He didn't express this opinion.
MR. WISNER: He's talking about a fact, not an opinion
11:33:59 being expressed.
THE COURT: Proceed.
BY THE WITNESS:
A. They didn't actually work from all the trials that had been done. So although you have the drugs here and all the
11:34:08 companies involved, there was a number of trials that had been done that don't feature in here.
So for instance, when we did the work that was referred to earlier, the Ferguson article, we had actually more trials than the FDA had. The FDA were trying to purify things,
11:34:25 as it were, and just take a very limited window.
For instance, they didn't include the withdrawal period at all; they excluded that. So FDA were operating within -- well, look, they had to cope with a bunch of issues in terms of what were the best trials to look at.
11:34:42 Q. When the FDA got this data, where did the data come from?

A. The data came from the companies. Most people think the FDA has this data; they don't. What is actually coming from the company is a report. It's not the actual data.
Q. Well, doctor, if the data is not being generated or created by the FDA, couldn't that cause problems?
A. A lot of people think there is someone completely independent who has the data and looks at it; there isn't. Everybody depends on the companies to acting in good faith --
MR. BAYMAN: Your Honor, he's now characterizing the company conduct.
THE COURT: Yeah. Proceed.
BY THE WITNESS:
A. So FDA again, I mean they're working with the companies. FDA doesn't have a brief to be intensely skeptical or to be hostile to companies. They work with them.
Now, I don't want to -- I mean, I'm not trying to suggest by that that FDA are doing anything wrong. It's just, you know, for things to work, you have to be able to depend on the people that you're working with.
BY MR. WISER:
Q. Now, this study looked at two kind of different areas under the umbrella of suicidality, is that right?
A. Correct.
Q. One area was -- what were the two areas, doctor?
A. Well, I mean, they looked at more than two areas, but the

two big areas were suicidal ideation and suicidal behavior.
Q. And we talked about a lot about the difference between ideation and behavior. Why do you think they broke it up that way?
11:36:29 A. Well, I would've always thought that ideation was a way to hide the problem. I mean for me, the issue is to look at completed suicides and to look at suicidal acts. These are things that, for the most part, were going to be more accurate about. You can depend on the figures being offered. Having
11:36:54 said that, you know, I don't think even those figures are entirely reliable. We may not have all of the suicidal acts. But ideation -- when you combine two different things, like ideation and behavior, you can cloud the picture.
Q. We talked about the collection of data of suicidal
11:37:10 ideation. You mentioned that there was methodological problems. Do we have that same problem with suicidal acts in completed suicides?
A. Well, it isn't absolutely perfect if you don't have the raw data and see what -- I mean, you know, for the jury to pick
11:37:24 through the raw data and pick out the ones that they think is a clear act, they may find that they pick out more acts than the companies would, for instance.
Q. So, I mean --
A. But it's better data, yes.
11:37:36 Q. Yes. Let's get a sense of that. So, for example, if a

person in a clinical trial slits their wrist, is that something that you could hide in a clinical trial?
A. Well, it can disappear. There are various different ways in which it can disappear --
11:37:51 MR. BAYMAN: Your Honor, company conduct again.
THE COURT: Overruled.
BY THE WITNESS:
A. There are ways it which it can disappear. And it can disappear without the company necessarily doing anything bad. You know, not trying to make it disappear, it can just disappear in the mix.
11:38:06
BY MR. WISER:
Q. In your opinion, is looking at behavior a more reliable source of data than looking at ideation?
A. Even with, you know, the caveats that some of the acts can go missing, yes, it's much more reliable than looking at ideation.
11:38:19
Q. Now, the FDA study characterizes the analysis of ideation as a primary analysis, is that right?
A. Yes.
11:38:36
Q. And the behaviors as a secondary analysis?
A. Yes.
Q. What does that mean?
A. Well, it means that their primary focus has been on ideation, and the secondary focus has been on behavior.
11:38:48

Now, there's all sorts of things that can come into play with that. Some people would say you should only apply statistical significant test to the primary outcome, but the actual fact with the data we have here, I'm not sure anything should've been called primary or anything should've been called secondary, and so the role of statistical tests --

MR. BAYMAN: Your Honor, he's not a regulatory witness. He's now criticizing the FDA.

THE COURT: Overruled.

Proceed.

BY THE WITNESS:

A. So this -- I mean, the FDA had the tricky job of handling a vast amount of material. And they opted -- I mean, we don't know quite know why, they don't make it clear, to make ideation what they've called the primary outcome and behavior the secondary outcome.

BY MR. WISER:

Q. Would it have been scientifically appropriate to do the behavior as the primary outcome and ideation as the secondary?

A. Yes, I would've thought it was probably more so, but, you know, I mean, this isn't a big issue from my point of view.

Q. Now, because something is called a primary or a secondary outcome, does that mean the data isn't important?

A. No, the data is always important. And it's, as I keep stressing, really what we need here is access to all the data

and you can't be sure that we have all of it here.
Q. All right. Let's look at table 16 in the FDA's analysis.
What is table 16 generally showing, doctor?
A. Well, this is looking at suicidal acts. This is not
11:40:26 ideation. There is a number of tables which look at ideation and then there's a number of tables that look at a mixture of ideation and behavior, and this is the one that's looking at behavior.
Q. Now, it says "preparation or worse," does that also include
11:40:43 actually people who kill themselves?
A. Yes.
Q. Okay. And it has it listed by drug and by class. Can you explain to the jury what that means.
A. Well, the SSRIs are a drug class. Now, it's really a
11:41:00 marketing class. There's a lot of drugs other than the SSRIs that inhibit serotonin and reuptake. So duloxetine you could include in the class of serotonin reuptake inhibitors, but, in fact, people tend to put it in a different class, the SNRIs, that's serotonin and norepinephrine reuptake inhibitors.
11:41:21 So we have a breakout of the drugs here and the drug class you are seeing up on the screen here is the SSRI class.
Q. And so we're looking here and it has it broken down, I see citalopram, escitalopram, these are different what?
A. These are different SSRIs.
11:41:38 Q. Now, we talked a bit about odds ratios, right. And I want

to focus on that for just a brief second.

The odds ratio here for all SSRIs is right there, right (indicating)?

A. It is.

11:41:54 Q. And so what is the overall odds ratio for suicidal or worse as reflected here for all SSRIs?

A. It's 1.23.

Q. Now, is that an indication of risk?

A. It is.

11:42:06 Q. Why?

A. Well, anything over 1 is an indication of risk. It may be strong safety signals even with an odds ratio less than 1. If you remember when we put up the Ferguson image showing that from 1988 the signal was 2.0 or more, before '88 it was less

11:42:30 than one, but partly that's because the acts weren't reported in the trials. If they're not reported, we couldn't register them.

So it looked like there was a safety signal there when, in fact, I know that there were acts that just weren't in

11:42:44 the reported literature. And the safety signal right from the early '80s probably shouldn't even been greater than 2.

Q. Now, if we go down here, we have the FDA's analysis of each of the drugs. There's Paroxetine. Do you see that, doctor?

A. I do.

11:42:58 Q. What is that odds ratio?

A. That's 2.76.
Q. What does that tell us?
A. Well, again, that's a very high odds ratio. It's heading towards 3. It's a very strong signal. Not just that the drug
11:43:13 is causing a problem, but it's -- you know, the risks, perhaps not just from the drug but the way it's been used.
Look at the drug, it's not the risk necessarily from the chemical alone, it's a chemical plus information. So it's the risk from the chemical plus the information doctors and
11:43:36 patients have been given when they take this chemical.
Q. Now, a minute ago we saw that 6.7 odds ratio from GSK's briefing document?
A. Yes.
Q. That included -- that was for MDD, is that right?
11:43:48 A. Yes.
Q. What is this 2.76 relate to?
A. Well, this is from a larger group of patients. These includes some trials done people who are being anxious also. So you've got a larger group of patients. The odds ratio drops
11:44:03 down, but if you see the confidence interval gets tighter. This is not necessarily because it's stronger evidence the drug causes the problem, it means we've got more patients and we can give a better and more precise estimate.
Q. Are you familiar with the phrase or term statistical
11:44:24 significance?

A. I am.
Q. What is it?
A. Well, I've written articles about this, and I've got a book which is currently written and hopefully will be in press soon, looking at the origins of this and origins of controlled trials.

And it was, strictly speaking, a measure that was introduced by a man called Ronald Fisher. And what is all about was showing that you knew what you were doing when you did something, and that the only way things wouldn't turn out the way you predicted was because of some freak chance.

The term "statistical significance" gets applied to the antidepressant data, and all drug trial data in a very different way to what Fisher, who introduced the term, would have meant by it. It means that it just describes the distribution of the data.
Q. If an odds ratio is not statistically significant, does that mean it should be disregarded?
A. Oh, gosh, no. The people who introduced odds rations and confidence intervals -- you see the confidence interval here is 1.6 to 6.6. The people who introduced confidence intervals were a different group of people to Fisher. And it was rather like Catholics and Protestants or Shiite and Sunni are Orthodox and reformed, they hated Fischer and they thought his ideas were all wrong and he hated them and thought their ideas were

confidence intervals.

So often we get people in the field today saying that an odds ratio of 1.16 to 6.6 is the same thing as a statistical significance figure of 0.02. Well, Fisher on the one hand and Naman Pearson on the other would roll in their graves at the thought of this. And both I and a lot of other people for data like this would use the confidence interval rather than statistical significance.

11:46:17

Statistical significance is great for efficacy, that's where it's got a better place. It should probably not be used for adverse events at all.

11:46:34

Q. Now, we talked about statistical significance. There's a term that floats around called the P value. What is a P value?

A. Well, that refers to the probability value. And if the probability is less than 0.5, that's what Fisher introduced. We can say, you know, if 19 times out of 20 you get the results that you said you're going to get because you understood what you were doing, that's a good indication that you really do understand what you're doing. We can accept the fact that one time out of 20 -- let's say we put a plaster on a broken arm, and one time out of 20 the arm doesn't heal. We can say, yeah, we still think that the people who say paster for a broken are a good thing are probably right. You know, we accept that one time out of 20 maybe things, for whatever reason, just don't

11:46:45

11:47:08

11:47:33

heal.
Q. Now, the typical P value that is significance is what?
A. It is P less than equal to 0.05.
Q. 0.05. And that's for a 95 percent confidence?
11:47:52 A. Well, as I said, neither Fisher nor the people who talked about confidence would want you to say that, they just wouldn't, but there, yes. I mean, if you're speaking confidence language, that translates into P less than 0.05 in statistical significance language.
11:48:11 Q. So what if you want a confidence of 90 percent, what would the P value have to be?
A. That would be P at less than equal to .1.
Q. Okay. What if you wanted 50 percent, like more likely than not, what would the P value have to be about?
11:48:27 A. Oh, more -- no, I mean -- you mean if we think there's no impact?
Q. No, no. Let's say we want the confidence level to be at 50 percent, okay. What would the P value need to be below?
A. Well, if -- if -- if we were saying that the data from the
11:48:44 clinical trial was even on either side, that the drug caused a problem or not caused a problem, the P value would be .5.
Q. What is the general -- strike that.
So we have here Paroxetine. It has a confidence interval of 1.16 to 6.6, do you see that, doctor?
11:49:05 A. I do.

Q. And you said that's a wider, narrow confidence interval?
A. Well, that was a lot narrower than the one GSK gave you in the document that you read earlier.
Q. Okay. And it has a P value of .02?
11:49:20 A. Yes.
Q. Is that considered statistical significance even under the 95 percent level?
A. For the people who use that kind of language, yes, it is.
Q. Okay. Now I want to just remark on a few things here.
11:49:35 I'm looking at all the confidence intervals in this class of drugs. Do any of them, besides Paxil, go above 1?
A. No, they don't go above 1, but there may be an artifact here. To some extent, all the companies are putting their best foot forward here. So in actual fact, the data for all of them
11:50:03 may be worse than it looks here.
The Zoloft data that went into the U.S. regulator the year before this --
MR. BAYMAN: Your Honor, this is now getting into the U.K., regulators, company conduct. This is, again, getting way
11:50:17 far afield. I object.
MR. WISNER: I don't believe GSK manufactured Zoloft and we're not talking about --
MR. BAYMAN: And it's not in his expert report, these allegations.
11:50:27 MR. WISNER: They literally cross-examined him on it

in his deposition.

THE COURT: Proceed.

BY THE WITNESS:

A. For instance, for me looking at this, there's two or three striking things. And I think for the jury also, the figures that will leap off the page at the jury here, and just to emphasize, there's nothing --

MR. BAYMAN: Objection, Your Honor. Talking to the jury, showing the page.

THE COURT: Proceed.

BY THE WITNESS:

A. There's nothing rocket science about this, okay. And you don't want to think that only experts can read this. What you're seeing up there on the page is the 5.67 will stand out, and 2.76 will, and the other one that will stand out is 0.25, and that's the one that had me scratching my head when I saw it, particularly because I've had access to data, other data, that went to the U.K. regulator and the Pfizer article that came out shortly afterward which gave a completely different figure --

MR. BAYMAN: Same objection, Your Honor.

BY THE WITNESS:

A. A published peer-reviewed article from Pfizer -- .

MR. BAYMAN: Aside from the scope of his report, Your Honor, he's into Pfizer data, the U.K. regulators.

THE COURT: Doctor, you can confine your comments to what you see on this document.

THE WITNESS: Yes.

BY THE WITNESS:

11:51:41 A. I have strong reasons to believe from data available to me and in the published literature that the figure here is unusual. It may not reflect anything bad about company behavior. It may just be FDA trying to handle this terribly tricky problem that had been built up over 20 years thought, 11:52:01 look, we'll try and handle it by asking the companies for these trials and not that.

And there was some quirk about what they asked for that meant that the data here looks unusual. The other data published in the peer-reviewed literature that anyone can get 11:52:18 access to, the jury can get access, the court can get access to, would give a figure more like 2.25 if you had --

MR. BAYMAN: Strike that. He is asking the jury --

THE COURT: No, it may stand, sir. He's explaining the document.

11:52:33 Proceed.

BY THE WITNESS:

A. If you were to add that figure in here, the overall odds ratios for all SSRIs would be over 2, which is quite like the figure that I had in my article the year before this --

11:52:41 THE COURT: Now, doctor, you're rejecting these

figures, is that what you're doing?

THE WITNESS: Well, no, I'm saying that the court needs to be aware that --

THE COURT: There's other data.

11:52:53 THE WITNESS: FDA were operating under a lot of constraints. I think the GSK data -- actually, I think GSK, with this figure here, may have been unusually reliable, the other companies may have been less reliable.

THE COURT: All right.

11:53:05 BY MR. WISER:

Q. Let's focus on Paxil.

THE COURT: Tell us what these figures show you, as you read them here irrespective of what other data you have.

BY THE WITNESS:

11:53:16 A. Okay. As you read the figures here, the SSRIs, as a group, cause a problem. It would appear to a lot of doctors if you're going to pick a safe SSRI, you'd pick sertraline, I wouldn't, based on what I know, but among the figures that here, one of the worse is what the figures for Paxil. Some people would say

11:53:39 the figures for Paxil are the worst because the confidence interval is over 1.0. I'm not sure I'd agree with that, but that's what a lot of people would say.

Q. So, doctor, Paxil has a nearly three-fold increase and it's the only one with the confidence interval of above 1, is that

11:53:57 right?

A. Yes.
Q. Let's look at the P values. Paroxetine looks like it has a P value of under .005, is that right?
A. Yes.
11:54:13 Q. So with a risk ratio of 2.76 and the P value of .02 and a confidence interval above 1, what does that tell you about the drug Paxil?
A. Well, there's two things here; one is what it will tell me and one is what it would tell a lot of other people. I think
11:54:34 the 2.76 is the key figure here. The confidence interval is probably the next useful figure. And the statistical significance figure is the least useful figure. Lots of other people would say they would be most persuaded by the statistical significance figure and they'd say that's the one
11:54:50 for them --
MR. BAYMAN: Your Honor, he is now speculating what other people would say.
THE COURT: Overruled.
Proceed.
11:54:57 BY THE WITNESS:
A. They would say that's the one that counts. So but, I mean, for anyone looking at these figures, whatever point of view you come from, whatever way you handle figures, whatever you think is important, all of the figures here, the confidence interval,
11:55:13 the odds ratio, the statistical significance figures all point

to a problem.
Q. And, in fact, when you look at this data, in the context of the 6.7 figure we saw from GSK's data, does it show, even using placebo controlled clinical trials and even using statistical
11:55:35 significance that Paxil induces suicidal behavior?
A. It does.
Q. Now, are you familiar with the concept of multiple comparisons?
A. Yes.
11:55:51 Q. What is that concept?
A. Well, just as when you design an experiment, things can go wrong by chance. When you apply statistical tests, if you are doing lots of them, just by chance the result can hop out and can appear to be statistical significant when there's not a
11:56:15 real finding here. I mean, there's no reason to think that the person knew what they were doing when they produced this result.
I mean, people have been aware for a long time that we need to take care, just because you get a statistical
11:56:29 significant finding doesn't necessarily mean that, you know, you need to take this very seriously. You have to control for it by using other tests to make sure this isn't just a chance statistically significant finding.
Q. Now based on the fact that GSK's own data showed a 6.7
11:56:44 increase, do you have any reason to doubt that the Paxil

finding in the FDA study was just a product of chance?
A. No, I don't. There's a consistency here. And the consistency, in fact, goes back to 1989. The figure, the odds ratio has all this from placebo control trials very clearly there, it's been over 2.0 pretty well the whole way through. So there's a consistency here that you need to bear in mind also.
Q. Okay, doctor. Have other researchers taken a look at the FDA's analysis?
A. Well, yes, they have. There was the -- well, not the FDA's but the GSK's figure the Aris and others, lots of people have poured over these figures.
Q. All right. Can you please turn in your binder to Exhibit 33. I think it's exhibit 33.
A. All right.
Q. What is Exhibit 33?
A. This is an article that appeared in 2008 and the first author is Corrado Barbui.
Q. And what journal did it appear in?
A. This appeared in the Canadian Medical Association journal.
Q. Is this a journal -- strike that.

And did you review this journal as part of coming to your understanding of Paxil suicide?
A. Yes, I did.
Q. And is this a reliable article to the best of your

knowledge?
A. Yes, it is.
MR. WISNER: At this time, Your Honor, permission to publish portions to the jury.
11:58:48 THE COURT: You may proceed.
(Exhibit published to the jury.)
BY MR. WISER:
Q. All right. Doctor, let's start off with the author. Who is Corrado Barbui, MD?
11:59:00 A. Well, I don't particularly know him. I know one of the authors, Andrea Cipriani, I met him, but I have not met Dr. Barbui.
Q. Okay. Can you read the title to the jury?
A. Yes, it's about:
11:59:19 "... the effectiveness of Paroxetine in the treatment of acute major depression in adults, a systematic reexamination of published and unpublished data from randomized trials."
Q. All right, doctor, I don't want to go into the efficacy
11:59:35 issue with Paroxetine.
A. I don't either.
Q. Okay. Let's go to page 304 on the bottom.
Well, before that, doctor, is this a peer-reviewed article?
11:59:50 A. It is.

Q. Okay. And do you know if Dr. Barbui or any of those other authors work for pharmaceutical companies?
A. I don't know. I have no idea.
Q. So on this page, I've blown up a paragraph here, and it reads:

> "... there remains uncertainty about the safety of Paroxetine and other selective serotonin reuptake inhibitors, which may cause worsening of suicidal ideas in vulnerable people. The present analysis, which suggests that Paroxetine is associated with a statistically significant increase in the risk of suicidal tendency, expands the results of previous reanalysis of GlaxoSmithKline data."

Do you know what that analysis is referring to?
A. Well, we'd have to look at the references and that will let us know, let everyone know, and it refers to the Aris papers, both of the Aris papers that we've looked at yesterday.
Q. Okay. Great. It goes on:

> ".. in particular in the analysis carried out by GlaxoSmithKline of suicide attempts by adults with major depression, the frequency was higher among patients who received Paroxetine than among those who received placebo ... "

And then you have the numbers in there and then you

have an OR 6.7, do you see that, doctor?
A. I do, yes.
Q. And if you look at the citation, it says citation 27. Where is that number coming from?
12:01:19 A. That's coming from the -- that's coming from GSK's briefing document that we've looked at earlier.
Q. Okay. Great. It goes on:

> ".. the recently released reanalysis by the U.S. Food and Drug Administration of 372 placebo-controlled antidepressant trials involving almost 100,000 patients with any psychiatric disorders confirmed these figures."

12:01:38 I'll stop right there. It says that the FDA's analysis involved 372 trials, do you see that?
12:01:55 A. Yes.
Q. I know you did a meta analysis. How many trials did yours include?
A. Well, I've done a few of them. And the Ferguson article that we referred to again, we had over 300 clinical trials 12:02:10 there also. It was around the same number of trials and patients as FDA.
Q. Okay. And it goes on:

> "... it confirmed these figures by showing that, among the selective serotonin reuptake 12:02:27 inhibitors and newer antidepressants only

Paroxetine was significantly associated with an excess risk of suicidal behavior."

Do you see that, doctor?

A. Yes.

12:02:37 Q. Do you know what analysis it is referring to in that sentence?

A. Well, excuse me one minute. I slightly dipped off there while you were reading it.

Q. (Laughing)

12:02:48 (Brief pause).

BY THE WITNESS:

A. This is referring back to what often called Stone Jones report that we had up earlier where you were looking at table 16, the behavioral outcomes in the SSRI placebo-controlled

12:03:06 trials. This was at the table that gave Paxil odds ratio of 2.76 and the odds ratio of 0.25, that's what they're referring to here.

Q. Now, what does it mean by confirm that only Paxil was statistically associated, what does that mean?

12:03:28 A. Well, they're saying that their approach to the data confirms that Paxil has a particular problem.

Q. All right. In the analysis done by the FDA, did the FDA also analyze different age strata?

A. They did, yes.

12:03:43 Q. And did they break that down by drug as well?

A. Ah, I'm sure they will have done, but at the presentation of the material in the FDA document doesn't do that.
Q. Well, let's take a look at Joint Exhibit 13 again.
MR. WISNER: Your Honor, this is already in evidence. Permission to publish.
12:04:03
THE COURT: Yes.
MR. WISNER: Okay.
(Exhibit published to the jury.)
BY MR. WISER:
Q. We looked at table 16 earlier. Let's take a look at table 24.
All right. This is table 24. It's the suicidality, so this includes ideation, odds ratio for active drug relative to placebo, it's ideation or worst, subjects under age 25. So what does this refer to you, doctor?
12:04:08
12:04:35
A. This shows you, first of all, that I've slightly misled you with my last answer. There is more material that refers to a breakout by age than I had remembered clearly when you asked me the question.
What we're seeing here is the data broken out by age.
12:04:50
Q. And we have it also by drug, right?
A. We have it by drug as well.
Q. Okay. And we have Paroxetine down here, do you see that?
A. I do.
Q. It has an odds ratio of 2.33, right?
12:05:03

A. Right.
Q. Again, that's similar to the odds ratio for all adults of those all ages?
A. Yes, but that was behavioral only, this is ideation and
12:05:15 worst, but --
Q. Fair enough. And, again, I just want to point out that amongst all the SSRIs here, Paxil is the only one with the confidence interval above 1, right?
A. It is, yes.
12:05:27 Q. Let's look at the P values. Do any others SSRI's have a P value that goes below .05?
A. No, they don't.
Q. Does it suggest that Paxil, at least in this chart, looks like it's worst than the rest?
12:05:41 A. Well, yes, if you look at it from the chart, some people will say Paxil is worst than the rest. I probably wouldn't say that this necessarily says that.
Q. Okay. Let's look at table 25.
So now this is again suicidal behavior for active drug
12:06:04 relative to placebo for patients under 25, all psychiatric disorders; do you see that?
A. Yes.
Q. Okay. So this is the same analysis that we saw for all adults but now for --
12:06:14 A. Restricted to just behavior, yes.

Q. Okay.
A. I would think it's the better thing to be looking at.
Q. Okay. Now, let's look at the odds ratios here. Now, they're much higher, aren't they?
12:06:26 A. Yes.
Q. Specifically what is it for Paxil?
A. Well, it's 4.36. And the interesting thing here is that there's much less behavioral events. So given that there's much less behavioral events than ideation and behavioral
12:06:41 events, you'd expect the confidence intervals to get broader. They do get a little broader, but at the same time not much. This is a very strong result.
Q. And again, let's look at these confidence intervals for all the drugs. Which drug has the confidence interval that goes
12:06:57 above 1?
A. Paxil.
Q. Do any of the others?
A. No, they don't.
Q. All right. We'll take P values. Do any of the drugs have
12:07:04 a P value that goes below .05?
A. No; other than Paxil.
Q. Okay. So Paxil is the only one again.
A. Yes.
Q. All right. Based on your clinical experience, of the
12:07:23 SSRIs, which ones have you seen have the most potent effect on

patients engaging in suicidal behavior?
A. Based on my clinical experience and based also on research, which points to the fact that Paxil is the most potent of the serotonin reuptake inhibitors, that suggests that if the
12:07:45 problem is coming from the serotonin system and interfering with the serotonin system the way SSRIs do, you might expect more problems from Paxil than from other SSRIs, you certainly wouldn't expect less problems.
Q. And these charts that we just looked at where Paxil
12:08:04 appeared to have the only confidence intervals above 1, as well as the only statistical significant result, does that lend support to your view.
A. It does. And there's a further aspect to it, which is this reflects -- you are only getting here the data here from the
12:08:23 arm effect, that is, when we give the drug to the person, what happens, problems could also happen when you withdraw the drug, those problems aren't here.
So the overall problems a drug may be causing, in a sense, you only got half of them here. And Paxil comes with a
12:08:37 reputation for having withdrawal problems --
MR. BAYMAN: Your Honor, now we're getting in to withdrawal and you ruled this out pretrial. This is not a withdrawal case, Your Honor.
THE COURT: Overruled.
12:08:49 BY THE WITNESS:

A. One of my -- I mean I use, I've told you, I used the SSRIs. I'm not hostile to them as a drug group. We need SSRIs. I need SSRIs to treat people. But I don't use Paxil, and I don't use it because of the risk you see here, but also because there
12:09:09 are withdrawal risks which need to be added in here, that's one big factor for me using the others rather than Paxil.

BY MR. WISER:

Q. If a physician were told that Paxil, when it comes to adult suicide, is just like every other SSRI, is that true?

12:09:28 MR. BAYMAN: Calls for speculation.

THE COURT: Yes. Sustained.

BY MR. WISER:

Q. Is Paxil just like every other SSRI?

A. My experience is that a lot of clinicians, if you look at
12:09:43 hospital formeries around the U.K. I could can this with confidence, and this is not speculation --

MR. BAYMAN: Objection; he's now talking about other clinicians and not himself. Same problem, Your Honor. It's the same problem, Your Honor. It's speculation.

12:09:54 THE COURT: No, he's an expert.

You may continue.

BY THE WITNESS:

A. In the hospital where I work SSRIs are on the hospital formary. The ones that are on the hospital formary do not
12:10:06 include Paxil. There is a discouragement to all doctors

working in the hospital that say if you SSRIs don't use Paxil. That decision has nothing to do with me. I have no input to the hospital people making that decision. They came to their own view based on what the clinicians in the hospital were
12:10:29 saying to them and data like this.

BY MR. WISNER:

Q. Now, we've looked at the FDA's analysis and we've looked at GSK's analysis, what types of clinical trial data were they looking at?

12:10:40 A. Sorry, can you repeat that.

Q. Sorry, I spoke very quickly.

A. Almost as quickly as me.

Q. I apologize to the court reporter.

We looked at the FDA's, we've looked at GSK's
12:10:53 analysis, what type of clinical trial data were they focused on?

A. This is randomized control trial data, and controlled trial data, and the trial data can include what's called open label where clinicians and patients -- I mean, the FDA data is only
12:11:08 randomized placebo controlled trial data, but overall what people have looked at includes a broader range of trials. We're looking at trial data rather than what's called cohort data or case report data or any other kind of data.

Q. All right. So GSK's analysis, as well as the FDA's
12:11:26 analysis focused on placebo controlled data, right?

A. Yes.
Q. Okay. When it comes to looking at the clinical trial data that exists for Paxil, would you say a large portion of it is not considered?
12:11:40 A. Yes, I would.
Q. What portion is that?
A. Well, when I say not considered, I don't want you to think that it shouldn't be considered. My view is it should be considered, but there's a large number of trials other than
12:11:55 just the placebo-controlled trials. There's trials when one antidepressant has been compared to a different antidepressant.

I've helped run a GSK trial which didn't involve any placebo, it involved Paxil against a different antidepressant you don't have here in the U.S. which acted on the
12:12:13 norepinephrine system, for instance. So those trials which can give lots of information.

Then there's what's called open label studies where doctors are encouraged to give the patients where they know, the patient knows what the drug is but they're monitoring them
12:12:30 much more closely than usual clinical practice, they may be using rating scales, and they're recording in 100 patients say that I gave Paxil to, here is what the outcomes were.
Q. So to be clear, if a patient was given Paxil in a clinical trial in open label trial. So they knew they were getting the
12:12:49 drug and they went and killed themselves on the drug, that

incident wouldn't be included in the FDA's analysis?
A. No.
Q. Well, would it be included in GSK's analysis?
A. Well, look, there has been one that GSK have done where these things are taken into account, but in this one, no.
Q. Okay. Do you think that's appropriate to not consider -- well, strike that.

In regular practice, when a patient is prescribed Paxil, are they unaware that they're being given Paxil?
A. No, they're not unaware that they're being given Paxil.
Q. So an open label trial, then, does that more closely approximate what actually happens in real life?
A. It is much closer to real life than randomized trials are, but it's different to case reports where if I have 2 or 3 patients come in the door and they have a problem after I gave them Paxil, in this case I may be asked maybe to say look at a hundred patients. So we're just not focusing in on the people who were doing poorly. We're taking a big group of patients in the course of which some may have an adverse response but others won't.
Q. Now in the GSK analysis it mentioned 11 suicide attempts, do you recall that?
A. I do.
Q. Based on GSK's clinical trial database, including all clinical trials, were there only 11 suicide attempts?

A. No, this was just the major depressive disorder trials. The randomized controlled -- randomized placebo-controlled trials, it excludes the trials done in people under 18, for instance, which was a lot of --

12:14:31 MR. BAYMAN: Your Honor, he mentioned the data again. You told him not to get into it and he's getting into it.

BY THE WITNESS:

A. I'm not getting into it.

THE COURT: Overruled.

12:14:41 Proceed.

BY THE WITNESS:

A. This is a restricted age group and we're looking at just the MDD trials, that's all. So there were -- I mean, it's certainly well over 10,000 patients that have gone into GSK

12:14:57 trials. Probably closer to 15- to 20,000 patients that have gone into GSK trials. You are looking at a very small subgroup here, something of the order of possibly 3,000, 3,500 patients.

Q. And then --

A. Hang on. Maybe a little bit more. About 4 and a half

12:15:16 thousand patients.

Q. And that's out of how many total patients have been in clinical trials?

A. Well, it's a much bigger figure. Again, I don't know what the ultimate figure is, but I guess my hunch would be it would

12:15:26 be well over 20,000.

Q. All right. Well, when was Paxil approved?
A. Paxil was approved in the United States in 1992, I believe.
Q. So we're 25 years later?
A. We are.
12:15:40 Q. In the 25 years that you have been practicing medicine, has GSK ever told you, as a physician, that Paxil can induce adults over the age of 25 to engage in suicidal behavior?
A. No, and it hasn't ever. And its gone a bit further. When I've raised the issue of SSRIs, not Paxil in particular causing
12:16:07 problems, but when I raised the issue about SSRIs causing these problems, GSK delisted me as a speaker for the company.
MR. BAYMAN: Objection, Your Honor.
THE COURT: Yes. That may go out.
MR. BAYMAN: Thank you.
12:16:19 BY MR. WISER:
Q. So, doctor, let's --
MR. WISNER: I'm sorry. Did you sustained the objection, Your Honor? I didn't hear it.
THE COURT: Yes.
12:16:27 MR. BAYMAN: Could you ask the jury to disregard that, Your Honor?
THE COURT: Yes, it's not relevant.
MR. WISNER: Okay.
BY MR. WISER:
12:16:33 Q. So to the point I'm getting at, doctor, you've never been

told that Paxil can induce adult suicidal behavior, correct?
A. Everything that I've read from the company has been quite the opposite, it says that it's protective.
Q. And, in fact, you've investigated all the work that GSK has done over that entire time period, is that right?
12:16:50
A. Well, I've looked at a great deal of stuff, yes.
Q. And how many documents are we talking about here?
A. Ah, it's a large number of documents. I'm not sure.
Q. Okay. And over that 25 year or so investigation, have you observed what GSK has done with the data in disclosing it to FDA and other forms of institutions?
12:17:06
MR. BAYMAN: Objection, Your Honor, I think it's company conduct again.
THE COURT: Overruled.
BY THE WITNESS:
12:17:17
A. Yes, I have.
BY MR. WISER:
Q. And in your professional opinion, has GSK adequately disclosed the data during that 25 year period?
A. My view is no, they haven't.
12:17:29
Q. Now, prior to taking the stand, did you sit down and come up with a list of all the ways GSK's did not disclose this data?
A. Well, for a long time I've had a list of ways that companies, not just GSK, have handled the data so the risks get
12:17:46

minimized.

MR. BAYMAN: Your Honor, same objection. And this is being a demonstrative that I objected to yesterday, Your Honor.

THE COURT: Well, overruled.

12:18:03 BY THE WITNESS:

A. This is an issue I've been lecturing on widely. It's got nothing to do with this particular trial that we're in here today.

BY MR. WISER:

12:18:11 Q. How long have you been lecturing about this?

A. I've been lecturing about these issues probably since the late 1990s.

Q. All right. I'm going to have you turn to Exhibit 36 in your binder. We're not going to be putting it up, but I want

12:18:34 you to have them in front of you.

Do you know what this exhibit is, doctor?

A. I do, yes.

Q. What is it?

A. Well, this is the kind of mental checklist that I have

12:18:46 about things to -- you know, that the jury should be looking at in the kinds of documents that I've looked at it. I mean, what we're talking about is no one with expertise, the jury would be able to spot the kinds of things that I can spot.

MR. BAYMAN: Excuse me, Mr. Wisner. May I have a copy

12:19:05 of that? I asked you for it.

MR. WISNER: I gave it to you yesterday.
MR. BAYMAN: His Honor has it.
MR. WISNER: Okay. Sorry. I didn't check my e-mail during trial.
12:19:18 BY THE WITNESS:
A. I have this one here if you want it (indicating).
(Brief pause).
(Document tendered.)
BY MR. WISER:
12:19:32 Q. Let's start with the top here. What is the first way, in your opinion -- well, let me get the opinion out first. Do you believe GSK hid the suicide risk?
A. There are a lot of ways that you can handle the data that will make the problem go away.
12:19:47 Q. All right. Let's go through the different ways that you have on this list that you created.
What's the first one?
A. Well, it's the use of the washout period. This is the thing that we referred to early on yesterday afternoon, maybe
12:20:01 early on today, where when the person is taken off the prior treatment, before they actually go into the after trial. So they have a period of time where they may be taking a placebo pill, but they're not actually being treated, and they may be possibly suffering the effects of withdrawal from prior
12:20:20 treatment.

Q. And have you observed that GSK used data obtained during this washout period to wash out suicide signals?
A. Well, yes. There's things that happened during this period, which the company should collect the data, it's what you do with the data that becomes the critical thing. I'm not saying you shouldn't collect the data, you should, but what you do with it then becomes the critical thing.
And what's happened among the Paxil data is the data has been used to minimize the risks from Paxil.
Q. Okay. Well, why don't you turn your attention to Plaintiff's Exhibit 75.
A. Yes, I have it here.
MR. WISNER: Your Honor, at this time I believe 75 previously has been admitted into evidence.
(Exhibit published to the jury.)
BY MR. WISER:
Q. So what is this document, doctor?
A. Okay, this is -- this is a safety -- safety summary from the Paxil trial data compiled around the time that GSK were applying to get Paxil approved in the United States and the United Kingdom and elsewhere.
Q. It says an integrated summary of safety. What is the purpose of this document?
A. Well, this is one of the documents. This is a typical of the kinds of documents that all companies produce for all the

drugs that they're applying to FDA with to brief FDA reviewers on what the issues look like with their drug, both from the point of view of what the company has observed outside clinical trials but also in clinical trials.

12:22:06 Q. It's dated November 1989. What's the significance of that date?

A. This was either the data close to the date when GlaxoSmithKline, the first application to FDA to get Paxil approved.

12:22:19 Q. Okay. Let's go into the document a little bit, doctor. And let's -- well, did this document get into potential suicide or suicidal events?

A. Well, you'd expect that the events would be there in the case of any antidepressant and any trials that are done,

12:22:39 because people who were depressed can go on to become suicidal, you'd expect a document like this to include some discussion of that.

Q. All right. If you turn to the page, the page that is numbered at the bottom, 274.

12:22:56 And I'll represent to you, doctor, that this document is not the entire document. How big is this document in its entirety?

A. Well, it's a bigger document than what I have here, but what I have here goes up to 396 pages and it looks like it goes

12:23:13 on further.

Q. Okay. All right. I'm pulling up what is a table. Do you see this, doctor?
A. I do, yes.
Q. And what is this table --
12:23:21 MR. BAYMAN: Your Honor, we talked about the rule of completeness. This is not the complete Document.
THE COURT: It's not the complete document, did you say, sir?
MR. BAYMAN: Yes.
12:23:31 THE COURT: That's correct.
MR. BAYMAN: Yes, the asterisk needs to be below. There's information missing.
THE COURT: I can't hear you, sir.
MR. BAYMAN: He needs to show where the asterisk is,
12:23:41 Your Honor. The jury should be entitled to see.
MR. WISNER: It's there, Andy. We're getting there. We'll get to the asterisks.
MR. BAYMAN: All right.
BY MR. WISER:
12:23:53 Q. All right. Doctor, so what is this document here?
A. This is looking at the deaths that have been reported in --
MR. BAYMAN: Your Honor, he needs to pull up the asterisk when he blows this up to the jury, under the rule of completeness.
12:24:13 MR. WISNER: We'll get to that in a couple of seconds,

Your Honor.

THE COURT: All right.

BY MR. WISER:

Q. All right. Let's get the question that's pending answered.

12:24:19 What is this table, doctor?

A. This is looking at the Paxil clinical trials. And there have been 2963 patients gon on Paxil. There's 531 patients gone on other antidepressants. And one of the things -- there's nothing rocket science about anything I'm going to say

12:24:38 to the jury over the next file. Any of the jury going through this, someone on the jury would spot the fact that there's no number for the placebo patients here and would be a little puzzled by it.

I mean, you have to remember, you know, a person like

12:24:53 me even going through this, it's not from the point of view of an expert often. You're looking at these things and a thing like this hits you and you say, why is the number of patients missing. And you don't always have an answer for it. The answer becomes clear a little while later.

12:25:08 Q. All right. Well, by referencing a placebo column, what is that telling the person reading it?

A. Well, you have -- I mean, you see, you expect that there's two deaths on placebo.

Q. Fair enough. We'll get to the deaths in a second. I just

12:25:25 want to make sure I understand what the column is supposed to

reflect. Who are the people there that are in the placebo column? Who are supposed to be there?
A. I would expect at this point is the people who have been put on placebo in the Paxil trials.
12:25:36 Q. Okay.
A. And there's been 12 deaths on Paxil but 3,000 patients. So I'm not too alarmed by this table when I see it first.
Q. So it says 2 deaths in the placebo and then there is an asterisk. And I pull up the asterisk here, it says 2 deaths
12:25:52 occurred during the placebo run-in period, do you see that?
A. I do.
Q. Are those patients in the placebo group?
A. They are not in what I would've expected. My expectation when I'd see this first would be that 2 deaths have happened
12:26:04 after the trial proper has begun. I don't expect that the deaths happened in that tricky week or two before the event, which is what the asterisk is telling me.
That the deaths didn't happen in the trial proper, they happened before the trial proper had started and somehow
12:26:24 the impression has been conveyed that they happened in the placebo arm of the trial.
Q. Now, doctor, I want to make sure I understand this --
MR. BAYMAN: It doesn't say that, Your Honor; objection.
12:26:36 THE COURT: Overruled. You may cover that on

cross-examination, sir.

MR. BAYMAN: Thank you.

BY MR. WISER:

Q. Now, doctor, I'm confused. In these placebo-controlled trials, which patients go through the washout period?

12:26:45

A. Everybody goes through the washout period. Now, I happen to know that something like 554 patients who go on placebos. This is the missing number.

There's a few ways you can handle it. If you look at it, if you do a quick math, you'll see there's roughly 4,000 patients altogether going on Paxil or other antidepressants are placebo. So you could say, if you wanted to include the placebo run-in period deaths here, you could say it's 2 patients from -- it's 2 deaths from 4,000 patients, but you should not say this is 2 deaths from 554 patients.

12:27:01

12:27:23

Q. Well, let me ask you another question. Let's say we did it that way and put the actual in properly and then a suicide happened actually in the placebo treated arm, could you put that number in there or would it have to go to a different column?

12:27:42

A. Well, this is where it gets complex and tricky. If you did add to that number in there, then, of course, the number would be 3, but you're mixing two different groups of -- well, 2 -- 2 different populations.

Q. All right. Well, let's go to the next one. Let's talk

12:27:57

about the suicide --

THE COURT: Well, wait, before you leave that. Are you finished with that?

MR. WISNER: With that table for now, yes. Yes, we're done with that table.

12:28:08

THE COURT: Put that back up there.

MR. WISNER: Oh, sure, Your Honor.

THE COURT: Explain to me and to the jury what happens with that number 2.

12:28:21

THE WITNESS: Well, strictly speaking, if it had been me that had compiled the table, you'd have the 554 placebo patients there --

THE COURT: It says 531.

THE WITNESS: No, no, that's active control. There's a missing number, Your Honor.

12:28:36

THE COURT: Oh, there's a missing number.

THE WITNESS: There's a missing number, which is the number of patients who go on placebo, which is something like 554. I may have slightly the wrong number, but that's close to it. And you would have zero deaths from 554 patients, that would be the proper way to report this data.

12:28:50

If you want to include -- if you want to let people know that 2 deaths occurred during the placebo run-in period, and I've written on this, I produced an article on just this trying to work out how risky the placebo run-in period is, you

12:29:06

should have 2 deaths from 4,000 patients, that's 2963 added to 531 and added to 554.

THE COURT: Okay.

BY MR. WISER:

12:29:24 Q. Now, if that 2 should be actually zero -- well, strike that.

If the 2 deaths occurred during the run-in period, can you scientifically and appropriately compare that death to someone who committed suicide after they got Paxil?

12:29:40 A. No, you shouldn't. And it becomes oddly complex in that because of the run-in period, people in the placebo group may be at greater risk than the people in the -- in the -- the Paxil group. So the placebo run-in period is a very complex beast. It turns out to be the riskiest period of all these

12:30:04 trials.

Q. Why is it so risky?

A. Well, because you've been withdrawn from prior treatment. And the Paxil patients in these trials -- it's supposed to be randomized trials. You'd take everything out of the mix. So

12:30:16 Paxil has been treated equally to placebo, but, in fact, the Paxil patients are getting an advantage in these trials compared to placebo, because if the person is say on a prior antidepressant, one of the other tricyclic antidepressants, most of these are serotonin reuptake inhibitors, but if you

12:30:34 stopped them abruptly, there can be problems, and Paxil can

potentially alleviate those problems.

So in a sense, the randomization, these randomized controlled trials, is solving all problems, no bias can come into them. In fact, the placebo run-in period gives anti-treatments, like Paxil, an advantage over placebo.

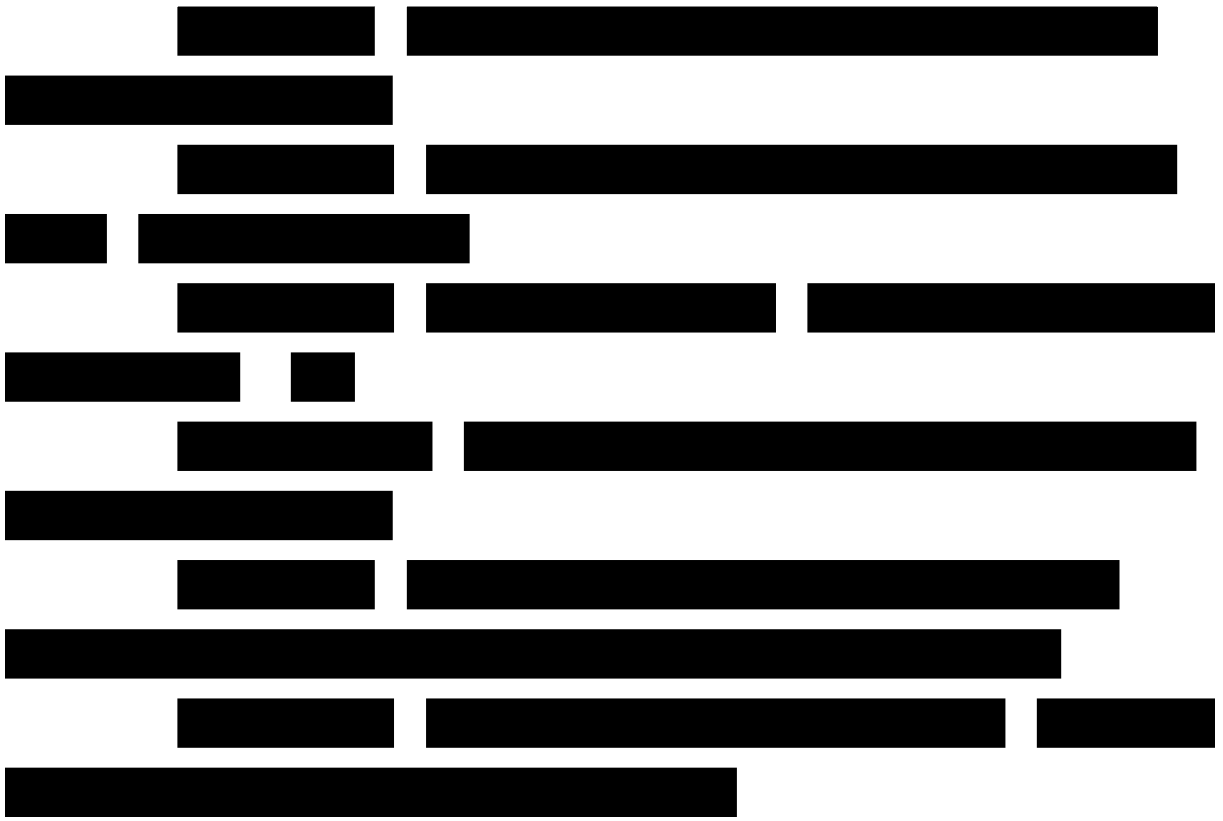
Q. How many deaths occurred in the placebo arms at the clinical trials?

A. None.

Q. All right.

THE COURT: We'll break here, then, ladies and gentlemen until 1:30.

(The following proceedings were had out of the presence of the jury in open court:)



12:32:33