TAB 1

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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IN RE: '318 PATENT INFRINGEMENT LITIGATION, : CIVIL ACTION : NO. 05-356 (KAJ) : (Consolidated)

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Wilmington, Delaware
Friday, March 3, 2006 at 9:30 o'clock, a.m.
TUTORIAL CONFERENCE

- - -

BEFORE: HONORABLE **KENT A. JORDAN**, U.S.D.C.J.

- - -

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P R O C E E D I N G S

(REPORTER'S NOTE: The following tutorial conference was held in open court, beginning at 9:30 a.m.)

THE COURT: Good morning. Please be seated.

We have a couple things to deal with today. This has been on the calendar for some time for a tutorial. I appreciate everybody being here.

Before we get the cameras rolling on us for the tutorial, I did want to -- and I gave a heads up to you kind of late in the day but I gave a head's up yesterday that I was wanting to talk to you about the motions to strike the willfulness or the motion to dismiss the willfulness claim. And I am going to go ahead and nobody has to say anything more than they have said in the papers if they don't want to but if there is something you want to add to the papers, this is a pretty straightforward issue, I'll hear you on it.

Ms. Matterer, is there anything from your side? I believe it's Mylan's motion.

MS. MATTERER: That's correct, Your Honor. This is William Rakoczy from Rakoczy Molino Mazzochi Siwik.

MR. RAKOCZY: Good morning, judge.

THE COURT: Good morning.

MR. RAKOCZY: Should I approach the podium?

THE COURT: Sure, that's fine. Please.

MR. RAKOCZY: William Rakoczy for the Mylan defendants on the motion in which all the defendants have joined. We would just add, we just want to confirm the Court in fact got the last citation we submitted.

THE COURT: I did. I got that Northern District of Georgia case a couple days ago.

MR. RAKOCZY: Unless Your Honor has any questions for us, we have nothing outside what is in our papers.

THE COURT: I don't.

Mr. Pappas.

MR. RAKOCZY: Thank you, Judge.

MR. PAPPAS: Good morning, Your Honor. George Pappas on behalf of the plaintiffs.

I would just say in slight addition to our papers that having reviewed the authorities that have been cited by the defendants, it's clear to us that this is an issue on which District Courts throughout the country disagree. The Federal Circuit has not clearly spoken to it and we believe that the willfulness claim should proceed and particularly on our particular facts, we have to develop a full record.

THE COURT: Okay. Thanks. Well, there is going to be plenty on this case for me to be writing memoranda

orders and opinions and holding forth at length on various aspects of patent law. I don't think I need to add to the written opinions that already exist on this. I'm granting the motion.

Judge Sleet has already spoken on this subject in this District. I think the Glaxo case is clearer than some people might think it is. When they say mere fact that a company has filed an ANDA application or certification cannot support a finding of willfulness, I don't think that leaves the door open the way the plaintiffs seem to say, well, this isn't a mere filing, it's a baseless filing and, therefore, it's somehow more problematic than that.

And that argument was specifically addressed the in the Lupin case, which was an Eastern District of Virginia case that came out just last month, January of this year. And I don't think I can say it better than this. That Court noted that -- headnote one, it's page seven of the slip opinion -- that even a baseless ANDA filing could not constitute an act of willful infringement, although a baseless ANDA filing could constitute an exceptional case. I think that Court has it right.

I'm saying nothing about whether or not there may be some litigation, misconduct or purpose or a foundation for sanction at some point. I'm just not getting into that. I'm making a statement solely on the issue of whether

there is a claim for willfulness; and I think the courts, the authority is steadily building against the plaintiffs' position. I accept the authority that says they don't have a claim in this case for willfulness.

So I'll issue an order that says for the reasons stated in open court, the motion to dismiss willfulness claim is granted. And, again, I reiterate I'm basing this and adopting the logic set forth in Lupin and Judge Sleet's opinion, the Allergan vs. Alcon case as well as the more recent, I guess it's a February 28th decision coming out of the Northern District of California that was submitted.

Okay. Since we were all together, I thought it would be productive to get that taken of. That way we know what we're dealing with going forward.

This is also now my opportunity to have you folks take me to school and I appreciate your all being here and prepared and ready to do that for me. And why don't I give the podium first to Mr. Pappas to speak on behalf of the plaintiffs.

MR. PAPPAS: Your Honor, again George Pappas on behalf of the plaintiffs.

Your Honor, this is our chance to give you the tutorial on the basic fundamental technology we think will assist you in this case. We have chosen to proceed electronically today. We had advised the other side we

would proceed with an electronic presentation. I wanted to tell the Court we're doing it for a very basic reason. We have a number of graphics that demonstrate to you what happens in the brain and in order for that to live and be meaningful for you, we needed to join that with the text. So we will begin playing that in a minute.

I have notebooks with the transcript of my remarks, Your Honor, as well as the pictures you will see and would like to hand them to you and your clerks and the other side so you can make notes as the presentation proceeds and then I will be back up ready to respond hopefully thoroughly and completely to any questions you may have.

THE COURT: Okay.

MR. PAPPAS: I would just say, Your Honor, you may see some pictures in here of an Alzheimer's patient. It comes from a special called Quick Brown Fox and we obtained approval from the producer and the production company before including this. So I just wanted to comfort Your Honor that you're not viewing something in your courtroom in an intellectual property case for which approval has not been obtained.

So with that, Your Honor, I'd like to hand up the notebooks and proceed.

THE COURT: Thank you.

MR. PAPPAS: I can tell Your Honor the presentation you are about to see will take exactly 30 minutes.

THE COURT: All right.

(Documents passed forward.)

MR. RAKOCZY: Your Honor?

THE COURT: Yes.

MR. RAKOCZY: May we sit over in the box so that we can see the screen?

THE COURT: Sure, that is fine, if you will have a rough time seeing it.

MR. RAKOCZY: Thank you, Judge.

THE COURT: Sit where you need to sit.

MR. PAPPAS: We ready to go. Your Honor, for the record, so you know what we've handed you, you will see hard copies of all of the graphics that you will see for the Court's further use and for the law clerks, your clerks as well. Now and perhaps next year. I don't know when your clerks change, Your Honor. In addition, there is a CD in the front so that it can be replayed as often as you would like.

THE COURT: All right.

MR. PAPPAS: Thank you.

(Digital video disc played.)

"Mr. Pappas: Good day, Your Honor. I'm George

Pappas, a partner at Covington & Burling in Washington, DC. We submit this DVD technical tutorial on behalf of Janssen Pharmaceuticals and Synaptech Inc. --"

MR. PAPPAS: Excuse me, Your Honor. Could we dim the lights?

THE COURT: Yes, we'll take care of it.

MR. PAPPAS: Thank you.

"Mr. Pappas: -- in the matter of the '318 Patent Infringement Litigation, Consolidated, Case No. 05-356-KAJ.

Alzheimer's Disease is a degenerative disease of the brain that produces progressive dementia characterized by memory loss, disorientation, language loss and loss of self-care functions. Ultimately, Alzheimer's Disease causes death, but the terrible disease at the center of this dispute is even more than that.

It slowly destroys people's ability to function, leaving them lost, confused and angry. It cruelly separates couples in the twilight of their years, rendering them often alone. It robs caregivers of their freedom, stripping patients of their dignity. Ultimately, it takes away lives -- the lives of its victims and their loved ones.

Alzheimer's Disease is a major public health problem for the United States today because it has such a huge impact on individuals, families, the healthcare system

and society. It is estimated that up to 4 million people now have Alzheimer's Disease.

Yet Alzheimer's Disease has proven extraordinary hard to attack, in part because it involves an extremely complicated cascade of processes affecting the most complex structure known -- the human brain.

It triggers a series of biochemical processes that are difficult to interrupt without harming the patient. And, importantly, the disease kills tissue that our bodies cannot regenerate: the nerve cells, or neurons, of the brain.

Despite the resources dedicated to the addressing this disease, there is no cure for Alzheimer's today. In fact, sadly, the last quarter century of concerted scientific effort has yielded only five drugs approved by the FDA to treat Alzheimer's.

By contrast, there are over 125 drugs approved for treating cancer patients and many of those patients are cured -- yet not one single Alzheimer's patient has ever been cured.

The dispute before Your Honor concerns one of the treatments that offer help for these patients and their caregivers -- Razadyne, a galantamine-based treatment for Alzheimer's Disease.

Now, to understand Alzheimer's Disease, it is

important to understand how the brain functions. The brain is comprised of interconnected anatomical compartments called lobes. Within these anatomical structures are billions of nerve fibers, called neurons. These interconnected cells are the means by which messages in the brain are communicated. Each neuron has a cell body which contains a nucleus that controls all of the cell's activities.

The neuron also has a long process called an axon. Axons contain micro-tubules that work like tiny pipelines connecting the cell body to the nerve endings. These delicate tubules are supported and held open by tau proteins woven into their walls.

Dendrites also branch out from the cell body and receive messages from the axons of other nerve cells. As a neuron receives messages from surrounding cells, an electrical charge or nerve impulse builds up. The charge then travels down the axon until it reaches the end and a structure called the presynaptic bouton. This is where chemical messengers called neurotransmitters are stored, ready to carry impulse to the next neuron.

Here, the bouton releases neurotransmitters which move across a tiny gap called the synapse. The neurotransmitters bind to specific receptor sites on the far side of the synapse, continuing the impulse in the

post-synaptic neuron.

During any one moment, millions of these signals are speeding through the pathways in the brain, allowing it to receive and process information, make adjustments and send out instructions to various parts of the body. There are many types of neurotransmitters at work in the brain, perhaps 100.

Some neurotransmitters inhibit nerve cell function making it less likely that a nerve cell will send an electric signal down its axon. Other neurotransmitters stimulate nerve cells priming the receiving cell to become active or send an electronic signal down the axon. However, individual neurons use only one neurotransmitter each, so they are distinguishable by type.

By far the most numerous are neurons that use the two neurotransmitters, GABA and glutamate, between them accounting for about the 90 percent of the brain's neurons.

At issue in this case is another neuron, the cholinergic neuron and its neurotransmitter called acetylcholine, which is critical to attention and memory.

It is also important that there are two kinds of neurotransmitter receptors associated with cholinergic neurons -- nicotinic and muscarinic receptors. Muscarinic receptors are associated with recent memory (also known as short term memory). Nicotinic receptors are associated with

attention.

It has long been known that Alzheimer's brain tissue is characterized by two particular pathologic features, "plaques" and "tangles." Understanding the nature of these plaques and tangles sheds light on the pathophysiology of the disease.

Plaques are small accumulations of protein, surrounded by a zone of inflammation. We can think of them as lesions that "form" scars in the brain, disrupting normal impulses and harming adjacent cells.

Plaque formation begins with a normal protein we all have called APP or amyloid precursor protein. It is present in certain brain cells, lodged in the membrane, partially inside the cell and partially outside.

In Alzheimer's, something causes an enzyme to metabolize or clip-off the ends of the APP, and the middle or "beta" section is released outside of the nerve cell. These beta amyloid pieces tend to aggregate or clump together -- and that is the genesis of a plaque. Plaques grow and begin to impinge on and irritate adjacent cells, provoking an immune response.

Microglial and other immune cells release fibrous material and oxidants -- as to if to combat infection -- but these actions initiate a vicious cycle:

More cells are irritated, and more immune cells

are summoned.

A zone of inflammation forms around the plaque. It grows to displace normal tissue, and disrupts transmission of impulses through surrounding nerve junctions.

Neurotransmitter supply is also disrupted in the axons of these adjacent neurons. This is caused by formation of the second earmark of Alzheimer's: neuro-fibrillary tangles.

It is currently believed that beta amyloids lead to tau proteins becoming detached from the walls of micro-tubules and are released into the body of the neuron. Micro-tubules collapse and no longer transport critical elements like neurotransmitters and their synthesizing enzymes to the nerve ending.

The tau proteins distort and aggregate, forming tangles characteristic of Alzheimer's.

Tangles pose a double threat to nerve cells: neurotransmitter protein production that sustains the neuron is hampered or stopped altogether, and transport along the axon is obstructed.

The result is poor conduction -- there is not enough neurotransmitter at the nerve ending, so impulses are not propagated normally. Other vital cell functions are compromised, until the cell fails entirely and dies.

A wide variety of neurotransmitter systems are compromised by the disease, including norepinephrine, serotonin, somatostatin, vasopressin, beta-endorphin and "substance P." Slowly, the symptoms of disease begin.

Alzheimer's Disease begins insidiously. Often, Alzheimer's is first recognized by the loss of recent memory, with the patient repeating questions minutes after asking them or forgetting visits or phone calls. Depression and apathy are common signs. Loss of brain tissue may be substantial.

Patients also exhibit a decline in what is known as "executive" function or the ability to get things done. Patients lose the ability to do complicated tasks like balancing their checkbook, finding the right key among several on a key-ring or preparing a meal. Patients also experience a loss of empathy, and lose interest in people and subjects they used to be passionate about.

Even in the early stages, the burden on the caregiver can be overwhelming, since the patient rapidly becomes increasingly dependent on the caregiver.

With advancing disease, there is a progressive worsening of the early symptoms and the emergence of new ones. Language ability suffers, and aphasia, or forgetting words and their meanings, combines with language confusion -- a compromise in the ability to follow the

meaning of a conversation.

As disease progresses, patients lose the ability to monitor and control their own behavior. Many patients become disruptive and agitated irritability often gives way to angry uncooperativeness. Personal grooming and hygiene suffers, even among the formerly fastidious.

Disrupted sleep cycle, delusions and aggressive outbursts can overwhelm the caregiver. It is often around the patient's refusal to bathe that upsets often become more than the caregiver can handle, and families turn to institutionalization.

Institutionalization or close supervision is essential as patients tend to wander off and become lost or injured. The outlook at this point in the disease is bleak. The cerebral cortex, including a wide range of neurons, is severely affected.

At its advance stages, Alzheimer's patients experience breakdown of motor control, and lose coordination, their limbs becoming rigid. They are bed or wheelchair-ridden, unable to move and eventually unable even to swallow. Urinary and bower incontinence occur. It is often the difficulty with eating, accompanied by food aspiration and pneumonia that is the cause of death.

As destructive as the disease is on the mind of its victim, it is equally devastating to those people, often

family members, who care for these patients. Caregivers often must provide round-the-clock supervision and care to Alzheimer's Disease patients. In return, they are often subject to inappropriate and sometimes aggressive behavior.

Treatments for Alzheimer's like Razadyne can alleviate the caregiver burden and help not only the patient but also the caregiver as well. By improving a patient's cognitive abilities, these treatments enable the patient to handle more tasks, freeing the caregiver and providing them time to escape his or her burden from time to time.

It is thought that such treatments not only provide the caregiver with relief but also may delay institutionalization. "Senility" simply means being old, and for centuries, diminished mental capacity and loss of memory were thought to be a normal part of aging.

Alzheimer's was first described as a distinct disease in pre-senile individuals -- that is, those under 65 -- in 1907 by the German researcher Alois Alzheimer. While examining the brain tissue of a woman who in her 50s had died of a dementing illness, Dr. Alzheimer recorded the plaques and tangles that marked the disease that came to bear his name.

By the 1960s, science recognized that Alzheimer's appears in several forms, including the rare early-onset disease that runs in families, and the more

common form in the elderly often referred to as "senile dementia of the Alzheimer's type."

Today we know that Alzheimer's is far from rare. It is recognized as an epidemic that strikes almost half of us who live into our mid 80s. And, the over 85 age group is the fastest-growing segment of the U.S. population. As more in our society live longer, it is inevitable that Alzheimer's will emerge as an increasingly urgent public health challenge.

By 1985 -- just over 20 years ago -- there was significant awareness in the scientific and medical community of the disease, tremendous demand for help from medical science, yet not a single FDA-approved treatment.

At that time, there was only the most primitive understanding of the biologic chain of events that leads to cell death and loss of brain tissue in Alzheimer's Disease. Understandably, without clear strategies for attacking the disease process, there could be very little agreement among scientists about where to begin looking for a treatment.

Dr. Gene Cohen of Cold Spring Harbor Laboratory and the eventual director of the National Institute of Mental Health, wrote in 1983: "no treatment is presently available that can prevent or arrest the underlying pathologic process of the disorder ... a present-day mystery within medicine in the whodunit sense)."

Indeed, researchers report a bleak prospect for finding any pharmacologic treatment. Dr. David Drachman, a leading neuroscience researcher wrote in 1985, and I quote, "Despite sporadic reports of barely detectable improvements with various drugs or drug combinations, therapeutic efforts have, in general, failed to produce improvement of clinical value."

A look at the work that was being done at that time and in the years since shows a wide ranging field of study, with some studies in direct theoretical opposition to others. For example, because of the prevalence of depression amongst Alzheimer's patients, researchers tried treating with antidepressants. The antidepressants in use had an anticholinergic effect, reversing the effect of acetylcholine at the neural synapses.

Drs. Burton Reifler and Belinda Teri at the University of Washington tried unsuccessfully tried to treat Alzheimer's patients with Tofranil. As we will see, other researchers at the time tried to add choline to make more acetylcholine -- also without success.

Dr. G.M. Petracca at the Institute of Neurological Institute in Buenos Aires tried serotonin reuptake inhibitors like Prozac to compensate for the serotonin deficiency we see in the Alzheimer's brain -- and it didn't work.

Similarly, norepinephrine agonists should work to counteract the deficit we see in Alzheimer's for norepinephrine. Researchers, including Dr. Thomas Chase, at the National Institute of Neurological and Communicative Disorders and Stroke in Maryland tried guanfacine, a norepinephrine agonist, and it didn't work either.

Yohimbine, a drug that blocks a norepinephrine receptor, should have been effective in restoring the norepinephrine deficit. Researchers like Dr. Gerry Yesavage tried it, and it was not.

There was great hope for a class of drugs called monoamine oxidase inhibitors or MAO inhibitors. They had been shown to not only increase norepinephrine at the neural synapses, but also increases dopamine and serotonin. Dr. Mary Sano, an investigator with the National Institute on aging-supported Alzheimer's Disease cooperative study or ADCS tested selegiline.

Unfortunately, it just didn't work in treating Alzheimer's -- and no MAO inhibitor has yet to be approved for the treatment of Alzheimer's Disease.

Researchers such as Dr. Don Crapper-McLachlan at the University of Toronto tried chelation -- a therapy to remove aluminum from patient blood and tissue. There was a belief that aluminum from cookware had accumulated in Alzheimer's patients bodies and hope that its removal could

arrest or reverse the disease. However, both the theory and the therapy were disproved, though only after a national scare about aluminum pots and pans.

Researchers like Dr. Steven Dekosky with the University of Pittsburgh had been investigating reported benefits from the herbal remedy, ginkgo biloba. It appears that those benefits were also either illusory or too small to measure -- another false hope.

Prednisone has been called a miracle drug, and it has earned that reputation as a most effective weapon in fighting inflammation. Alzheimer's is a disease that destroys tissue, at least in part, through inflammation. So researchers, such as Dr. Paul Aisen, at Georgetown University, believed that prednisone should work. Once again, it didn't help. In fact, patients in the study got worse.

Similarly, a retrospective study of non-steroidal anti-inflammatories looked good, but when tested on patients by the ADCS, proved ineffective. No NSAID has been approved for treatment for Alzheimer's Disease.

Researchers like Ruth Mulnard at the University of California, Irvine, directing the ADCS multi-site study, tried estrogen as a therapy. This large study showed it to be ineffective in Alzheimer's. In addition, the Women's

Health Initiative study demonstrated that estrogen may even harm cognitive function in older women.

Based on evidence that blow flow is reduced in Alzheimer's patients, scientists in Europe and elsewhere have tried vasodilators, like papaverine, cyclandelate, and isoxsuprine -- without success.

There was also interest in a group of drugs called "metabolic enhancers" that were believed to improve nerve cell function. These included ergaloid mesylates and nootropics such as Piracetam. A review of these studies by Dr. Pierre Tariot at the University of Rochester demonstrated these treatments are in effective against Alzheimer's.

With time, none of these once promising therapies has proven effective in the United States. Even those researchers who focused on the cholinergic system still went in wrong directions and encountered multiple dead ends.

The first strategy tried to increase acetylcholine was to enhance the supply of precursors or the chemical ingredients the body uses to make acetylcholine. A variety of precursors was tried, such as choline and lecithin -- none helped.

A second way was to directly stimulate the cholinergic receptor. As noted, there are two types of

cholinergic receptors -- nicotinic and muscarinic.

The prominence of memory problems in Alzheimer's Disease led many researchers to focus on the muscarinic receptor. The drug company Lilly, for example, devoted resources to the development of the drug xanomeline. This proved to be another dry hole in search for an effective treatment -- the drug did not work.

Two other agonists, arecoline and bethanechol failed as well.

A third way to enhance acetylcholine would be to find a way to reduce the brain's normal breakdown of acetylcholine that is released by an neuron.

The body releases the enzyme cholinesterase to break down acetylcholine in the synapse.

Use of a cholinesterase inhibitor may help to increase the effective levels of acetylcholine in the brain by interfering with this breakdown of acetylcholine in the synapse, thereby giving the acetylcholine released into the synapse more time to stimulate receptors.

However, there were a number of reasons many experts didn't expect cholinesterase inhibitors to work.

First, as many as 100 neurochemical pathways are affected in Alzheimer's. Acetylcholine is only one, representing only a few percent of neurons in the brain and a small minority of the neurons in the temporal cortex where

Alzheimer's strikes first.

Another problem was that for a cholinesterase inhibitor to work, there has to be a sufficient number of functioning cholinergic neurons. A cholinesterase inhibitor cannot increase the amount of acetylcholine produced in the brain. Rather, it works to protect the acetylcholine that is produced by blocking its removal.

Hence, if the cholinergic system were selectively attacked by Alzheimer's Disease or otherwise too degraded by it, the drug would be targeting cells that were no longer capable of functioning. And cholinesterase inhibitors could be quite toxic. Indeed, researchers were discouraged by the difficulty of finding one with a sufficiently broad therapeutic index to be safe for elderly patients.

Dr. R.J. Wurtman at MIT writes in 1985, and I quote, "A drug that inhibited acetylcholinesterases everywhere, as physostigmine apparently does, and thus enhanced cholinergic transmission everywhere, would have too many side-effects to be used clinically ..."

Thus, there was substantial controversy over the potential use of cholinesterase inhibitors in the scientific community. But the utter failure of so many other avenues led a number of researchers in the late 1980s and the early 1990s to focus on them as a potential therapy.

Drug companies joined this search, and by 1996 there were at least 13 cholinesterase inhibitors in clinical trials.

Of all these cholinesterase inhibitors tried in humans 10 years ago, only four: tacrine, donepezil, rivastigmine and galantamine -- were ultimately approved by the FDA. The approaches may have varied but the results were generally the same -- failure. Thus, for many researchers since 1985, being in the right haystack didn't help to find the needle.

In the 1980s, galantamine was by no means the most promising cholinesterase inhibitor. It had several significant disadvantages over other candidate drugs:

It is a weaker cholinesterase inhibitor than many and indeed has essentially no effect on one of the types of cholinesterase inhibitors in the brain -- namely, butyrylcholinesterase. It is a natural product, and there was no technology to synthesize it in the 1980s. This raised concerns for purity, toxicity and source of supply -- critical for commercialization of a drug.

Unlike some of the other candidates, galantamine is metabolized in the liver, a less-desirable drug for elderly patients.

Ezio Giacobini, a leading researcher on cholinesterase inhibitors, writes as late as 2000, and I

quote, "This difference is clinically important since elderly patients show decreased hepatic metabolism, and therefore drugs that are not hepatically metabolized are preferred."

In the late 1970s and early 1980s, Dr. Bonnie Davis was a medical doctor, studying the so-called "neuroendocrine window," the way in which hormones in the blood can shed light on what is going on in the brain.

Using this novel approach to the problem, she came to understand the unique properties that galantamine offered and invented a method for treading Alzheimer's using galantamine or galantamine acid salts in a range of dosages. She applied for a patent in January of 1986.

But even after issuance of the '318 patent, skepticism of galantamine as a treatment for Alzheimer's Disease continued. Dr. Davis' method was rejected by numerous drug companies that she approached. For example, Wyeth, Upjohn, and Bristol-Myers Squibb turned her down.

Dr. William Cressman, Assistant Vice President for Licensing and Business Development for Wyeth declared that "the potential for success of tacrine and physostigmine and other anti-cholinesterase products is not very positive."

Dr. Norman Pollack, Contract Consultant and Research Liaison for Upjohn stated it was "already fully

committed to other mechanistic approaches to Alzheimer's Disease which we consider more promising than that offered by galantamine."

And Gary King, Associate Scientific Director for what is now Bristol-Myers Squibb stated that "the therapeutic benefit and long term safety and tolerability of galantamine is still a matter of speculation."

Additionally, Ciba, who initially licensed it for the U.S., terminated the license after a first clinical trial.

After years of effort, Dr. Davis finally saw her invention brought to market and the patients who needed it when Janssen's galantamine drug Reminyl, now Razadyne, was approved in by the FDA in 2001.

Galantamine works in at least two ways to reduce or delay symptoms of Alzheimer's:

First, it interferes with the breakdown of acetylcholine at the synapse by inhibiting acetylcholinesterase.

Secondly, and separate from its cholinesterase activity, galantamine enhances the response of nicotinic receptors to stimulation by acetylcholine. This specifically enhances the nicotinic function in Alzheimer's patients, helping to compensate for the reduced levels of acetylcholine in Alzheimer's patients.

Clinical studies have shown that patients who start treatment with galantamine and remain on it for an extended period of time generally have better cognition and ability to function than those who do not.

Through the past 20 years, thousands of compounds examined, hundreds tested and 30 approved for clinical trials, there are only five drugs approved by the FDA for treating Alzheimer's.

One, memantine, is an NMDA antagonist that reduces glutamate toxicity, and the other four are cholinesterase inhibitors.

Galantamine is the only one that acts directly on both the nicotinic and muscarinic systems and is the only one shown in FDA reviewed pivotal trials to be effective in all four major trial outcomes -- global, cognitive, functional, and behavioral.

Razadyne is a resounding commercial success with over $200 million in sales in the U.S. last year alone. It is the fastest-growing cholinesterase inhibitor in the marketplace.

Galantamine is, according to authorities and certainly for many patients, a long-awaited and much-valued treatment choice for today.

We look forward to arguing the merits of this case before you. Thank you, Your Honor, for your attention

to this tutorial brief."

(Digital video disk recording ends.)

THE COURT: Thank you very much. Let's go ahead and have the lights up.

And let me ask who on the defense side is prepared to go forward with the tutorial.

MR. SQUIRE: Good morning, Your Honor. It's Monte' Squire from Young Conaway. And I'm joined by Ed Donovan and Corey Manley from Kirkland & Ellis and Mr. Donovan is going to do the presentation.

THE COURT: All right. Thank you.

MR. DONOVAN: Good morning, Your Honor.

THE COURT: Mr. Donovan.

MR. DONOVAN: If we can have a second to bring up our presentation?

(Pause.)

MR. DONOVAN: May I hand them up to the Court?

THE COURT: That would be helpful. Thanks.

(Documents passed forward.)

THE COURT: Please proceed.

MR. DONOVAN: Good morning, Your Honor. My name is Ed Donovan from Kirkland & Ellis and I am representing the Teva defendants in this case. I'll be doing the joint presentation on behalf of all of the defendants.

The defendants are presenting their presentation

in a little different way than the plaintiffs did. We have a PowerPoint presentation that I'll present as we go along.

THE COURT: That's fine.

MR. DONOVAN: At the outset, I should say there was quite a bit in the presentation of the plaintiffs that we can agree with, particularly as it relates to technology. Obviously, there is some argument in there that we disagree with. Among those things would be the arguments as to commercial success, failure of others. Whether or not galantamine acts in two different ways, that is something that at least the FDA is not saying in their papers. So there are disagreements, and I should say that at the outset.

THE COURT: Well, you know what will be helpful to me is -- and I will give Mr. Pappas a chance to respond to this.

You don't have to talk about the obviousness criteria.

The secondary considerations, I think I may be able to pick up on that piece of it and anticipate that you would disagree with it.

The technical stuff, that is what we're here for. So if there is disagreement with any of the technical scientific information that was portrayed, that's helpful for me to know.

And the last point you just made, why don't you make sure you touch on that in the course of your presentation then. And then I will give Mr. Pappas an opportunity on behalf of plaintiffs to respond to anything you say on that; all right?

MR. DONOVAN: I will. Thank you.

Much of what the disagreement was about with plaintiffs, our presentation, simply what is relevant to the issues in this case. We can agree on a lot of things. The brain is very complex. Alzheimer's is a very serious disorder. Much of the details about that are not important to the case. And,

So to begin our presentation, we started at the outset with the patent in this case. This is a patent infringement lawsuit. It's not a lawsuit about the standard for getting a drug approved with the FDA. That is a very different standard.

There is one patent-in-suit in this case, filed in January 1986. That is an important date. It's only two columns long. One patent, two columns long. That is the entire specification.

What is the relevant technology for this one patent-in-suit?

I know Your Honor doesn't want to talk about claim construction and I don't intend to do so here but it

is important to know there are only two claims at issue in this case. The first is an independent method claim. It's a method for treating Alzheimer's by administering pharmaceutically a therapeutically effective amount of galanthamine or its salt.

The second claim is a method claim that is dependent from the first and it claims to administering it orally and within a specific range.

So those are the two claims at issue in this case.

There is no dispute, we saw this in plaintiffs' presentation, that galantamine is a known drug. So the compound galantamine itself is really not at issue in terms of the synthesize or creation of this compound. This is a compound that has been known for a long time.

So if we boil it down, we're in a patent infringement lawsuit. One patent, very short patent, two claims at issue. What is really at issue here is the alleged invention. It's a new use for an old drug: Treating Alzheimer's Disease or related dimensions with galantamine or one of its salts. And then, more specifically, administering that drug galantamine orally within a range, albeit a large range.

Our technology tutorial today will focus on those subjects and specifically Alzheimer's Disease and

related dimensions. That is certainly relevant in a broad sense since this is a patent that relates to a drug for treating Alzheimer's. Drugs for treating Alzheimer, but more specifically, the type of drugs in this case are acetylcholinesterase inhibitors. Not all drugs are treating Alzheimer's.

I think we saw in the plaintiff's presentation, and we can get into a little more date, there is no treatment for Alzheimer's. So this is a class of drugs, acetylcholinesterase inhibitors, for treating certain symptoms.

And then, lastly, galantamine. What do we know about galantamine by 1985? That is an important concept in this case. Because the claims are directed toward galantamine, and galantamine is something that was known in the first column of the patent. That it candidly acknowledges galantamine was known for certain pharmacological uses.

Alzheimer's Disease, that was certainly known by 1985, the time of the patent. Dr. Alzheimer in Germany was the first to observe it. The disease wasn't given that name until much later, but Dr. Alzheimer is the one who is credited with knowing it, finding it.

No one knows what causes Alzheimer's Disease. That is true today. This isn't a case about the cause of

Alzheimer's Disease. Dr. Davis doesn't claim, she did not find the cause of Alzheimer's Disease. We don't know.

There is no cure for Alzheimer's Disease. This is not a case about the cure for Alzheimer's Disease. Dr. Davis's invention doesn't purport to cure Alzheimer's Disease. It is a treatment for a symptom of Alzheimer's Disease.

What do we know about Alzheimer's Disease? We can look at it clinically and we can look at it from its pathological sense, pathology sense. Clinically, it is characterized by dementia. An important part of dementia is loss of memory. A famous example of this, and we saw this in the plaintiffs' presentation, is President Reagan.

Pathology, how do we know it's Alzheimer's? The hallmark of Alzheimer's Disease are the so-called plaques and tangles. There is no good way to find the plaques and tangles until a patient is dead; but what happens is, -- and we saw an animation of that in plaintiffs' video -- there is progressive fallout of neurons.

What is a neuron? It's a nerve cell in the brain and the nerve cells in the brain start to die. There is no way to stop them from dying. Those nerve cells make acetylcholine; and we agree with the statements in plaintiffs' presentation about that. These nerve cells create acetylcholine, eventually they die, and we don't have

acetylcholine. So that is the pathology of Alzheimer's Disease. There is no stopping it. Once it starts, it will eventually kill you unless you die of some other causes.

So certainly that is a point of agreement between plaintiffs and defendants. This is a very serious disorder.

Clinically, it's a brain disorder. This is a disease of the brain. It starts with mild memory loss -- and I'll try to speed with some of this because we saw quite a bit of this. Changes in personality. Decline in thinking abilities. Progresses to a loss of speech and then eventually to death.

Alzheimer's Disease. One important characteristic of it is dementia. This is the scientific definition taken from the Merck manual, but essentially it relates to loss of cognitive ability, loss of memory.

Pathology, Alzheimer's Disease. How do we know it's Alzheimer's Disease? Well, if you look into a patient with Alzheimer's, you will find the plaques and tangles. I won't spend a lot of time on this. But we see in the bottom corner healthy cells and those healthy cells, you can see they're sort of tangled. There are dendrites that hang down.

If I may move to the --

THE COURT: Sure.

(Mr. Donovan approaches the screen.)

MR. DONOVAN: I've got a pointer but the pointer doesn't always work so well.

This is a nerve cell. This is another nerve cell. These nerve cells need to speak to one another. They speak to one another through the neurotransmitters.

Alzheimer's patients have a blocking of that communication; and I'm speaking generally here. They have tangles and plaques. The plaques and tangles, they relate to protein building that we saw in plaintiffs' video. So this is the signature of Alzheimer's Disease in the brain, the plaques and tangles.

Those plaques and tangles block the normal transport of electrical messages. As they die, the brain shrinks and the ability to function deteriorates. This is a quote right out of the FDA consumer magazine. Much of the presentation is from that.

Excuse me.

Treatments for Alzheimer's Disease. How do we treat this very serious disorder? There is no cure for Alzheimer's Disease. There are some drugs to treat the symptoms.

One of the drugs to treat the symptoms are the acetylcholinesterase inhibitors. That is a class of drugs used to treat certain symptoms. What do those

acetylcholinesterase inhibitors do with respect to the plaques and tangles? Nothing. They don't do anything. It treats a symptom. Ultimately, there is no drug that treats the plaques and tangles. There are significant research going on about that and people are spending millions of dollars to try to find a way to either slow Alzheimer's or cure Alzheimer's but that is not what is going on with these particular drugs.

THE COURT: Well, help me out when you say that's not what is happening here.

Do these galantamine and salts of it, do they not have the effect of slowing the progression of the disease?

MR. DONOVAN: That is a very good question, and I'm going to get to a slide on that; but let me answer it upfront now. The answer is there is no evidence that they do. And it's a very difficult thing. What happens is the acetylcholinesterase inhibitors has, as plaintiffs say, it suppresses the destruction of acetylcholine in the brain. The brain generates acetylcholine. Alzheimer's has a deficit of acetylcholine. These inhibitors prevent the destruction of the acetylcholine that is there. Whether that does anything to stop the Alzheimer's or just treats the deficit is not clear and the FDA won't say, and I don't believe there is anything that will say definitively right

now whether these drugs actually effect the organic causes of the disease itself as opposed to treating a symptom. It's certainly clear that at some point they don't work anymore.

They're indicated from mild to moderate Alzheimer's Disease. And once that disease starts taking its course, these drugs can help you. These drugs can help you. These drugs, the acetylcholinesterase inhibitors can sort of help you get your affairs in order. You know, buy you some time. But eventually the disease keeps on going and it will kill you. And I don't think there is any dispute about that.

THE COURT: So the science of this is it doesn't slow the destruction in the brain associated with fibrillary plaques and tangles. It does enough to save that neuro-transmitter while the destruction is going on. The symptoms are retarded even though the disease progression is not. Have I understood you correctly?

MR. DONOVAN: Yes, you said it better. Yes. That's correct. Now, it certainly is the case that nobody knows everything about the science of these drugs but it is the case that they're not -- there is no evidence and the FDA won't say that these drugs effect the organic cause of Alzheimer's Disease.

THE COURT: Thank you.

MR. DONOVAN: So if we summarize some of the topics here on Alzheimer's Disease: Cause is unknown. It's not a case about the cause of Alzheimer's. It's characterized by plaques and tangles in the brain in this case. An understanding of plaques and tangles and the details of that isn't necessary for this case. There is nothing about that in the patent. There is nothing about galantamine that cures plaques and tangles. That is the indicia of Alzheimer's Disease. But this isn't a plaques and tangles case.

No cure yet for Alzheimer's. We're not talking about the cure-all for Alzheimer's, stop the research, no reason to spend any more money. That is certainly not the case. It's at best a treatment for symptoms of this disease. And --

THE COURT: That's not bad; right?

MR. DONOVAN: No, it's not. I don't mean to diminish the drug's beneficial effect.

The next topic is the acetylcholinesterase inhibitor drugs for treating the symptoms of Alzheimer's Disease. And acetylcholinesterase inhibitor drugs have been in clinical use, and we'll show you this, for Alzheimer's Disease since 1970s.

And this is a class of drugs -- and my clicker stopped.

THE COURT: Does someone want to help this man out?

MR. DONOVAN: Can you go to the next screen, please?

THE COMPUTER OPERATOR: It's frozen up.

MR. DONOVAN: Our computer is frozen.

THE COURT: You know what? I actually have the hard copy in front of me, so I'm happy to turn manually to page 16.

MR. DONOVAN: If you would take it down, PowerPoint full screen, and bring it back up.

THE COURT: While he is doing that, why don't you talk to me about Acetylcholinesterase Inhibitors Treat Ad Symptoms.

MR. DONOVAN: We're on page 16 of the presentation.

THE COURT: Right.

MR. DONOVAN: And there are four different approved FDA drugs right now that are acetylcholinesterase inhibitors. And what they are indicated for use by -- "indicated for use" is a technical term used by the FDA -- is mild to moderate Alzheimer's Disease.

THE COURT: Let me stop you for a second just to make sure.

MR. DONOVAN: Sure.

THE COURT: This Reminyl, that's the generic name for the Razadyne, which is the brand name. Have I got that right or wrong?

MR. PAPPAS: If I may. Your Honor, it was originally called Reminyl. That was the brand name. And then for reasons having to do with the name, the FDA asked us to change the name, and that is how it became Razadyne. So when you see Reminyl, it's Razadyne.

THE COURT: Razadyne.

MR. PAPPAS: Yes.

THE COURT: I want to make sure I don't mispronounce it. Ra-za-dyne (phonetic). Razadyne is Reminyl. Reminyl is Razadyne.

MR. PAPPAS: That's correct.

MR. DONOVAN: That's right. And there is no dispute about it.

THE COURT: All right.

MR. DONOVAN: Galantamine would be the generic name.

THE COURT: All right.

MR. DONOVAN: Oh, it's back.

(Computer presentation unfrozen.)

MR. DONOVAN: There are four that are approved. They're approved for mild to moderate Alzheimer's Disease -- The Reminyl being the last that's approved. One of these

FDA drugs has since been withdrawn from the market due to side effects.

One of the things that did come up in plaintiffs' presentation that we should note here is that there is a significant difference between the standard for getting an FDA approved drug to clinicals to test for side effects, to test for side effects and toxicity, all those things as compared to what it takes to get a patent.

THE COURT: I'm with you.

MR. DONOVAN: Okay. In the FDA's words, all four of these drugs work by the same mechanism. And that is a distinction I think on the technical side, as we alluded to at the beginning of the presentation.

Plaintiffs I know were making the claim that galantamine works through a second mechanism, and that is by how it effects the receptors as well as acetylcholinesterase inhibitors. We'll get to that in a little more detail. They stop the destruction of acetylcholine. In addition, they're making a second claim, it effects certain receptors. We would take exception to that. I don't know whether that has been scientifically proved at this point.

THE COURT: And the name of those receptors sound suspiciously like nicotine?

MR. DONOVAN: Exactly. Nicotinics and muscarinics. There are two receptors. I'm probably

mispronouncing them but that's correct.

THE COURT: Okay.

MR. DONOVAN: From our perspective, that is sort of a red herring issue. I know they disagree. That will be a disputed issue as to the relevance of that, perhaps not as to the technology.

How do these acetylcholinesterase inhibitors work? And this is taken directly from the FDA. The drugs increase the level in the brain of acetylcholine, a chemical that nerves use to communicate with each other.

And there is really four important points we want to bring out about the acetylcholinesterase inhibitors:

The first is acetylcholine. And that is something we've heard a fair amount about. What is acetylcholine? Acetylcholine is a neurotransmitter that sends a message from one nerve to another. Acetylcholine is both in the brain and outside the brain, but in the brain it's associated with memory and cognitive function.

It's probably easier if I demonstrate it quickly on the next slide. When we see here a representation of a brain cells -- if I could walk over here.

THE COURT: Fine.

(Mr. Donovan approaches the screen.)

MR. DONOVAN: These are nerve cells in the brain. As I said before, this is one nerve, this is another

nerve. They've got to talk to one another. They're not connected. There is a space between them. This is the end of the nerve. This is the end of another nerve.

Again, I'm summarizing. This space, it's called a synapse. And what happen is nerves work through an electrical charge. The electrical charge comes down to the end. Then it has to send that message to the next nerve. It does so chemically by releasing a neurotransmitter. These little globs here are neurotransmitters represented.

They are released. They come over here to the receptors. The receptors are specific for the neurotransmitter. That receptor comes over here, hits the transmitter, and that triggers another electrical release and, boom, down goes the electrical pulse the other way.

So we go electrical -- sorry, chemical to electrical and back down. These are the neurotransmitters. There are lots of neurotransmitters. The one we're talking about in this case is acetylcholine. That is one of the neurotransmitters.

If we go back the neurotransmitter acetylcholine it's commonly found in nerve-to-nerve connection, so you have a nerve to another nerve. Sometimes, you have a nerve to an organ. A nerve-to-nerve connection that sends a connection from one nerve to the other.

And in the brain, blocking that or those

connections are related to cognitive function and memory. So that is the first concept: acetylcholine neurotransmitter in the brain.

The next concept is what do you do with the acetylcholine after you are done? And that is the last bullet. That's the last bullet. When the message is completed, excess acetylcholine is eliminated by, among other things, an enzyme -- an enzyme called acetylcholinesterase. And I'm shorthanding it there.

What is acetylcholinesterase? I don't have a good picture of acetylcholinesterase.

THE COURT: I'm with you. I think I got the picture.

MR. DONOVAN: It's natural, it's in the body, and it's like people depict them as Pacman. They'll eat up this neurotransmitter. So after the message is sent, it's destroyed by, among other things, acetylcholinesterase and in healthy humans you have a balance of this. So that's the second concept.

The third concept, acetylcholinesterase inhibitors. What are these? These are compounds, and they have been known for a long time, long before the filing of the patent, that suppresses the action of the enzyme. So the acetylcholine sends the message, the enzyme destroys it. If you put an inhibitor in there, you will end up keeping

more acetylcholine longer. It doesn't add acetylcholine, it prevents its destruction.

They've been known for a while and there are a couple different types. One is irreversible, and those are commonly insecticides or toxins. They can be very dangerous. Some are reversible. Galantamine is one of them. And they are used as pharmaceuticals and they have various uses.

The fourth concept is that it was found Alzheimer's Disease have an acetylcholine deficiency. By the 1970s, people had found one of the characteristics of Alzheimer's Disease patients, they are missing acetylcholine. That caused researchers to investigate various ways how to get or keep the acetylcholine in the brain.

One of the ways that was discussed -- and this is from a textbook or chapter in the textbook -- is to try acetylcholinesterase inhibitors, and trials were ongoing in the 1970s trying to see if these would work. And in fact, many of them did work, and that is essentially how acetylcholinesterase inhibitors work. It goes into the brain, suppresses the enzyme and increases or prevents the destruction of acetylcholine in the brain and this helps Alzheimer's patients at least temporarily to increase their cognitive and memory functions.

The 1970 test in the United States, among the most famous of them were up in the Bronx, the Mt. Sinai Hospital, and they showed the validity of the approach; not just talking about it, they did it with Alzheimer's patients in the 1970s showing that physostigmine was effective in Alzheimer's patients in increasing their memory.

So what do these acetylcholinesterase inhibitors do? They all use work by the same mechanism, at least so says the FDA. The drugs temporarily delay the symptoms, they don't necessary cure them or don't cure Alzheimer's Disease. And again, this is the FDA speaking here, their consumer magazine.

There is no evidence these drugs have any affect on the underlying progression of the disease. I don't mean to diminish the importance of the drugs but they are not a cure for Alzheimer's.

In summary, Alzheimer's patients are lacking acetylcholine. Acetylcholine is a neurotransmitter, important for cognitive function. Acetylcholinesterase inhibitors suppress the destruction of acetylcholine. The drugs are believed to delay dementia symptoms such as Alzheimer's.

THE COURT: Let me ask a question here. And I'll just use your Pacman analogy. If I understand acetylcholinesterase to be Ms. Pacman up there, the

acetylcholine, galantamine is somehow like the ghosts that go out there and eliminate or reduce the effectiveness of Ms. Pacman. Have I got your analogy correct?

MR. DONOVAN: That is a good analogy.

THE COURT: It hits those enzymes?

MR. DONOVAN: (Nodding yes.)

THE COURT: Is the disease process -- I understand you both to be saying the disease process is somehow, the deletions, it's the tangles and the plaques and the death affects or it disturbs the normal brain chemistry so you've got like, what, too much of this enzyme breaking down?

MR. DONOVAN: I would put it a little differently.

THE COURT: So somehow it gets out of balance I guess that is what I'm trying to get at. How does it get out of balance? And this may be neither here nor there. I'm just trying to gets my hands around the science.

MR. DONOVAN: Let me address that. And if plaintiffs want to address that, they can do that as well.

In Alzheimer's patients, these patients get the plaques and tangles. Among they things the do, they block the neurotransmitter acetylcholine. Eventually, it kills the brain cells itself. So there is no stopping them. You eventually will have no acetylcholine, you will have dead

brain cells.

THE COURT: So it's not that you get too much enzymes, it's that you don't get enough of the neurotransmitters.

MR. DONOVAN: Exactly.

THE COURT: Is that it?

MR. DONOVAN: That's right.

THE COURT: Okay. You guys agree?

MR. PAPPAS: Yes, Your Honor. Basically what happens is, God forbid anybody in this room contracts Alzheimer's disease, we know that your brain stops producing as much acetylcholine. Now add to that the already existing acetylcholinesterase that destroys the acetylcholine is still out there pumping. So your Alzheimer's, you are getting less acetylcholine and the little bit, much much less you are getting is now being attacked by the acetylcholinesterase, breaking it down further.

THE COURT: That's fine. Thank you. That helps me understand how the imbalance is.

MR. DONOVAN: The next topic we wanted to talk about is galantamine, specifically. And again, there is no dispute that galantamine is not a new drug or a new compound. It's quoted here from a famous Russian scientist Luria, we're talking about 1951. Galantamine

was studied, and had been shown to be the strongest known acetylcholinesterase inhibitors. So there is no dispute people know about acetylcholinesterase inhibitors long before the patent. They knew about galantamine being an acetylcholinesterase inhibitor long before the patent.

Where does galantamine come from? This is a natural compound. This comes from daffodils, the same daffodils you have growing in your front yard. It's a natural compound extracted from daffodils and certain other forms.

That has some interesting side lights we'll talk about in a minute. But one of the things is that since it is a natural drug, people didn't know about it, it's been sold in Eastern Europe since before the filing of the 1985 under the trade name Nivalin. And it's continued to sell today under trade name Nivalin. Type in the name "Nivalin" and you will get lots and lots of hits about galantamine. Nivalin was a drug administered in Eastern Europe that was known to be an acetylcholinesterase inhibitor. It degrades -- inhibits the enzymes that degrade acetylcholine. None of this was new as of 1985.

What was it used for? It was used as a drug. It was used as a drug in patients and humans prior to '85. And it was used, among other things, for patients coming out of anesthesia. Coming out of anesthesia, you are kind of in

a stupor or fog. And this was used as a way to start of bring your cognitive abilities back out a little quicker. I don't think there is proof of that in the United States but they did use it in Eastern Europe.

As well as, again this is the Luria textbook talking about galantamine being used in a wide variety of functions in the central nervous system. What is the central nervous system? That is your brain and spinal cord. People knew you could administer this to humans and it would get into your brain.

People administered it. Again, this is old stuff. You could know that it was administered parenterally, intravenously or orally.

How old is galantamine?

THE COURT: What exactly is parenteral administration?

MR. DONOVAN: Parenteral administration includes intravenous, so it included intramuscular as well.

THE COURT: All right.

MR. DONOVAN: I got prepared on that last night. I am glad you asked.

Galantamine, it's been postulated that people have known about this since the time of Homer. I should say up front I'm not a Greek scholar but it's been postulated to be the molly that was given to Odysseus to overcome Circe

poison. If you know Homer, you probably know better than I.

But this is an old natural drug and the other interesting side light about this particular article was one of the authors was one of the scientists at Mt. Sinai working on that physostigmine clinical trials in the 1970s.

How does galantamine stack up vs. other acetylcholinesterase inhibitors? Well, it's certainly known to reach the brain because people are using it for central nervous system disorders. It is also known to have a long duration of action and less toxicity as compared to other acetylcholinesterase inhibitors. And specifically with respect to physostigmine, one of the big advantages of galantamine, it lasts longer in the brain. Physostigmine would have a shorter duration of action.

So if we sum up on our galantamine, what was known prior to 1985? Well, it was certainly known as a pharmaceutical used in humans.

It certainly known to reach the brain through normal modes of administration, including orally.

It was an established acetylcholinesterase inhibitor. There is no dispute about that.

Effective inhibiting the enzymes in the central nervous system. Long duration of system and less toxicity as well than other acetylcholinesterase inhibitors.

Those are the points, Your Honor, that

defendants wanted to discuss in terms of the technology tutorial: Alzheimer's Disease and dementia, acetylcholinesterase inhibitors and galantamine.

If Your Honor has any questions, we'll be happy to address them.

THE COURT: No. Thank you very much. I appreciate it, Mr. Donovan.

Mr. Pappas, I did tell I'd give you an opportunity, if you wanted it, to say something with respect to the one point that I take is in dispute on the technology front. I understand there is plenty of dispute about some of these other things, whether it was known as galantamine, whether secondary considerations, a bunch of stuff that you could go back and forth and argue about; but on this one scientific point about whether the drug in question Razadyne acts both to inhibit the breakdown of the acetylcholine and also somehow acts on the receptor. Have I got you right? That's the point?

MR. DONOVAN: That's correct.

MR. PAPPAS: Yes, Your Honor. Can I address that?

THE COURT: Sure.

MR. PAPPAS: Thank you. And, Your Honor, while I trust you understand that we have numerous disagreements with basically the approach as to arguing whether it's

obvious or not, I'm going to stick just to scientific points and the one you had specifically.

First of all, everyone -- and this is established scientifically -- everyone agrees that galantamine preserves the function. And, that is, it extends the cognitive function in patients with Alzheimer's. So while there is no known cure for the plaques and tangles, those in the know, those skilled artisans, all agree that it does extend the cognitive function of Alzheimer's patients.

THE COURT: And I didn't hear -- let me just point out I don't hear any disagreement with that; correct?

MR. DONOVAN: There is no disagreement with that.

MR. PAPPAS: There is some evidence also that you will hear at trial that it slows the disease progression but that has been difficult to measure, but we maintain that it does, but you will hear more about that later.

Now, the second point. It is clear that galantamine that is used in Razadyne works in two ways. It inhibits the acetylcholinesterase and it also enhances the nicotinic receptors. We'll show this to you at trial.

But the FDA has allowed the company, Janssen, to represent to doctors both of these mechanisms of action. What is unclear to the FDA at this time is how to apportion the clinical benefits of galantamine among these two

mechanisms. And, therefore, out of an abundance of caution they simply refer to galantamine as a cholinesterase inhibitor. But they do permit Janssen to tell doctors that galantamine works in both ways: inhibiting the production of acetylcholinesterase which, of course, destroys the already-reduced amount of acetylcholine and also enhances the nicotinic receptor which is one of the two receptors that allows a more robust production of acetylcholine which then fires the synapses, carries the message and makes your brain work better.

Second, Your Honor, or third, I want to contrast the matter of science for you. And I'm going to try and stay short of argument, but I want to, I think it's important to contrast this issue of science today.

The defendants have focused strictly on the cholinergic hypothesis in galantamine, in other words, have done the Monday Morning Quarterback Look Back on Dr. Davis's invention. What we've shown you as a matter of science is how many different varied hypotheses there were in science, as a matter of science, as many of the best physicians tried to solve of the disease.

THE COURT: Okay.

MR. PAPPAS: Your Honor, there is a fourth point we disagree with scientifically. Mr. Donovan suggested that there was -- referred to reversible

cholinesterase inhibitors and irreversible and said irreversible cholinesterase inhibitors were insecticides but that pharmaceuticals were reversible. That is not correct. There is an irreversible inhibitor that has been tried in Europe; specifically, metrifonate. It was irreversible and it was tried as a cholinesterase inhibitor, irreversibly, it was an irreversible one, to treat Alzheimer's but it failed in phase three.

Finally, while we don't disagree that the drug galantamine was known in Europe for the treatment of anesthesia patients, on this point as far as we know from the literature there can be no disagreement. Prior to 1985, when Dr. Davis filed her application, no one had discovered or said that galantamine could be used for the treatment of Alzheimer's Disease.

THE COURT: All right.

MR. PAPPAS: Thank you, Your Honor.

THE COURT: Thanks.

Look, I appreciate everybody coming in today very much. This is a big help to me to learn about this.

Can we go ahead and shut off now?

Thanks. Is the tape and everything off?

(Video camera operator nods her head yes.)

* * *

(Sealed by the Court, bound separately.)

* * *

THE COURT: Okay. Is there anything else we ought to address while we're all here together? From the plaintiffs' side, Mr. Pappas?

MR. PAPPAS: Nothing from the plaintiffs, Your Honor. You have our notebook and our CD -- or our DVD, I think is the correct term.

THE COURT: Yes. Thank you very much.

Mr. Donovan?

MR. DONOVAN: Nothing on behalf of the defendants, Your Honor.

THE COURT: Okay. I thank you for your time today and attendance.

(Tutorial Hearing ends at 10:49 a.m.)