

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,
 Plaintiff,
 v.
 MSN LABORATORIES PRIVATE
 LIMITED, et al.,
 Defendants.

J. Caleb Boggs Courthouse
 844 North King Street
 Wilmington, Delaware

Wednesday, October 25, 2023
 8:30 a.m.
 Bench Trial

BEFORE: THE HONORABLE RICHARD G. ANDREWS, U.S.D.C.J.

APPEARANCES:

MORRIS NICHOLS ARSHT & TUNNELL LLP
 BY: ANTHONY D. RAUCCI, ESQUIRE
 BY: JACK B. BLUMENFELD, ESQUIRE

-and-

WILMERHALE
 BY: KEVIN S. PRUSSIA, ESQUIRE
 BY: LISA J. PIROZZOLO, ESQUIRE
 BY: AMY KREIGER WIGMORE, ESQUIRE
 BY: JONATHAN A. COX, ESQUIRE
 BY: KEVIN M. YURKERWICH, Ph.D.

For the Plaintiff

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2 HEYMAN ENERIO GATTUSO & HIRZEL LLP
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9 BY: ELIZABETH GRDEN, ESQUIRE
10 BY: KEVIN BOYLE, ESQUIRE
11 BY: BRIAN O'GARA ESQUIRE

For the Defendants

Also Present:

Dr. Kondal Reddy Bairy

11

08:18:06

*** PROCEEDINGS ***

08:18:06 12

08:20:27

08:20:27 13

DEPUTY CLERK: All rise. Court is now in

08:30:57 14

session. The Honorable Richard G. Andrews presiding.

08:30:57 15

THE COURT: All right. Good morning, everyone.

08:30:59 16

Please let's continue.

08:31:08 17

MS. PIROZZOLO: Thank you, Your Honor. One

08:31:09 18

housekeeping matter, we inadvertently put up the wrong

08:31:12 19

version of the slide that --

08:31:13 20

THE COURT: That's right. I remember.

08:31:15 21

MS. PIROZZOLO: -- Dr. Myerson referenced, and

08:31:17 22

I'd agree with Mr. Lombardi that Lines 18 to 19 of Page 700

08:31:23 23

of the transcript could be stricken.

08:31:26 24

THE COURT: All right. Well, I will strike

08:31:28 25

those two lines, and I'm sure the court reporter will take

Myerson - Direct (Continued)

08:31:33 1 care of it.

08:31:35 2 MS. PIROZZOLO: Thank you, Your Honor.

08:31:36 3 DIRECT EXAMINATION (Continued)

08:31:36 4 BY MS. PIROZZOLO:

08:31:38 5 Q. Good morning, Dr. Myerson.

08:31:39 6 A. Good morning.

08:31:41 7 Q. Now, Dr. Lepore and Dr. Donovan mentioned several

08:31:44 8 references offering your obviousness opinions.

08:31:47 9 MS. PIROZZOLO: Could we put up Slide 13 of your
08:31:50 10 presentation?

08:31:50 11 BY MS. PIROZZOLO:

08:31:53 12 Q. Do any of the references discussed by Drs. Donovan
08:31:57 13 and Lepore teach the method for synthesizing cabozantinib
08:32:00 14 (L)-malate that's disclosed in the '349 patent?

08:32:03 15 A. No.

08:32:04 16 Q. Do any of the references discussed by Drs. Donovan
08:32:08 17 and Lepore teach that 1-1 could be a process impurity or a
08:32:12 18 degradation process in the synthesis of cabozantinib
08:32:17 19 (L)-malate?

08:32:17 20 A. No.

08:32:19 21 Q. Do any of the references discussed by Drs. Donovan
08:32:23 22 and Lepore teach that the 1-1 compound was genotoxic?

08:32:27 23 A. No.

08:32:28 24 Q. Do any of the references discussed by Drs. Donovan
08:32:32 25 and Lepore describe a formulation of cabozantinib (L)-malate

Myerson - Direct (Continued)

08:32:36 1 essentially free of the 1-1 impurity?

08:32:39 2 A. No.

08:32:40 3 MS. PIROZZOLO: Now, let's look more closely at
08:32:42 4 the Brown reference which is in -- at Tab 10 of your binder,
08:32:47 5 and it's Defendants' Exhibit 291. And if we can put that
08:32:53 6 up.

08:32:53 7 BY MS. PIROZZOLO:

08:32:57 8 Q. This is the reference that Drs. Lepore and Donovan
08:32:59 9 referred to; correct?

08:33:00 10 A. Yes.

08:33:01 11 Q. What is Brown directed to?

08:33:04 12 A. It's directed to the malate salt of cabozantinib and
08:33:11 13 discloses two crystalline forms of the malate salt.

08:33:14 14 Q. Does Brown suggest that one with -- the 1-1 impurity
08:33:18 15 should be minimized in its synthesis of cabozantinib
08:33:22 16 (L)-malate?

08:33:22 17 A. It does not.

08:33:24 18 Q. Does Brown suggest that the 1-1 is a harmful
08:33:28 19 impurity?

08:33:28 20 A. It does not.

08:33:30 21 Q. Now, Brown refers to the 1-1 compound; correct?

08:33:34 22 A. Yes.

08:33:36 23 Q. Dr. Lepore has offered the opinion that a skilled
08:33:39 24 artisan would be motivated to control for 1-1 because it is
08:33:42 25 a starting material in the Brown synthesis.

Myerson - Direct (Continued)

08:33:47 1 Do you recall that?

08:33:47 2 A. I do.

08:33:49 3 Q. Do you agree with that opinion?

08:33:50 4 A. I do not.

08:33:52 5 Q. Could you explain why not?

08:33:53 6 A. Yes. Well, of course, starting materials can carry

08:34:00 7 through to the final product, but as we heard from

08:34:04 8 Dr. MacMillan, we have a continuous process with multiple

08:34:10 9 steps. 98 percent of the 1-1 starting material is used up

08:34:16 10 at the beginning of the first step, and then there are

08:34:20 11 multiple purification processes and other steps with

08:34:24 12 purification processes, thus that at the end of the fifth

08:34:28 13 step, we would not expect any significant amount of 1-1 to

08:34:34 14 carry through. We just would expect it to be de minimis.

08:34:39 15 Q. Would a skilled artisan looking at Brown understand

08:34:43 16 that the 1-1 impurity forms as a degradation process during

08:34:47 17 synthesis?

08:34:48 18 A. No. Again, as we heard from Dr. MacMillan, that

08:34:53 19 would not be expected by a person of ordinary skill.

08:34:58 20 Q. Now, Brown refers to the process that you discussed

08:35:01 21 earlier that Exelixis referred to as the A- 2 process;

08:35:06 22 correct?

08:35:06 23 A. That's correct.

08:35:09 24 Q. Is Example 1 in Brown that Dr. Lepore discussed

08:35:14 25 different from the synthetic scheme for making cabozantinib

Myerson - Direct (Continued)

08:38:09 1 Q. To summarize, what are your opinions on the key
08:38:11 2 differences between Brown and the '349 patent?

08:38:17 3 A. Well, the first key difference is that the '349
08:38:21 4 patent has a different synthetic process which was designed
08:38:25 5 to minimize the 1-1 impurity at very low levels.

08:38:30 6 Secondly, the '349 discloses formulation of the
08:38:37 7 1-1 impurity that's essentially free -- I'm sorry,
08:38:41 8 formulation of cabozantinib (L)-malate which is essentially
08:38:45 9 free of the 1-1 impurity. Brown does not disclose any
08:38:49 10 specific formulation or discuss specific formulations.

08:38:54 11 Q. Okay. So, let's turn to Dr. Lepore's inherency
08:39:01 12 opinion.

08:39:01 13 MS. PIROZZOLO: And go to slide 15, please.

08:39:01 14 BY MS. PIROZZOLO:

08:39:04 15 Q. Looking at the first point on this slide, for the
08:39:11 16 asserted claim of the '349 patent, what must be essentially
08:39:15 17 free of the 1-1 impurities?

08:39:17 18 A. The pharmaceutical composition.

08:39:20 19 Q. Now, if an API has less than 200 PPM of 1-1, will the
08:39:27 20 formulated composition necessarily be free of the 1-1
08:39:30 21 impurity?

08:39:30 22 A. No, because as we've seen, the process of blending
08:39:36 23 with excipients and making it into a drug product can result
08:39:41 24 in increase in the 1-1 impurity. Thus, it's possible to
08:39:44 25 start with an API that's essentially free, but end up with a

Myerson - Direct (Continued)

08:39:49 1 drug product that's not essentially free due to the
08:39:51 2 additional formation of the 1-1.

08:39:54 3 Q. Did Exelixis' own work show that the 1-1 impurity
08:39:57 4 could form during manufacturing of a drug product?

08:40:00 5 A. Yes.

08:40:02 6 Q. Could you explain why that's your opinion?

08:40:06 7 A. Well, certainly. We first saw the excipient
08:40:08 8 compatibility studies which showed that the 1-1 could --
08:40:14 9 would increase in contact with a number of different
08:40:16 10 excipients. Secondly, we see the Exelixis studies that
08:40:20 11 showed that the 1-1 impurity would increase when exposed to
08:40:26 12 temperature, heat -- heat, moisture, and potentially
08:40:33 13 physical force, which are used in manufacturing of tablets
08:40:37 14 and capsules.

08:40:39 15 Q. Now, let's turn to your second point.

08:40:48 16 Do you agree with Dr. Lepore that the synthetic
08:40:52 17 process in Brown does not inherently result in less than
08:40:55 18 200 PPM?

08:40:56 19 A. I do not.

08:40:58 20 MS. PIROZZOLO: Let's pull up Brown, Defendants'
08:41:03 21 Exhibit 291, at paragraph 213.

08:41:03 22 BY MS. PIROZZOLO:

08:41:08 23 Q. What does this paragraph in Brown teach?

08:41:11 24 A. Okay. I'm just getting it on my...

08:41:19 25 Q. I think it's on the screen, if that's...

Myerson - Direct (Continued)

09:03:04 1 have to add a glidant. Generally, all capsules and -- all
09:03:12 2 capsules and tablets will have fillers.

09:03:16 3 MS. PIROZZOLO: So, let's put up Claim 3 of the
09:03:20 4 '349 patent.

09:03:20 5 BY MS. PIROZZOLO:

09:03:21 6 Q. Now, you heard Dr. Donovan testify that a skilled
09:03:24 7 artisan would have been motivated to formulate cabozantinib
09:03:29 8 (L)-malate as set forth in Claim 3.

09:03:32 9 Do you agree with that?

09:03:33 10 A. No.

09:03:38 11 Q. Could you explain why not?

09:03:39 12 A. Well, first of all, the formulation of any drug
09:03:50 13 product requires you to understand the dosage form, the
09:03:56 14 dose, and the physicochemical properties of the API. So,
09:04:01 15 before you know how you're -- how you're going to formulate
09:04:06 16 something, you have to do all that work. And then you can
09:04:09 17 decide what classes of excipients you're going to employ.

09:04:13 18 Q. Okay. Have you heard the term "physicochemical
09:04:16 19 properties"?

09:04:17 20 A. Yes.

09:04:18 21 Q. What physicochemical properties are important to
09:04:22 22 formulation scientists?

09:04:24 23 A. Well, certainly the solubility, the permeability, the
09:04:30 24 crystal size distribution, the crystal shape, the
09:04:35 25 hygroscopicity, the carrying electric charge, the

Myerson - Direct (Continued)

09:04:38 1 compressibility, the flowability. There are probably some
09:04:43 2 more but those are some of the main ones you're interested
09:04:46 3 in.

09:04:47 4 Q. Is chemical stability important?

09:04:49 5 A. Yes.

09:04:49 6 Q. And why is that?

09:04:50 7 A. Well, chemical stability will determine whether the
09:04:57 8 API is going to decompose, either due to interaction with
09:05:02 9 the excipients or through the manufacturing process.

09:05:09 10 Q. What were some of the kinds of physicochemical
09:05:12 11 properties that turned out to be important to how
09:05:16 12 cabozantinib (L)-malate was formulated?

09:05:18 13 A. Well, first was the chemical stability. And second
09:05:22 14 was the flowability.

09:05:24 15 Q. And why were those important?

09:05:25 16 A. Well, it turns out that cabozantinib (L)-malate could
09:05:33 17 decompose to the 1-1 impurity when exposed to moisture,
09:05:37 18 heat, and in the presence of certain excipients. In
09:05:42 19 addition, it was poorly flowing. The API was poorly
09:05:48 20 flowing.

09:05:48 21 Q. Okay. As of 2011, was the chemical stability of
09:05:52 22 cabozantinib (L)-malate known in the prior art?

09:05:55 23 A. No.

09:05:57 24 Q. As of 2011, was the flowability of cabozantinib
09:06:01 25 (L)-malate known in the prior art?

Myerson - Direct (Continued)

09:06:02 1 A. No.

09:06:04 2 Q. Okay.

09:06:05 3 MS. PIROZZOLO: Let's put up paragraph 82 of the
09:06:08 4 Brown reference, Defendants' Exhibit 291.

09:06:08 5 BY MS. PIROZZOLO:

09:06:11 6 Q. At Tab 10 in your binder.

09:06:16 7 Dr. Donovan referred to paragraph 82 in Brown in
09:06:20 8 her testimony. Do you recall that?

09:06:21 9 A. Yes.

09:06:23 10 Q. In your opinion, does paragraph 82 in Brown suggest
09:06:27 11 formulating cabozantinib with a glidant?

09:06:30 12 A. No. A glidant is not a class of excipients that's
09:06:33 13 listed in paragraph 82.

09:06:36 14 Q. Now, Dr. Donovan pointed in this paragraph to the
09:06:39 15 excipient talc. Do you recall that?

09:06:42 16 A. I do.

09:06:43 17 Q. Is talc listed as a glidant in this paragraph?

09:06:46 18 A. No, it's listed as a lubricant.

09:06:49 19 Q. Okay. Have you seen any reference identified by
09:06:54 20 Dr. Donovan that would motivate a skilled artisan to include
09:06:58 21 a glidant?

09:07:00 22 A. To include a glidant in the --

09:07:03 23 Q. In a composition for cabozantinib (L)-malate?

09:07:05 24 A. No.

09:07:12 25 MS. PIROZZOLO: Now, let's pull up Defendants'

Myerson - Direct (Continued)

09:07:19 1 Exhibit 335, which is a patent application.

09:07:19 2 BY MS. PIROZZOLO:

09:07:23 3 Q. Do you recall Dr. Donovan discussing this patent
09:07:26 4 application?

09:07:26 5 A. Yes.

09:07:28 6 Q. Does this patent application relate to cabozantinib?

09:07:32 7 A. No.

09:07:33 8 Q. What, at a general level, does this patent
09:07:36 9 application relate to?

09:07:37 10 A. It relates to several other APIs that are tyrosine
09:07:43 11 kinase inhibitors.

09:07:45 12 Q. Does the -- does the '081 application, which is
09:07:49 13 Defendants' Exhibit 35 -- 335, teach that cabozantinib
09:07:54 14 (L)-malate should be formulated with a filler, disintegrant,
09:07:57 15 glidant, and lubricant?

09:07:59 16 A. No.

09:08:00 17 Q. Could you explain why not?

09:08:01 18 A. Well, it's because it's about different APIs, and
09:08:05 19 different APIs have different properties. It doesn't really
09:08:08 20 inform you if you have formulation for a completely
09:08:14 21 different API how you're going to formulate a different API.
09:08:18 22 Because you don't know -- the physicochemical properties are
09:08:21 23 going to be different.

09:08:24 24 Q. Now, let's turn to the Lachman reference that

09:08:27 25 Dr. Donovan discussed which is Plaintiff's Exhibit 553A.

Myerson - Direct (Continued)

09:08:34 1 What is the Lachman reference?

09:08:36 2 A. This is a reference on pharmaceutical dosage forms.

09:08:43 3 Q. Did you hear Dr. Donovan testify that a skilled

09:08:46 4 artisan would be motivated by Lachman to formulate

09:08:50 5 cabozantinib (L)-malate with one or more fillers,

09:08:54 6 disintegrants, glidants and lubricants?

09:08:56 7 A. I did.

09:08:57 8 Q. Do you agree with Dr. Donovan's opinion?

09:08:59 9 A. No, Lachman is -- is a general reference on

09:09:02 10 formulation. And, of course, it talks about all classes of

09:09:06 11 excipients, but it also -- I think we saw the paragraph

09:09:10 12 already -- talks about how each formulation is a unique --

09:09:15 13 unique development project where you develop the formulation

09:09:21 14 based on the properties of the API.

09:09:25 15 MS. PIROZZOLO: So, let's turn to Page 76 of

09:09:27 16 Lachman, which is Page 3 of the PDF.

09:09:27 17 BY MS. PIROZZOLO:

09:09:33 18 Q. And looking at the sentence that begins with, "The

09:09:35 19 correct selection," is that what you're referring to,

09:09:39 20 Dr. Myerson?

09:09:39 21 A. Yes. "The correct selection and balance of excipient

09:09:43 22 materials for each active ingredient or ingredient

09:09:48 23 combination in a tablet formulation to achieve the desired

09:09:52 24 response (i.e. production of a safe, effective, and highly

09:09:58 25 reliable product) is not in practice a simple goal to

Myerson - Direct (Continued)

09:10:02 1 achieve."

09:10:04 2 Q. Do you agree with that statement in Lachman?

09:10:06 3 A. Yes.

09:10:07 4 Q. Could you explain why?

09:10:08 5 A. Well, because, again, each -- each formulation of a
09:10:15 6 new API is a unique problem. And you might run into
09:10:19 7 problems with flow or chemical stability or the ability to
09:10:24 8 make a tablet that is -- doesn't break into pieces or is --
09:10:35 9 has appropriate hardness, has the right dissolution
09:10:38 10 properties. So, in fact, in my own experience, you go
09:10:43 11 through lots and lots of iterations of excipients and blends
09:10:47 12 and tablet press pressures and various other things to make
09:10:53 13 a safe and effective and reliable formulation.

09:10:59 14 Q. So, we've talked about Brown, the '081 application
09:11:04 15 and the Lachman reference. Do any of those, in your
09:11:08 16 opinion, provide a motivation to formulate cabozantinib
09:11:12 17 (L)-malate in the manner claimed in Claim 3 of the '349
09:11:17 18 patent?

09:11:17 19 A. No.

09:11:19 20 MS. PIROZZOLO: Now, let's go to "Reasonable
09:11:21 21 Expectation of Success." That's Slide 17 of your slides.
09:11:21 22 BY MS. PIROZZOLO:

09:11:32 23 Q. Going to the first point, you heard Dr. Lepore
09:11:37 24 testify that a skilled artisan would have simply added a
09:11:41 25 recrystallization step to the synthetic process in Brown to

Myerson - Direct (Continued)

09:16:06 1 a skilled artisan with reasonable expectation of success to
09:16:11 2 add a recrystallization step to the Brown process to achieve
09:16:15 3 cabozantinib (L)-malate essentially free of the 1-1
09:16:18 4 impurity?

09:16:18 5 A. No.

09:16:20 6 Q. Could you explain your opinion?

09:16:22 7 A. Well, I mean, this -- this talks about purification
09:16:26 8 and mentions that you can try to purify something via
09:16:31 9 crystallization, but that wouldn't motivate a person to
09:16:35 10 modify Brown because, first of all, they don't know the 1-1
09:16:41 11 impurity is a decomposition product. And, as I note, a
09:16:48 12 recrystallization step could be ineffective in this type of
09:16:51 13 process. So, no, I don't believe it would.

09:16:55 14 MS. PIROZZOLO: Let's go to Slide 17.

09:16:55 15 BY MS. PIROZZOLO:

09:17:00 16 Q. So, we've talked about whether there would be a
09:17:04 17 reasonable expectation of success for controlling 1-1 in the
09:17:08 18 API of cabozantinib (L)-malate. Let's move to controlling
09:17:14 19 1-1 in the pharmaceutical composition. Okay?

09:17:17 20 A. Yes.

09:17:19 21 Q. Without the information provided by the '349 patent,
09:17:23 22 would a skilled artisan looking at the Brown reference have
09:17:27 23 had a reasonable expectation of success in achieving
09:17:30 24 cabozantinib (L)-malate composition with the claimed
09:17:34 25 excipients free of the 1-1 impurity?

Myerson - Direct (Continued)

09:17:36 1 A. No.

09:17:36 2 Q. Could you explain why not?

09:17:38 3 A. Because the Brown process, first of all, would make
09:17:45 4 API with variable amounts of the 1-1 impurity, including
09:17:49 5 cases where the 1-1 impurity would already be greater than
09:17:54 6 200 PPM. But even if it was below 200 PPM, it doesn't
09:17:59 7 describe any information on excipient compatibility or any
09:18:05 8 other thing that would allow you to formulate into a drug
09:18:09 9 product that was essentially free.

09:18:16 10 Q. What were the properties of cabozantinib (L)-malate
09:18:20 11 that were not in the prior art that would be needed to
09:18:24 12 formulate cabozantinib (L)-malate essentially free of the
09:18:27 13 1-1 impurity?

09:18:28 14 A. Well, first of all, you would have to know about its
09:18:32 15 chemical stability. You'd have to understand whether it
09:18:38 16 decomposed under various conditions, and you would also have
09:18:43 17 to know the list of physicochemical properties I mentioned
09:18:48 18 before, including the excipient compatibility studies, and
09:18:56 19 because you're formulating it, you would still have to know
09:18:58 20 about the flowability and the crystal size, crystal shape,
09:19:04 21 all of those other things.

09:19:05 22 Q. Okay. Were those properties you just mentioned known
09:19:09 23 in the prior art?

09:19:10 24 A. No.

09:19:13 25 Q. Without knowing about these properties and without

Myerson - Direct (Continued)

09:19:18 1 the benefit of the teaching of the '349 patent, could a
09:19:21 2 person of skill have predicted how cabozantinib (L)-malate
09:19:26 3 or levels of the 1-1 impurity would be affected by
09:19:30 4 formulation?

09:19:30 5 A. No.

09:19:31 6 Q. Could you explain why not?

09:19:32 7 A. Again, there's no information on the effect of
09:19:39 8 excipients, heat, moisture and processing conditions on the
09:19:45 9 formation of the 1-1 impurity. In fact, we don't even know
09:19:48 10 it's a degradation product, which is the key piece of
09:19:51 11 information.

09:19:53 12 Q. Okay. Now, did you consider objective indicia in
09:19:57 13 rendering your opinions in this case?

09:20:00 14 A. I did.

09:20:02 15 Q. What products -- and we can look at Plaintiff's
09:20:05 16 Demonstrative Slide 3. What products practice Claim 3 of
09:20:12 17 the '349 patent?

09:20:12 18 A. The tablets, Cabometyx, and the capsules, Cometriq.

09:20:21 19 Q. Did you consider whether there was a nexus between
09:20:26 20 the objective indicia in Claim 3 of the '349 patent?

09:20:29 21 A. I did.

09:20:31 22 Q. What is your understanding of the nexus between the
09:20:37 23 '349 patent and the objective indicia.

09:20:39 24 A. Well, the '349 patent was crucial because it
09:20:42 25 disclosed a synthetic process to produce cabozantinib

Myerson - Cross

09:46:53 1 A. Yes.

09:46:55 2 Q. This is what formulators do day in and day out; is
09:46:58 3 that right?

09:46:58 4 A. Every time they have a new API, they do excipient
09:47:03 5 compatibility studies. I agree with that.

09:47:05 6 Q. And then the person of skill in the art determines
09:47:07 7 which excipients are necessary; is that right?

09:47:10 8 A. After they do the excipient compatibility studies and
09:47:16 9 they have determined a dose and a type of drug product, they
09:47:20 10 then start selecting individual excipients to make -- to
09:47:26 11 make trial formulations.

09:47:28 12 Q. Okay. And you determined which excipients will be
09:47:35 13 compatible with a particular API; is that right?

09:47:40 14 The formulation scientists?

09:47:41 15 A. That's correct. You're looking, of course, to
09:47:43 16 minimize any decomposition.

09:47:46 17 Q. Okay. Ultimately, a POSA knows that you want to use
09:47:50 18 only the excipients that are physically and chemically
09:47:54 19 compatible with the API; is that right?

09:47:57 20 A. Right. That's the first step. Yes.

09:47:59 21 Q. Okay. And that's something that persons of skill in
09:48:02 22 the art are well qualified to do?

09:48:05 23 A. I agree with that.

09:48:07 24 Q. The patent doesn't claim any novel ways of
09:48:11 25 determining whether there's a chemical interaction between

Myerson - Cross

09:48:14 1 cabozantinib and the excipients used; is that right?

09:48:19 2 A. That's correct.

09:48:21 3 Q. It's done using known methods; correct?

09:48:25 4 A. I'm sorry?

09:48:29 5 Q. Let me -- that was not a great question. Let me ask
09:48:32 6 that again.

09:48:33 7 The patent suggests just using known methods to
09:48:36 8 make that kind of determination; isn't that right?

09:48:38 9 A. I don't actually remember the passage related to
09:48:42 10 that, so we'd have to see it. But it wouldn't surprise me.

09:48:45 11 Q. Okay. That's consistent with your understanding as
09:48:47 12 an expert in this field; is that right?

09:48:50 13 A. (Witness nods head.) Yes.

09:48:51 14 Q. Now, let's go to the last one, the discovery that the
09:48:54 15 1-1 impurity is genotoxic, do you see that one?

09:48:57 16 A. Yes.

09:48:58 17 Q. Okay. Now, a person of skill in the art would have
09:49:01 18 been motivated to determine whether any of the impurities in
09:49:06 19 the compound -- in the composition are genotoxic; correct?

09:49:11 20 A. Yes. And at somewhere in the development process,
09:49:17 21 that would be the case.

09:49:18 22 Q. Okay. A POSA would have wanted to control for
09:49:23 23 genotoxic impurities in a formulation; right?

09:49:26 24 A. Yes. Generally you wish to control within certain
09:49:30 25 limits on genotoxic impurities.

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09:49:33 1 Q. Okay. And genotoxic impurities, I mean, just so --
09:49:38 2 genotoxic is -- refers to testing that has shown that
09:49:42 3 something can cause the chromosomal makeup of cells; isn't
09:49:48 4 that right?

09:49:48 5 A. It -- well, it's -- a genotoxic impurity is something
09:49:53 6 that will interact with DNA. And the initial test, of
09:49:59 7 course, is a bacterial test called the Ames test.

09:50:02 8 Q. Okay. All right. But the idea is that you're
09:50:06 9 concerned with the genotoxic impurity -- if something is
09:50:09 10 genotoxic, it can harm DNA; is that right?

09:50:12 11 A. Yes; potentially harm DNA in people, though not
09:50:15 12 always.

09:50:16 13 Q. Yeah, not always. But you do laboratory tests on
09:50:19 14 this?

09:50:19 15 A. That's right.

09:50:20 16 Q. And genotoxic impurity can cause genetic or
09:50:23 17 chromosomal damages -- damage. And some of those, some
09:50:27 18 could be carcinogenic; is that right?

09:50:29 19 A. That's correct.

09:50:30 20 Q. And that's why a POSA is particularly interested in
09:50:33 21 making the determination whether impurities are genotoxic;
09:50:36 22 is that right?

09:50:37 23 A. That's correct.

09:50:38 24 Q. Now, a genotoxic impurity is particularly concerning,
09:50:45 25 isn't it?

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09:53:06 1 Q. Okay. And then, the next step, if the structural
09:53:11 2 alerts give you some indication, is to do an Ames test?

09:53:15 3 A. That's right. In fact, always -- always follow
09:53:19 4 through with the Ames test.

09:53:20 5 Q. And that's what a person of skill in the art would
09:53:22 6 do, is always follow through with an Ames test; is that
09:53:24 7 right?

09:53:25 8 A. That's right.

09:53:25 9 Q. And when you follow through with the Ames test, you
09:53:27 10 make a determination whether an impurity is genotoxic; is
09:53:30 11 that right?

09:53:31 12 A. Right. If it's positive on the AMES test, it -- it
09:53:33 13 at least appears to be genotoxic.

09:53:36 14 Q. Okay. And with respect to the regulators, regulators
09:53:44 15 expect to be told about whether an impurity is genotoxic or
09:53:49 16 not; is that right?

09:53:50 17 A. That's correct.

09:53:51 18 Q. And when the -- when an impurity is genotoxic, then
09:53:58 19 you take steps in the way you formulate the product; is that
09:54:04 20 right?

09:54:04 21 A. You take steps in controlling the level of that
09:54:10 22 impurity in the formulated product and on storage.

09:54:14 23 Q. Okay. Now, a POSA would have known that cabozantinib
09:54:21 24 was potentially genotoxic based on structural alerts; is
09:54:25 25 that right?

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09:54:26 1 A. Right. Yeah. The quinoline, so you would have --
09:54:29 2 you would have checked. But that's right.

09:54:31 3 Q. Okay. So, that's -- you got one step ahead of me,
09:54:35 4 but 1-1 is something called a quinoline; correct?

09:54:40 5 A. Right. I mean, cabozantinib is a quinoline. 1-1's a
09:54:43 6 quinoline. And we're talking about a lot of quinoline
09:54:46 7 structures here.

09:54:47 8 Q. Okay. And a quinoline structure is a kind of
09:54:49 9 chemical structure?

09:54:50 10 A. That's right.

09:54:51 11 Q. And it's a kind of chemical structure that you find
09:54:54 12 in cabozantinib?

09:54:55 13 A. Yes.

09:54:56 14 Q. And it's in 1-1?

09:54:57 15 A. Yes.

09:54:58 16 Q. And -- and that is a red flag for a person of skill
09:55:02 17 in the art?

09:55:03 18 A. It's -- it's -- it's a structure that has to be
09:55:09 19 furtherly -- further evaluated. Because, of course, as we
09:55:13 20 know, there are lots of quinolines that are actually drugs.
09:55:17 21 And there are quinolines that are -- that are genotoxic. So
09:55:22 22 you have to -- you have to say -- you have to study each
09:55:24 23 particular quinoline to determine whether it's useful, not
09:55:29 24 harmful or harmful.

09:55:31 25 Q. So, to a person of skill in the art, determining that

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09:55:35 1 something's a quinoline, which they could tell -- let me

09:55:38 2 just ask you this first: You can tell if something's a

09:55:40 3 quinoline or not by looking at the chemical structure?

09:55:43 4 A. That's right.

09:55:44 5 Q. The drawing on the page. Somebody of skill in the

09:55:46 6 art could say, "That is or is not a quinoline based on that

09:55:51 7 structure"?

09:55:51 8 A. That's correct.

09:55:52 9 Q. And when something is a quinoline, you actually --

09:55:55 10 that is a structural alert right there; isn't that right?

09:55:58 11 A. That's correct.

09:56:00 12 Q. So, a person of skill in the art would then take the

09:56:02 13 quinoline and put it in the Ames test; is that right?

09:56:05 14 A. Yes, again, at some point, that's correct.

09:56:08 15 Q. Yeah. And the Ames test is -- it's A-M-E-S; correct?

09:56:12 16 Named after a person; isn't that right?

09:56:15 17 A. That's right.

09:56:15 18 Q. Bruce Ames; right?

09:56:16 19 A. Right.

09:56:17 20 Q. And the Ames test is -- it's really one of the most

09:56:20 21 famous tests out there, isn't it?

09:56:23 22 A. That's right.

09:56:24 23 Q. It's widely used?

09:56:25 24 A. Yes.

09:56:26 25 Q. Persons of skill in the art know how to use the Ames

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09:56:29 1 test?

09:56:29 2 A. Yes.

09:56:29 3 Q. Persons of skill in the art use the Ames test
09:56:32 4 routinely?

09:56:33 5 A. Yes, I would agree with that.

09:56:35 6 Q. And persons of skill in the art understand the
09:56:38 7 results they get from an Ames test; is that right?

09:56:40 8 A. Yes.

09:56:43 9 Q. Okay. And a person of skill in the art, who had the
09:56:47 10 1-1 impurity, would determine -- first they determine that
09:56:52 11 the API was potentially genotoxic based on the quinoline
09:56:58 12 structure; isn't that right?

09:56:59 13 A. You mean the cabozantinib?

09:57:00 14 Q. Cabozantinib, I'm sorry. Did I say -- let me give
09:57:03 15 you another -- thank you. I'll give you another question.
09:57:05 16 I apologize.

09:57:06 17 Person of skill in the art would -- would look
09:57:11 18 at the structure for the 1-1 impurity and say, "That's
09:57:15 19 potentially genotoxic because it's a quinoline"?

09:57:19 20 A. Yes.

09:57:22 21 Q. And then they would do the Ames test?

09:57:24 22 A. Yes.

09:57:26 23 Q. And then they would find out in the Ames test that
09:57:28 24 it's positive?

09:57:29 25 A. Yes.

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09:57:30 1 Q. And then they would know that, in their formulation,
09:57:34 2 they need to do what they can to minimize that component?

09:57:38 3 A. That's correct.

09:57:41 4 Q. Okay. Now, there's no claim made in the patent as to
09:57:46 5 a novel way of determining genotoxicity; right?

09:57:50 6 A. Correct.

09:57:51 7 Q. You can use known techniques?

09:57:52 8 A. Correct.

09:57:56 9 Q. There's nothing claimed in the patent that's -- that
09:58:01 10 claims a novel way of determining that there's been --
09:58:06 11 there's an impurity that is genotoxic; is that right?

09:58:10 12 A. Could you repeat that?

09:58:13 13 Q. I'm sorry. I think I'm repeating myself, so I'll
09:58:16 14 just move on, Doctor.

09:58:17 15 Let me move to another subject here -- well,
09:58:40 16 actually, Doctor, while we're here lets -- you talked about
09:58:43 17 the pharmaceutical composition.

09:58:47 18 MR. LOMBARDI: If you could just put the
09:58:49 19 Doctor's demonstrative PDX-4.15 up.

09:58:49 20 BY MR. LOMBARDI:

09:58:58 21 Q. And, Doctor, I'm just focused, for the moment, on the
09:59:02 22 top one there. The essentially free limitation applies to
09:59:07 23 the pharmaceutical composition; is that right?

09:59:10 24 A. Correct.

09:59:11 25 Q. Okay. And your testimony was that it's not just the

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09:59:16 1 API that has to be essentially free of the impurity. It's
09:59:20 2 the entire pharmaceutical composition?

09:59:23 3 A. That's correct.

09:59:23 4 Q. Which would include the excipients; correct?

09:59:28 5 A. Pharmaceutical composition is the final drug product,
09:59:33 6 which includes the API plus all excipients.

09:59:36 7 Q. Okay. And the patent doesn't claim any novel way of
09:59:42 8 coming up with a composition that controls for those
09:59:47 9 impurities; is that right?

09:59:49 10 A. Other than disclosing a synthetic process that makes
09:59:54 11 an API exceptionally low, it doesn't then have an
09:59:59 12 additional -- anything additional that would control for the
10:00:03 13 1-1.

10:00:04 14 Q. And what the -- what the patent actually says is as a
10:00:08 15 matter of composition, people should use -- persons of skill
10:00:13 16 in the art should use known techniques; is that right?

10:00:15 17 A. I'm sorry, composition of?

10:00:17 18 Q. Pharmaceutical composition. The pharmaceutical
10:00:20 19 composition in this case, they should use known techniques?

10:00:23 20 A. I'm sorry. Known techniques to determine the
10:00:27 21 pharmaceutical composition, is that...

10:00:28 22 Q. To make it, yes. To make the pharmaceutical
10:00:30 23 composition.

10:00:30 24 A. Yes, that's correct.

10:00:32 25 MR. LOMBARDI: Okay. And if we look at the