UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INCYTE CORPORATION,
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner.

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Case IPR2017-01256
Patent 9,249,149 B2

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Record of Oral Hearing
Held: January 25, 2019

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Before ERICA A. FRANKLIN, TINA E. HULSE, and
RICHARD J. SMITH, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE PETITIONER:

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The above-entitled matter came on for hearing on Friday, January 25, 2019, commencing at 1:00 p.m. at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE FRANKLIN: Today is January 25th, 2019, and this is the final hearing in IPR 2017-01256 directed to claims of U.S. Patent No. 9,249,149 B2.

I am Judge Franklin, and on our monitors are Judges Hulse and Smith. Judge Hulse is appearing from California and Judge Smith is appearing from Texas, and we welcome everyone and thank you for attending.

At this time, I'd like counsel for the parties to introduce themselves and their colleagues, beginning with Petitioner.

MR. IRVING: May it please the Court, my name is Tom Irving. I am lead counsel for Petitioner Incyte.

With me today are Mr. Feldstein, back up counsel, who will make the argument; Ms. Courser, back up counsel; Mr. Christie, back up counsel; Mr. Ward, back up counsel; and we are fortunate to have with us today the Vice President of Intellectual Property of Petitioner Incyte, Dr. Scott Larson.

Thank you.

JUDGE FRANKLIN: Thank you and welcome, and for Patent Owner?

MS. HARDMAN: Good afternoon, your Honors. My name is Cynthia Hardman from Goodwin Procter. With me is Mr. Daryl Wiesen, Ms. Darrah Fisher, Ms. Molly Gravel, Mr. Cort Chase,

and from the company Concert Pharmaceuticals, Patent Owner, we have the CEO, Mr. Roger Tung, Mr. Robert Silverman, and Mr. Mark Russett.

JUDGE FRANKLIN: Thank you and welcome. Consistent with the hearing order each party has 75 minutes to present their arguments. Petitioner may reserve a portion of its time to respond to arguments presented by the Patent Owner, and Patent Owner likewise has an opportunity to reserve a portion of its time for surrebuttal.

Please be mindful that we do have judges appearing remotely and they may not be able to see the monitor when you display your demonstrative slides, so when referring to those slides, clearly identify which slide you're referring to by number so that they both may follow along.

And now Petitioner, after the indicating the time you'd like to reserve for rebuttal, you may begin.

MR. FELDSTEIN: We'd like to reserve half an hour for rebuttal, your Honor.

JUDGE FRANKLIN: One moment. You may begin.

MR. FELDSTEIN: Thank you. Your Honor, can we hand up at least to you a hard copy of the demonstratives?

JUDGE FRANKLIN: Sure.

MR. FELDSTEIN: Apologies we can't get them to Texas and California.

JUDGE FRANKLIN: Okay. They have copies, and before you begin, let me check with my panel members to make sure they can hear and see okay. Judge Hulse?

JUDGE HULSE: Yes, I can see you just fine. Thanks.

JUDGE FRANKLIN: Okay. Judge Smith?

JUDGE SMITH: All good here.

JUDGE FRANKLIN: Great.

MR. FELDSTEIN: And I can see our demonstratives on the display here. That one doesn't seem to be on, though.

JUDGE FRANKLIN: One moment.

MR. FELDSTEIN: Which I can continue without it --

JUDGE FRANKLIN: One moment.

MR. FELDSTEIN: -- as long as your Honors can see it.

JUDGE FRANKLIN: All right, and you may begin.

MR. FELDSTEIN: Thank you, your Honors, again Mark Feldstein for Petitioner Incyte.

Can we start on slide 37, please? I want to start just with a little background on deuterium. Slide 37, please. I'll be there in one second. Okay, perfect.

So this is Exhibit 1013, a June 2009 Chemical Engineering news article that gives some good background on the idea and what was going on as of 2009 with deuterium, and what it teaches and what it explains just as a news report is that deuterium is an old tool that's being reused, made new again to deuterate pharmaceutical

compounds, to take existing pharmaceutical compounds that have known safety, known efficacy, and to then deuterate them with the idea of slowing metabolism.

So the concept of deuterium substitution to slow metabolism and therefore change the PK properties of active pharmaceutical compounds is well known. It's to the level of news reports as well as, of course, journal articles and many, many patents.

So the purpose of that is to improve the PK. The benefit -- one of the huge benefits of deuterium is that it doesn't change the activity -- the pharmaceutical activity of the compound, and there's a quote from Concert CEO Dr. Tung at the bottom. At Concert, we've never seen any biologically relevant difference in target selectivity or potency of a drug when deuterated.

And so the import there is that when you deuterate a pharmaceutical, you can expect to get similar properties in terms of potency and selectivity, the activity of the molecule.

So given that deuterium is also the smallest structural change that can be made to a molecule, and that's sort of self-evident that deuterium and hydrogen are so very close. It's also taught in Exhibit 1041 on page 5 that it's the smallest structural change.

But deuterium substitution really is the epitome of structural obviousness. The smallest structural change, the expectation of retaining the activity -- the pharmaceutical activity that you desire.

So that's the general idea of deuterium substitution. For ruxolitinib there were things that were particularly known that made it an ideal candidate for deuteration.

Ruxolitinib before the date of the patent was already FDA-approved for treating blood cancer. It was in clinical trial for other conditions. It was taught to be useful for alopecia areata, an autoimmune disease. The symptom was hair loss and the metabolism was already known. The human metabolism was already known. As we'll see, that helps. That tells you exactly where the deuteration should be.

So another important foundational piece of evidence is that for ruxolitinib, it was also known exactly what happens when you inhibit its metabolism. And so deuterium -- the point of deuterium is to inhibit metabolism, p-450 metabolism in the body. Well, that was already done using a metabolic inhibitor.

And so Exhibit 1071 is an article by a number of people of Incyte that studied the effects of metabolic inhibitors on ruxolitinib administered to patients.

And what they found is that the biological clearance was slowed by almost a factor of two, the area under the curve. The exposure was proportionately doubled relatively, as was the half-life.

And so it was proven with ruxolitinib that if you inhibit metabolism, you get what's expected that you get inhibited metabolism, increased exposure, longer half-life.

And one of the important things about Exhibit 1071, the Shi paper, is that it really undermines the sort of parade of horribles that you hear, and we expect you'll hear from Concert, regarding all the reasons they say there was an affirmative reason not to deuterate ruxolitinib.

Well, they talk about all the horrible things that could happen in terms of side effects being increased. Well, we know that essentially doubling the exposure of ruxolitinib by inhibiting its metabolism, it was reported to be generally safe and well tolerated. And again that's Exhibit 1071.

JUDGE HULSE: But wasn't that study done in healthy individuals though?

MR. FELDSTEIN: That was done with healthy individuals.

JUDGE HULSE: That was Patent Owner's argument that you wouldn't necessarily see dose dependent toxic side effects in those healthy individuals?

MR. FELDSTEIN: Well, in fact, they argue, I believe, your Honor, that in alopecia patients, which are otherwise healthy compared to myelofibrosis patients, that they are related, and so I think that Concert's argument is that in alopecia patients -- healthy alopecia patients are a stand in for myelofibrosis and back and forth.

But you're right. These patients were not myelofibrosis patients. Neither are their intended audience of alopecia patients. But this is the data we have. The data we have is that essentially

doubling the exposure did not cause problems. That was important information in the prior art.

JUDGE HULSE: And what is your response to their argument that your arguments for motivation are overly broad and overly general, that under your logic, any FDA approved drug could be deuterated and that would be obvious?

MR. FELDSTEIN: Well, we don't argue that. We don't need to argue that. What we argue is that ruxolitinib, which is FDA approved, which helps point to it being a lead compound had other things known and had its hot spots -- metabolic hot spots known.

And so a couple being a known pharmaceutical FDA approved with the fact taught in Shilling Exhibit 1005 that you knew exactly where the metabolism was, and what type of metabolism it was. It was a metabolism of alkyl carbons -- hydroxylation of alkyl carbons, which is where deuteration is known to give you the biggest bang for the buck.

And so there are particular things about ruxolitinib that make it particularly obvious. Whether or not all FDA compounds are obvious is not the position we're arguing, we don't need to argue that. We have specific facts for ruxolitinib, including its known metabolism, the type of metabolism it has, and that even doubling its exposure was safe and well tolerated, at least in healthy individuals.

JUDGE HULSE: And can you talk a little bit about the various pathways and such that might affect -- so basically my

understanding of Patent Owner's argument is that just knowing where the metabolic hot spots are is not enough, that it is unpredictable because there are so many other factors involved in these biological pathways that could possibly affect the inhibition or the effectiveness of these drugs. Could you speak to that a little, please?

MR. FELDSTEIN: If you could go to slide 12, please. So slide 12 has -- it has the Shilling Exhibit 1005 paper on it, and it shows the -- excuse me, slide 10. I apologize. Slide 10, it shows the second ring on the left, where it's known that metabolites are formed dominantly on that ring.

And so that's where metabolism is dominated, and so those are really the logical places to try to inhibit metabolism, and you know that because the reactions are aliphatic oxidations, that's what the type of p-450, the metabolism occurs. You know they tend to give you a higher kinetic isotope effect, more bang for your buck as I said.

In terms of what happens in terms of the details, it's true Concert makes a lot of arguments regarding, well, which step in a metabolic pathway is going to actually be the rate limiting step that causes you to see the deuterium isotope effect.

We think that's fairly irrelevant which sub-step within the p-450 metabolism causes the kinetic isotope effect. What's known is that when you deuterate, you see a kinetic isotope effect. We have evidence in the record of the species that are described in the evidence.

There are 79 percent of them roughly show a kinetic isotope effect. There's testimony that for aliphatics it should be even higher, and in the experience of Dr. Reider, it is even higher than 79 percent.

And so whether or not you know exactly which step in the metabolic pathway causes that slowing, the fact is you see slowing especially for aliphatic hydroxylation.

And so what sub-step it is, whether there's water formed or not water formed in the metabolism, really becomes irrelevant to what is the expectation. The expectation is that if you put on deuterium, you're going to maintain the same potency. You're going to have similar properties in terms of potency and selectivity, and you're going to have inhibited -- you're going to expect inhibited metabolism to at least some degree.

But that's why we think, your Honor, given that the expectation of maintaining activity, the expectation of slow metabolism that really the case ends up being one of secondary considerations.

This is what happened during prosecution as noted in the institution decision. They relied on secondary evidence, some in vitro testing to overcome the examiner's prima facie case. That's how they got a patent, was based on secondary indicia.

We now have more evidence on the case of obviousness on all the reasons why it's particular to ruxolitinib why you'd be motivated and have an expectation of success, and now what we have in this IPR

is that Concert has no longer relied on the evidence they used here in prosecution. They have switched to new in vivo data to try and argue secondary indicia.

But to argue their new data is, A, neither unexpected, B, not significant, and C, not commensurate in the scope of their claims.

And so with that if you'll go to slide 13. Slide 13 describes and illustrates the single batch of what Concert's trying to call CPT-543. They use a single batch for, as we understand it, all of the data that they rely on or all in vivo testing data that they rely on.

And this compound is also referred to -- the molecule is also referred to as compound 111 in specification. It's the octadeuterated ruxolitinib analog where --

JUDGE HULSE: Can we pause for just a second?

MR. FELDSTEIN: Sure.

JUDGE HULSE: I just wanted to make sure there are no confidentiality issues with respect to this slide.

MR. FELDSTEIN: I believe, your Honor, that Concert has withdrawn their concerns about confidentiality. They can perhaps address that directly if they like.

JUDGE HULSE: Okay. Thank you.

MS. HARDMAN: Your Honor?

JUDGE FRANKLIN: Go ahead.

MS. HARDMAN: Patent Owner doesn't have any confidentiality concerns at this time.

JUDGE FRANKLIN: Thank you.

MR. FELDSTEIN: So this batch, Concert provides some testing information on it, and they report that the deuterium incorporation is 98.7 percent.

So by that number virtually all the places you see delisted in the structure, virtually all in the ensemble of molecules that they use in their batch, virtually all of them have deuterium, 1.3 percent don't, so it's not perfectly deuterated, but it's nearly 100 percent. It's 98.7 percent.

And so the commensurate scope problems are twofold. First, if we turn to slide 14, the octadeuterated ruxolitinib compound, compound 111, all the claims are much broader or don't even read on compound 111.

And so Claim 1, for example, by our count it's 384 different individual formula within the -- species within the claim formula. And so Concert has argued basically there is species by species variability in deuterated compounds. You've got 384 compound species covering in Claim 1. There's no way that deuterated ruxolitinib, a single species, is commensurate in scope with those claims. I don't even see that Concert has argued otherwise.

Some of the claims, 3, 4, 11, and 12, our reading of them, they don't even read on compound 111, so those claims, any data that Concert has on compound 111 seems irrelevant to those claims, and we don't believe that Concert even argues otherwise.

The smallest group is Claim 7. It has three compounds, two of them being different than compound 111, but again we don't think that Concert even argues that you can extrapolate from compound 111 its in vivo data to any of the other compounds.

So we don't even think they put on a -- we don't think they dispute really that compound 111 is not commensurate in scope with the many species covered by their original claims in 1-15.

And there's a further factor here that in terms of deuterium, the percent deuterium in the formula in Concert's claims -- and we'll get to claim construction later, but in Concert's claims deuterium doesn't mean deuterium. Deuterium means greater than 45 percent deuterium, meaning it could be 55 percent hydrogen.

So even if you were limited, even if the original claims were limited to ruxolitinib -- deuterated ruxolitinib per se, compound 111, they still have a problem of over breadth in terms of the amount of deuterium.

So they're not commensurate in scope. On slide 15 we're now talking about why the effects that Concert reports are not unexpected, so it's truly textbook science, going back to a fairly well known pharmacokinetics treatise by Rollins, Exhibit 2013.

It's something that Concert introduced in their case, that when -- just a matter of proportionality, a matter of basic metabolism in pharmacokinetics, if you reduce the rate of clearance, you're going to increase the exposure there under the curve.

And so that's shown in this figure on slide, 15 that there's a lower dark line. You reduce the clearance. You make the drug cleared. You catalyze more slowly. You get an increased exposure. You get a longer half-life. It's just textbook science.

And Dr. Baillie, who is Concert's expert, and we've used sort of color coding here. We've put the -- so you can keep track of the cast of characters. Concert witnesses are always identified in red.

So Dr. Baillie, Concert's witness, agreed that it's no surprise that when you reduce clearance that you increase the area under the curve, and so it's no surprise that when you inhibit metabolism you increase exposure.

So it's textbook science that that happens. It's well known. It's in many examples. We just have a couple here on slide 16. On slide 16 on the left you have deuterated ivacaftor, and as you deuterate it you increase the half-life and you increase the exposure, T1/2 of AUC.

Inhibited ruxolitinib, that's the -- it's not deuterated, but that's the ketoconazole, the metabolic inhibitor from Exhibit 1071. When you inhibit metabolism you increase the half-life and you increase the exposure.

Concert CTP-543 data, when you increase the half-life -- I mean, excuse me. When you inhibit metabolism of ruxolitinib you increase the half-life. You increase the exposure.

The only thing that -- so the trend is the same for all three. The only thing that's really notable is that for the CTP-543, the magnitude is fairly small, and as we'll get to, the magnitude is so small as to be trivial and not clinical meaningful.

So part of the reason on slide 17 on why it's not clinically meaningful is Concert makes a lot of arguments around, well, there's more exposure. There's more time above a floor level that they defined after 12 hours for the CTP-543, the deuterated rux.

But what happens is that both drugs, deuterated rux and CTP-543 at equal doses, 60 milligrams, they both stay above this floor up to 12 hours, and the drugs are generally intended for twice daily dosing, and so if you dose twice daily, anything that happens after 12 hours really is a wash. You don't see the effect after 12 hours.

And so clinically, taking the drugs twice daily you would see no difference in terms of how long they stay above the minimum floor that Concert has identified as being relevant to alopecia.

I should add that on a half-life, so this 12-hour, this longer time at 12 hours is a product of the half-life being extended, which we saw was somewhere around 12 or 14 percent increase for CTP-543.

If we go to slide 18, what Concert has said in this IPR on the left hand side is that there's a significant increase in half-life. It's actually 0.4 hours, 24 minutes is the increase that they're calling significant.

What they have in a press release that predated the IPR, they said that the half-life of CTP-543 was similar to deuterated ruxolitinib. In fact they were right the first time in the press release, Exhibit 1015, that it is similar. There's no clinical difference between an extra 24 minutes of half-life for patients.

We can go on to slide 19. Just some of the relevant case law is Galderma first of all. I don't think they dispute that it's relevant, and Galderma requires that there be a difference in kind, not really a difference in degree.

We think that Concert fails here pretty clearly because at best they have a small difference in terms of half-life and exposure, and in the consequence lifetime that gives you about 12 hours. It's pretty clearly just a difference in degrees, exactly what you would expect to happen when you inhibit metabolism.

And then from Lilly v. Zenith Goldline it explains that for secondary indicia to be relevant, they have to be unexpected and significant.

We think that Concert fails both elements of Eli Lilly, because as shown, it's textbook that the half-life increases and the exposure increases if you inhibit metabolism, and it was already seen in Exhibit 1071 what happens to the half-life and exposure of ruxolitinib if you inhibit the metabolism.

So it's not unexpected and it's not significant, because it's a 0.4 hour difference in Dr. Shapiro, our clinician, who specializes in the

treatment of hair loss disorders. He testified that the 0.4 hours could have no clinical impact, and I don't believe that testimony has been refuted.

So if we can go on to slide 20. Another point that Concert argues is that there is something special about an inverse relationship between magnitude of half-life improvement for the deuterated drug relative to the non-deuterated drug.

And their data they present in this IPR is the right hand box for CTP-543, and you get this sort of negative slope.

And so what Concert indicated in their Patent Owner response is that Concert is declaring it's not aware of another example where a comparison of a CYP-450 metabolized deuterated drug to a non-deuterated drug showed an inverse relationship.

Well, Dr. Harbeson, who is one of their declarants in this case and a former employee, and I believe inventor on the patent, he said, you know what? I am aware of a similar occurrence, which is the case of deutetrabenazine which is the only commercially available FDA approved deuterated drug.

So the one drug on the market is deuterated. It had the same inverse trend that Concert is now trying to say is unexpected and significant. Not only did it occur, according to Dr. Harbeson, for deutetrabenazine.

We looked at other data that Concert presented in this IPR for atazanavir, and if you take atazanavir and you plot the data the same way that Concert did for CTP-543 you see an inverse relationship.

And then for venlafaxine, a drug in the prior art, where there was data that allowed this sort of plotting, you see the same inverse relationship.

In fact there's not a single set of data that has been shown in this IPR any other trend, and so Concert says this is unexpected. This is significant. Well, there's no evidence of anything different than what they're saying is this relationship.

In terms of the magnitude again here what you're seeing is that the dotted line on the right hand side, the right hand figure, that's the 0.4 hours, and you see that Concert's data is scattered above and below. Some of the ones on the left are very close to 0.4 hours.

We've got a 0.4 hour increase, roughly that same 0.4 hour increase for all the small group of patients, and that 0.4 hour increase has no clinical significance. That's what Dr. Shapiro has testified to.

There's another argument from Concert relating to long felt need. Concert's argument is that there's a long felt need for -- and I'm paraphrasing what they argue, but essentially FDA approved treatment for alopecia areata based on clinical data and maybe also a first in class treatment. It's not clear. There's different formulations of what they say.

So one thing that's missing from their long felt need argument is any evidence in the prior art of an articulated need, there's no articulation in the prior art of a long felt need for such a treatment.

Now of course it would be great to have FDA approval, but what Dr. Shapiro testifies to on slide 21 is that he's been doing this for 30 years. He's always had a host of treatments, ones that he used before the patent came out as it was filed; ones that he uses now.

And so there was no shortage of treatments. There's likely always the case that there's room for improvement. There's likely always some motivation to make yet better drugs. That's part of what the original article that we're talking about -- Exhibit 1013 was talking about, that there's always a way to improve existing drugs, but there's not particularly a problem in the prior art that, oh no, we have nothing to treat alopecia areata and we tried and failed to get there.

And so there was no long-felt need. And if there had been a long felt need, on slide 22, it's pretty clear that that need would have already been met by ruxolitinib.

There's Exhibit 1014. It's a published PCT application for May 2012. This application teaches a method of treating hair loss disorder including alopecia areata using a JAK inhibitor. It's the class of drug that ruxolitinib is. And then specifically identifying ruxolitinib by its code number, what it was known by, INCB 018424.

So there's a specific teaching of using ruxolitinib to treat alopecia areata. And so if there had been prior to the time of

Concert's patent a need for treating alopecia areata, it was already taught by ruxolitinib. That need was already met.

JUDGE HULSE: Could you respond to Patent Owner's argument that the CTP-543 obtained fast track designation at the FDA?

MR. FELDSTEIN: Sure. And I will turn to slide 23. The FDA approval or not is, we believe, irrelevant to whether there was a long-felt need. Again, it's not a prior art fast track approval where there was a recognized need in the prior art.

It's true that there are no FDA approved treatments for alopecia areata. And so that for all we know is the FDA's motivation. But the FDA's motivation for getting something approved for the treatment of alopecia areata is not the same as a long-felt need or fulfilling a long-felt need.

And as we have in the bottom of slide 23, Concert is not alone in having FDA breakthrough or fast track designations. So they're not going to be a first in class treatment as they claim they are. The FDA had a breakthrough designation to Pfizer JAK inhibitor for AA and it gave fast track designation to an Aclaris JAK inhibitor.

But even if that was significant indicia to be given fast track approval, their theory of a long felt need was for FDA approved based on clinical evidence. They meet neither of those prompts. They're not FDA approved. They're not FDA approved for any indication, that is, Concert's CTP-543.

And you can contrast that with ruxolitinib. It is FDA approved, not for alopecia areata but for blood cancer, myelofibrosis. And tofacitinib, another prior art JAK inhibitor, was approved for another autoimmune disease, rheumatoid arthritis.

And so even if there was a long felt need, even if the FDA's fast track was some evidence of that, even though it comes at the wrong time, Concert doesn't need it. It's not FDA approved. And for the evidence they've put into this case, there's zero clinical evidence using CTP-543 in an alopecia patient to -- much less, an alopecia patient to demonstrate efficacy. In fact, they were relying on ruxolitinib's efficacy for the treatment of alopecia areata and inferred that for being equally applicable to CTP-543.

But my point, I guess, to summarize on this slide is that even if there was long felt-need, Concert can't meet it given that they don't have FDA approval and they don't have clinical data in its patent showing alopecia efficacy.

I'd like to move on to procedural evidentiary question regarding the Concert Backgrounder. It's Exhibit 1006. This is a document that Concert admitted in a request for admission. And Exhibit 1006 is a true and correct copy of a document that's prepared by or on behalf of Patent Owner and a declaration from Mr. Shelton as to where Exhibit 1006 was recovered from the source called WebCitation.

And the question Concert has raised is, well, okay, so there's a document that's available on the web. Has Incyte proven that it was publically available within the law?

On slide 25, we have some of the relevant case law here. GoPro, this came out over the summer and revised I believe around September. It's held that we have interpreted one too broadly, even finding relatively obscure documents qualify as prior art so long as the relevant public has a means of accessing that.

So GoPro, the Federal Circuit is one of their most recent statements on public accessibility. It's broadly interpreted. It's something that we've argued. It's a case that I believe Concert has failed to address in any of their papers.

A lot of Concert's arguments are focused on, well, is the WebCitation website indexed for searching? And the response there based on Lister is it doesn't matter. It'd be fine if it was. But it doesn't matter because indexing is not a necessary condition for public availability.

And that brings us to Blue Calypso. There are other ways a document can be publically accessible. And one is a published article with express citation to potentially invalidating reference would similarly provide the necessary guidance. That guidance being -- resulting in a document being deemed publically available.

So we have evidence here of actual dissemination. So we don't need to rely on indexing of the WebCitation website. We have evidence of actual dissemination on slide 26.

Six instances here of actual disseminations. Four of them, the ones in red on the left, being Concert's own hand. The first one being an article by Ms. Buteau, Exhibit 1018, that we'll talk about more.

And so there's clear evidence that actual dissemination, we don't need to speculate was it available. In fact, it was available. It's not a question of could someone find it. In fact, people did find it and disseminated it.

JUDGE FRANKLIN: Why don't you describe a little bit more about that dissemination. For example, you're pointing to the article. What is that telling us?

MR. FELDSTEIN: So the article -- and I will move forward to slide 27. First of all, it tells us that the article is disseminated to a person of ordinary skill. Exhibit 1018 --

JUDGE FRANKLIN: So you mean to one person or the number of authors of the paper?

MR. FELDSTEIN: Exhibit 1018 evidences that the Concert Backgrounder was in fact in the possession of and disseminated to a person of ordinary skill, i.e. Ms. Buteau. And we know Ms. Buteau is a person of ordinary skill. The article, in footnote 1 explains her background as a chemist in the pharmaceutical industry.

She meets both parties' definitions I believe of a person of ordinary skill. It was likewise noted in the institution decision that Ms. Buteau is a person of ordinary skill.

JUDGE FRANKLIN: So am I right to say we have an example where one person of ordinary skill in the art received the Concert document --

MR. FELDSTEIN: What we have --

JUDGE FRANKLIN: -- without any --

MR. FELDSTEIN: I'm sorry.

JUDGE FRANKLIN: It's okay. Because I'm just curious. We don't know how she received it. We don't know whether it was directed to her or whether she was able to access it somehow, at least not from that article.

MR. FELDSTEIN: True. But what we know is that it was disseminated to her. We know from slide 26 that it was disseminated also to a number of patent applications where examiners usually presume persons of ordinary skill.

But under GoPro, it actually isn't required that the dissemination be to a person of ordinary skill. The standard doesn't require dissemination to a person of ordinary skill. A presentation in a public forum doesn't require -- it's not required.

JUDGE FRANKLIN: Someone interested in the subject matter, I think we understand that standard.

MR. FELDSTEIN: Okay.

JUDGE FRANKLIN: I'm trying to understand your reliance on the article.

MR. FELDSTEIN: Okay. So the reliance of the article is twofold. One, in fact Ms. Buteau, who meets the standard of a person with ordinary skill, it was disseminated to her in some way. And if we move to slide 28, she points readers directly to the WebCitation source of Exhibit 1006 in footnote 268 of Exhibit 1018.

She said, the drugs represent an opportunity to prove that a profile for these new drugs and then cites directly to the backgrounder. And so this is the type of Blue Calypso express citation that would by itself be sufficient to find public accessibility.

And I think that it's also important to know that, if you go to slide 29, we believe that a person of ordinary skill in the art would also consider the Buteau article. I don't think it's required under Blue Calypso.

But you can look on slide 29, you've got again six references that cite to Buteau. The first three of them are again Concert patent prosecution. The fourth one is a scientific article that cites back to Buteau.

And so not only do we know that the Concert Backgrounder was disseminated to multiple people including Ms. Buteau, and not only do we know that Ms. Buteau's article has an express citation to the WebCitation source of Exhibit 1006, we know that Ms. Buteau's

article didn't just sit on a shelf. It was, in fact, considered. We have evidence of that, so --

JUDGE HULSE: That's a new argument that you presented in your reply, though, right? That it's evidence of public dissemination through the Buteau article?

MR. FELDSTEIN: No, that's in our petition, your Honor. Our petition says that the Buteau article provides further evidence of the -- I can find you the cite in just a second.

JUDGE HULSE: That would be great. You can come back to it too, if you need to.

MR. FELDSTEIN: No, no. My colleagues have saved me. If we can pull up slide 112. Slide 112, it includes Concert's argument making -- asking the question you just asked, your Honor. And we quote from paper 128. Public accessibility of the Concert Backgrounder via the cached WebCite page is further evidenced by its use in the law review article Buteau published in 2009 which cites the same WebCite page used in this petition.

And so the reliance on the Buteau article as further evidence of public accessibility has always been the argument. GoPro came out afterwards in terms of the legal standard and the legal test. GoPro came out after the petition.

JUDGE HULSE: All right. But in the petition, you're arguing that the Concert Backgrounder was publically accessible through the WebCitation page, right?

MR. FELDSTEIN: Correct. And we're still looking at it.

JUDGE HULSE: Correct, right. That's a given. But what you're now arguing, it sounds like, is that it was also available through this Buteau article, that a person of ordinary skill in the art could look at the Buteau article, see that citation to the WebCitation, and then go to that WebCitation page as opposed to going directly to the WebCitation page and somehow find the Concert Backgrounder.

MR. FELDSTEIN: Slide 25. The point is not that Buteau redisseminates or is a firm dissemination of the backgrounder. The backgrounder is its own argument. It's its own document.

The point for Blue Calypso at the bottom is that an express citation is the type of thing that evidences public availability. And so it is and always has been the underlying Concert document. But it's similar -- the way I see it, it's similar to looking at a card catalog.

The card catalog isn't the dissemination of the document. The card catalog points you to where to find a thesis on a shelf. And so that's the type of evidence, like a card catalog, that will point someone there. Then where a thesis on a shelf is found now to be public accessible is because, for example, there is no card catalog to point there to.

But the Buteau article is pointing directly to it. It's serving essentially as the card catalog directing persons of ordinary skill to the backgrounder itself at the WebCitation source that we've relied on since the petition.

JUDGE SMITH: Counsel, could you just clarify for me the -- do you have any evidence that someone who had the Buteau argument could go to that website and get the Concert Backgrounder article?

MR. FELDSTEIN: Well, the Exhibit 1051 which is the Shelton declaration, says that's exactly what was done, that you take the citation and you go directly to -- you can go back to --

JUDGE SMITH: And this is a good web address, and it would've been a good web address prior to the reviewed account?

MR. FELDSTEIN: Exactly. Slide 28, we can go back to it, it gives the exact web address. And the Shelton declaration, Exhibit 1051, says, I went to that web address and this is what I got.

JUDGE SMITH: Thank you.

MR. FELDSTEIN: Thank you. So if we go to slide 30, just to sort of tie this up on the Buteau article. Dr. Reider, our expert, was asked on cross examination essentially -- I'm not going to read the whole testimony. But he was asked on cross examination essentially would you rely on an article like Exhibit 2018 in Buteau. And Dr. Reider says -- Dr. Reider looks. He sees she's got over eight years of experience in synthetic organic chemistry within a pharmaceutical industry. She holds both master's of science and bachelor of arts, has two skill sets in science and law. I would include it along with other data.

And so we have evidence that Buteau, again, also isn't sitting on a shelf. Buteau is the type of article that has an express citation to the Concert Backgrounder per Blue Calypso and is the type of thing that a person of ordinary skill would, in fact, consider.

So my time is running short for now. I'm just going to turn back to slide 37. And so that's --

JUDGE HULSE: Actually, could you -- so you talked about the public availability of the Concert Backgrounder. Could you address that same issue with respect to Jakafi Label, please?

MR. FELDSTEIN: So with the Jakafi Label, sure, if we can just get the right slide for that. So go to slide 124, please. So the Jakafi Label, it has on its face a November 2011 issue date.

And what we know from the Shelton declaration, again, Exhibit 1051, and then listed on slide 126, we have significant corroborating evidence that the drug was approved in November 2011. And the label was available at that time on various sources including the Concert website and including the FDA website, so both were to check for the declaration.

This does include additional evidence that wasn't in the petition. And we put it in, in response to the institution decision and Concert's Patent Owner response challenging whether or not the Jakafi Label was a printed publication.

JUDGE HULSE: So the difficulty I have right now is that we found in our petition that -- or I'm sorry, in our decision on

institution as you're well aware that Petitioner did not make a sufficient showing as to the public accessibility or availability of this Jakafi Label, right?

MR. FELDSTEIN: Right.

JUDGE HULSE: So explain to me why this wouldn't be, quote-unquote, gap filling in your reply if we were to consider this additional evidence.

MR. FELDSTEIN: Sure. For the same reasons that your Honors found in Paper 74, we address this in an argument that Concert raised for a motion to exclude. They wanted to exclude this additional evidence that we had.

And in Paper 74, page 3, the order states that we agree with Petitioner that the reply in the response to institution decision even if not raised by Patent Owner in his response or Patent Owner may respond to Petitioner's arguments in the sur-reply if it chooses to do so.

So that was what was found before. It's consistent with Eastman Kodak, IPR decision IPR2014-00789 which found similarly in paper 34 that it's proper to respond to public accessibility arguments that are addressed in Patent Owner response in the Petitioner's reply.

JUDGE HULSE: Was that a case where there wasn't a sufficient showing initially in the petition to at least get a trial

instituted? Whereas here, obviously, we found that there wasn't anything.

MR. FELDSTEIN: I'm not sure on the institution decision. I expect so based on the timing of it as it probably predated SAS. So what Eastman approves is responding to arguments in the Patent Owner response. As is noted in Paper 74, we're also responding to the institution decision and under the trial practice guidelines are entitled to do that, we believe.

JUDGE HULSE: But our trial practice update also says that there should be no gap filling, right?

MR. FELDSTEIN: It's not a new piece of evidence. We put in corroborating evidence for what we argued before. And it's, we think, properly responsive to what was said in the institution decision and properly responsive to Patent Owner's arguments in its Patent Owner response.

We put in new evidence. It's true. And our position is that it was in response to arguments on printed publication status, not on the merits of the case. And that that is approved of by at least Eastman Kodak.

JUDGE HULSE: So at the end of day, though, you have two grounds. One based on the Jakafi Label, the other based on Rodgers, Shilling, and Concert. Do you need the Jakafi Label to make your case?

MR. FELDSTEIN: We do not. As the arguments from Patent Owner had come out, they don't have different arguments other than the printed publication status of the Jakafi Label. They don't have different arguments on their non-obviousness position for the two. And so substantively in terms of the motivation and expectation and secondary indicia grounds.

JUDGE HULSE: Thank you.

MR. FELDSTEIN: Thank you.

JUDGE FRANKLIN: Okay. And I just want to clarify on that point. So the ground involving Jakafi, could that exist without that label? In order words, is that label critical to the ground?

MR. FELDSTEIN: For ground 1 -- so ground 1, what Jakafi teaches is it teaches ruxolitinib and point to specifically to ruxolitinib. Shilling which is also part of ground 1, Exhibit 1005, also points to ruxolitinib.

JUDGE FRANKLIN: Right.

MR. FELDSTEIN: And so the ground likely could survive even without the Jakafi Label.

JUDGE FRANKLIN: And then one other quick question I had about Exhibit 1004 is exactly what it purports to be. Is this something that you're saying was submitted to the FDA or something that the FDA presented on its website? Or what was the source of this?

MR. FELDSTEIN: So it's basically when you open your box, your presealed drug, they have the detailed patient instructions --

JUDGE FRANKLIN: It's the package insert?

MR. FELDSTEIN: It's the package insert. And when the FDA approves the drug, it puts it on its website. That's where it was pulled from. It is also put contemporaneously on Incyte's own website for the Jakafi Label.

JUDGE FRANKLIN: But where did Exhibit 1004 come from?

MR. FELDSTEIN: From the FDA's website.

JUDGE FRANKLIN: From the website? Okay. And so we just know that because you just told us?

MR. FELDSTEIN: And Exhibit 1051, the Shelton declaration tells us also.

JUDGE FRANKLIN: Okay. So we've gone a little bit into your rebuttal time. Do you want to wrap up or do you want to --

MR. FELDSTEIN: I will stop right here and move on if there aren't any more questions.

JUDGE FRANKLIN: Thank you.

MR. FELDSTEIN: Thank you.

JUDGE FRANKLIN: Okay. Ms. Hardman, you may begin after you tell me how much time you'd like to reserve for rebuttal or surrebuttal.

MS. HARDMAN: We would like to reserve 25 minutes, please, your Honor. May I hand up our demonstratives?

JUDGE FRANKLIN: Yes, thank you. Okay. You may begin.

MS. HARDMAN: Thank you, your Honor. I will be speaking about motivation and reasonable expectation of success, issues associated with the so-called prima facie case of obviousness. And Mr. Wiesen then we will be splitting this block of time. He will be talking about secondary considerations and also Patent Owner's contingent motion to amend.

So I'd like to start if we could with the Concert Backgrounder and the printed publication status of that document. It is, of course, integral to both grounds that are at issue in this IPR. If we could please have Patent Owner slide 27.

I think what we have here going on is a bit shifting theories from the petition. We can see here Patent Owner's demonstratives 27 and also 28. But I'll start with 27, capture the argument set forth in the petition about the Petitioner's theory on printed publication status.

And I think a fair reading of this is really that what they were going for is trying to prove public accessibility because this document was posted on the WebCitation, or WebCite.

We can see if we go, please, to slide 28. They do reference the law review article, but they don't reference it as some of the new theories now that they were raising about it being a research aid.

The way they use the law review article in the petition is to say that the public accessibility of the Concert Backgrounder via the cached WebCite page is further evidenced by its use in a law review article which cited the WebCite page.

So what they're saying there is that a POSA found this article on WebCitation.org and that's the way they were using the law review article. So at most, even if we take -- to credit this argument, what we have here in the petition is one potential person of ordinary skill in the art, a law review author, and one author of an international search report in possession of this particular document.

JUDGE FRANKLIN: And I just want to stop you here. As the parties know, I'm coming to this case a little late. But I just want to clarify. Understanding that the burden is that of the Petitioner, is this Concert Exhibit is a document published or produced by Patent Owner?

MS. HARDMAN: It is a document that is authored by Patent Owner, yes. They did not choose to prove that in their petition. They did not choose to argue that --

JUDGE FRANKLIN: To prove what, that it's by Concert? That's on the face of it.

MS. HARDMAN: That we haven't any dissemination by Concert or authorship or anything like that. What they chose to do was prove that it was accessible via the WebCitation.org.

They did serve some discovery requests on us, which Patent Owner responded to. And they were asking questions about when it was housed on various websites and when it was disseminated and the like. And Concert responded to those discovery requests but was unable to confirm that it had been available in a time that would've made it a prior art.

JUDGE FRANKLIN: Even in light of the professional journal article citing to it?

MS. HARDMAN: I think they did in their reply or maybe even their sur-reply. They did cite a --

JUDGE FRANKLIN: I'm referring to how Patent Owner has responded.

MS. HARDMAN: I'm sorry, your Honor. Could you repeat the question?

JUDGE FRANKLIN: I thought you were discussing responses to a discovery request?

MS. HARDMAN: Yes.

JUDGE FRANKLIN: Okay. So I thought I heard you said they weren't able to determine when it was accessible or made publically available. And I'm saying, even in light of the reference in the published article?

MS. HARDMAN: I guess I'm unclear on which published article that you're referring to? The law review article?

JUDGE FRANKLIN: Yes.

MS. HARDMAN: I apologize, your Honor. The specific discovery questions that were asked, we're asking about its availability on particular websites. Concert of course has no control over WebCitation.org so is not able to verify when the document became available on that website.

There were other requests specific to availability on Concert's own website. And those were the questions that Concert was unable to confirm many years later.

So I do think that Petitioner -- this is a new theory on the research, this sort of -- I'll call it the research aid theory that has appeared in their reply. A prerequisite to being a research aid is the idea that a POSA would have had access to the particular research aid. And this is a law review article. And of course the question becomes, why would a POSA have had access to or how the POSA had come -- how would a law review article have come to the attention of a POSA?

In sur-sur-reply, they cite some testimony from their expert, Dr. Reider, which was asked in a different context. And he said that if it had come to his attention, he would consider it. But the problem is we don't know how it would have come to his attention at the appropriate time back in 2012.

Mr. Feldstein also talked about actual disseminations. But what is missing is disseminated by whom. How did these people get a copy of the article? How is it found, and was it available to people of ordinary skill in the art who were looking for it? Because of course we have one allegation that it's available on a website but no way of people of skill in the art to find it because there's no indexing and no keyword search functionality on WebCitation.org.

Turning now to the Jakafi prescribing information. In the petition, I think Petitioner was trying to get the package insert itself, Exhibit 1004, to do a lot of work. It was trying to, just on the face of it, have it establish the publication date of the particular label, the FDA approval date of the underlying drug.

And even if you credit, they did not do any pinpoint citations to any specific information in that label that they were claiming supported either of these pieces of information.

And even if you credit the arguments in the petition, what is missing there is any allegation that the particular label was actually disseminated with a product approval. So they tried to prove on the one hand publication date of the label and FDA approval on the other. But there's no even attempt to join the two together such that you can make an inference that this was, in fact, the version that was disseminated to the public.

JUDGE FRANKLIN: Well, let me jump to the question that I asked Petitioner and Judge Hulse asked also and that's could ground 1 survive without relying on the label?

MS. HARDMAN: Well, I think one of the foundational aspects of the petition was that this was an FDA approved drug. Mr. Feldstein started off with what was known in the art is that you take an already existing drug because it's already had a safety and efficacy profile that's been sort of stamped by the FDA. And that is your starting point.

So from that respect, they haven't made any allegations about why Shilling, which counsel said discloses ruxolitinib would have called the drug to the attention of a person of ordinary skill in the art.

JUDGE FRANKLIN: Okay. So it's not the content or the substance of Exhibit 1004 that you're saying would be required. It's really what it represents, this FDA approval?

MS. HARDMAN: I think that's really how they used it in the petition.

Now turning to the issue of structural similarity. Counsel called this the epitome of structural obviousness. I think the disconnect here, though, is that what the petition is directed to is the similar properties of selectivity and potency. And Patent Owner doesn't dispute that if you deuterate a drug candidate, you're likely to get the selectivity and potency as the undeuterated version of the drug.

But that alone is not sufficient to carry the day under the Aventis and Dillon cases that are cited in the petition. And the reason why is because Federal Circuit cases like the recent case of Anacor, which we see on Patent Owner slide 64, please. That case tells us that you have to look at not only expected similarities based on structural similarity but also any functional dissimilarities that you would expect.

And here Petitioner's -- one of the motivations that they are providing in the petition of getting a superior ADME profile, A-D-M-E, ADME profile, is actually a possession that you would expect different properties potentially from the deuterated version of the drug.

Now our experts don't concede that you would, in fact, expect superior ADME. But the point is that when you look beyond just the two properties of selectivity and potency, a POSA would in fact expect differences which takes us out of the Aventis and Dillon framework.

Even if you -- the other problem with their so called structural similarity argument is that there's really only -- it's really based on only hindsight motivation. There is nothing in the prior art that suggests that a POSA would have been motivate to deuterate a drug candidate only to end up with something with similar efficacy and potency.

Patent Owner -- or sorry, Petitioner's expert, Dr. Guengerich, concedes that in order to have a safe and efficacious drug, you need more than selectivity and potency. You need appropriate PK or ADME properties as well. And that's in his deposition on page 162 which you can see on Patent Owner's slide 74.

Dr. Guengerich also said in one of his prior art articles that deuterium substitution is useful only if you get a KIE that affects a pharmacokinetic parameter of interest. And that is in Exhibit 1012 at page 4.

So Petitioners have not carried their burden of showing that an expectation of achieving same potency and selectivity would by itself be a motivator to use deuterium substitution.

Turning to Petitioner's sort of second line of argument that an additional motivation and reasonable expectation of success, of potential ADME improvements would have motivated use of deuterium.

I think here this raises a really big hindsight flag. The petition fails to identify a single specific ADME issue with ruxolitinib that could be improved, let alone any attribute of the drug that a POSA would have wanted to improve by deuteration.

They really just in the petition argue that any known drug that had a known target and known metabolic hot spots, known clinical safety and efficacy profile would be a candidate for deuteration. And there's no indicate that Petitioner's expert took a holistic look at

ruxolitinib and its particular properties to evaluate whether they could positively be affected by deuteration.

Importantly, as we see in Patent Owner slide 37, Dr. Guengerich admitted that he didn't even consider ruxolitinib's side effects in opining on a motivation to deuterate ruxolitinib.

And as Patent Owner's experts point out, the potential toxicity, if, in fact, Petitioner is right that you would metabolic stability, we would also have a concern that that would increase Cmax dose dependent side effects associated with ruxolitinib which Patent Owner's experts point out would demotivate a POSA from selecting ruxolitinib.

JUDGE FRANKLIN: Is that because -- are you saying that toxicity would discourage a person of skill in the art from using it as a pharmaceutical composition? Because I assume that you're referring to the composition claim.

MS. HARDMAN: We have claimed -- it's not so much that toxicity would discourage a POSA from using it as a pharmaceutical composition. It's that the case law requires a specific reason to make the specific molecular modifications to the particular drug.

Petitioner's argument is that if you deuterate ruxolitinib, you would expect an increase in metabolic stability. So then the question becomes, well, why would you want to increase metabolic stability for ruxolitinib? Because if you do that, you have the possibility of increasing the toxicity of this drug had some known toxicity issues.

So it's not that it would deter a POSA from using the drug as a pharmaceutical. But the point that we're trying to convey is that the specific use of deuteration with ruxolitinib, the toxicity would've caused you to look for another candidate.

JUDGE FRANKLIN: But safety and efficacy is a balance, right? So sometimes those of skill in the art are willing to gain some efficacy for some increased toxicity. So how does that figure into your position?

MS. HARDMAN: I agree with you that it's definitely a balance, and POSAs would sometimes be looking to gain efficacy if it comes along with some toxicity.

But the point is here in their generic motivation arguments made in the petition, their expert didn't even consider this. It's just a very generic argument that you would basically use deuteration with any different molecule. He did not consider what would actually happen to ruxolitinib's efficacy and/or toxicity if it were successfully deuterated.

JUDGE FRANKLIN: Is there deposition testimony relating to this issue?

MS. HARDMAN: So on Patent Owner slide 74, we have Dr. Guengerich stating that drug safety and efficacy depends on having the appropriate ADME properties. He also says -- and you can see the excerpt on Patent Owner slide 37 -- that when preparing his

opinion submitted in this case, he did not consider ruxolitinib's toxicity.

And in one of the footnotes in our Patent Owner's response, footnote 11, we have testimony from Dr. Guengerich confirming that the facts that he relied upon in the petition are generic and really apply to really any and all FDA approved drugs.

JUDGE HULSE: Can you speak to the Shi article that counsel for Petitioner referred to earlier?

MS. HARDMAN: Yes. Just give me a moment. I need to know what's on the slide, and I have to remind myself which slide it was. Well, let me just say a few things.

So the Shi paper was I believe a single dose study in healthy subjects, as Your Honor pointed out. Here we're talking about the drug would be used for chronic disease. And Patent Owner's experts have pointed out that using a drug for chronic disease you are likely to see adverse events over a steady state dosing and over dosing for chronic for many years that you may not see in shorter term studies.

Furthermore, the Shi paper, by the way, was not even submitted with the petition. So it's something that now that I was surprised actually to hear counsel say that, well, we would've known what happens if you deuterate ruxolitinib because the Shi paper shows us what happens when you administer ruxolitinib with a metabolic inhibitor.

They didn't have anything in their petition about what effects deuteration would have on the PK profile with ruxolitinib. So this is sort of after-generated argument.

The Shi paper also -- again, it's not deuteration. It's administration with a metabolic inhibitor. And metabolic inhibitors work in very different ways. They blunt or affect all drugs and all substrates that are operating through that pathway, whereas deuterium is very specific to your particular drug. So we have no expert testimony saying that what patents with a metabolic inhibitor is, in fact, predictive of what happens with deuterium substitution.

The other thing that I want to point out is that the Jakafi Label itself warrants that if you're going to administer Jakafi with a metabolic inhibitor, you need to reduce the dose which again suggests that there would be a concern about the Cmax related adverse events as Patent Owner's experts have said.

JUDGE HULSE: But doesn't that also suggest that there's a solution for that, which is reducing the dose? Doesn't that support Petitioner's argument?

MS. HARDMAN: I don't think that's an argument that they made in the petition. They also don't have any expert support saying that -- their only expert on motivation was Dr. Guengerich. Again, he didn't consider this.

So they don't have somebody suggesting that, yes, I will go ahead through the time, expense, and unpredictability of deuteration.

Because if I got something that had increased toxicity, I would simply reduce the dose. That seems to sort of really undercut the whole motivation, or purported motivation, for deuterating in the first place.

Just in terms of the predictability of whether you would see a KIE, a K-I-E, if you deuterate. I was again surprised to hear counsel say that which step causes the KIE is actually irrelevant.

Their petition is completely premised on the theory of predictability based on the so-called CH bond breaking step being the rate limiting step of the catalytic cycle. And because that's the rate limiting step, you would have reasonable predictability of getting a KIE. They seem to now have abandoned that argument here at the oral argument.

But what Patent Owner has shown in the record is that, first of all, there was a debate where unlike what Dr. Guengerich has said that the CH bond breaking is necessarily going to be rate limiting. There's actually debate in the art about whether that step was in fact the rate limiting step. And without knowing whether it's the rate limiting step, you cannot predict whether you're going to get a KIE or not. And you can see that. I'll just refer you to in the interest of time Patent Owner slides 99 and 80.

But in particular with respect to ruxolitinib, if we could have Patent Owner slide 97, please. The enzyme that Dr. Guengerich says is responsible for ruxolitinib metabolism is CYP3A4. And as we can see on slide 97, Dr. Guengerich published in the prior art that there

was something special about this particular enzyme and that the bond breaking step appears to be less rate limiting for this particular enzyme than for other enzymes catalyzed by the p-450 catalytic cycle.

So because this is the particular enzyme involved with ruxolitinib, we really don't know if it's -- there's no predictability about whether you're even going to see a KIE to get the benefits that they're arguing derive from deuteration.

JUDGE HULSE: Is Patent Owner's argument that it's not predictable to determine the actual magnitude of the KIE? Or is it that it's not predictable to know whether there will be any KIE at all?

MS. HARDMAN: It's both levels. So just in terms of predicting whether you will get the KIE, Dr. Guengerich tells us that that will happen if the CH bond braking step is rate limiting. And we believe that there's no predictability with respect to that.

Then as a second level, even if you get a KIE, there's no meaningful way to predict the actual magnitude of that KIE.

And then furthermore, even if you do get a KIE in an in vitro scenario, once you get in vivo into the human body with all the competing processes that happen in there, you don't know if that KIE is going to be seen, if it's metabolic switching, it's going to ameliorate any benefit you might get from that KIE. You don't know what effect it's going to have on your PK profile, if it's going to do anything useful or if it's going to do even anything harmful, which is also a possibility.

JUDGE HULSE: Do we need to show all of the steps beyond whether -- I mean, you don't have to show absolute predictability, right? You don't have to be 100 percent certain that something will happen. So my understanding of Petitioner's argument is that, well, when you look at deuterated compounds as a whole, by and large, there is some effect that is shown. So could you respond to that, please.

MS. HARDMAN: Sure. So they say that based on Dr. Reider's analysis where he comes up with something like 75 percent of compounds show a KIE. The problem with that, that was a biased sampling as we pointed out. And in particular, they didn't draw any examples specific to the 3A4 enzyme.

Also, just in view of the unpredictability in the art, they're saying that this particular technique of deuteration has existed since the 1960s. But even as of the filing of the petition, there has not been any successfully deuterated drug. And the reason why you would need some sort of benefit, they're saying that a POSA have been motivated to deuterate to get improved ADME. But they really haven't shown any predictability that deuteration is going to result in improved ADME which gets back to the hindsight nature of the claim that somebody would be motivated to do this in the first place.

And unless your Honor had any further questions, I want to turn it over to give my colleague a chance.

JUDGE FRANKLIN: Okay. That's fine. You may begin.

MR. WIESEN: Thank you, your Honor. Daryl Wiesen for the Patent Owner. I'm going to start with secondary considerations and then turn to the contingent motion to amend.

If we can start with Patent Owner slide 11, please. Mr. Feldstein started by discussing the commensurate in scope issue and pointing out that the claims cover a series of compounds. What he failed to identify was that inside itself, Petitioner failed to establish the prima facie -- even attempt to establish the prima facie obviousness of anything but three compounds.

And so the focus for the case for obviousness is not on 300 compounds or 15 compounds. But for all but three compounds, the octadeuterated compound that's the main focus and two tetradeuterated compounds, there is no evidence even of a prima facie case of obviousness unless we accept generally that everything deuterated is prima facie obvious.

So for the secondary considerations, the only issue we need to address are the three compounds that they even attempted to show prima facie obviousness for. Otherwise, there's simply no evidence that the compounds that fall within the scope of the claims are, in fact, obvious.

JUDGE FRANKLIN: Do you have a case cite that you're referring to or relying on for that position, that we're looking at something other than the evidence being commensurate in scope with the claim versus the arguments relating to the claims?

MR. WIESEN: I don't have a specific case cite for that, Judge Franklin. I think it follows from the logic of whether -- if there is no reason or motivation to make the changes, then overall, those claims aren't obvious whether or not they show a particular benefit or particular advantage because they've not shown a motivation to even make the compounds that fall within the scope of the claim.

In the old version of the burdenship, it would be sort of a clearer analysis. Now that all the factors are considered together, it's a little less of a red line. But I think logically it still makes sense that the focus ought to be on the claims that they have even attempted to establish a POSA would've been motivated to make. And they've only --

JUDGE FRANKLIN: Those embodiments?

MR. WIESEN: Those embodiments.

JUDGE FRANKLIN: But you're not -- you don't intend through this argument to suggest that the claims should be limited to those embodiments?

MR. WIESEN: We do not, your Honor. And the reason we have the contingent motion to amend is to focus down if there is a concern over commensurateness, then claims 16, 17, 18, and 19 should resolve that which I'll get to in a few minutes.

I want to turn, then, to what the secondary iterations of non-obviousness are that Patent Owner has established. And I want to start with the advantage for the so called fast metabolizers.

If we look at Dr. Ortiz de Montellano's declaration, it's Exhibit 2057, and paragraph 51 on page 37. If you'd take a look at that. What Dr. Ortiz de Montellano did is, he's the only expert to tell -- Patent Owner's experts are the only ones to tell us what would be expected for patients when there is deuteration if the deuteration causes a pharmacokinetic effect.

And what Dr. Ortiz de Montellano tells us is, what we expect is across patients they metabolize differently. That's why we do a crossover study to control for the interpatient variability. But the effect of deuteration, if there is one, would be expected to be approximately the same relatively across patients.

In other words, if you slow down metabolism by ten percent for Patient 1, you'd expect it for Patient 2 and for Patient 3 and for Patient 4. And Petitioner hasn't challenged that evidence. No technical expert for Petitioner has disagreed with Dr. Ortiz de Montellano. Dr. Baillie, one of our other technical experts, says the same thing. That's Exhibit 2002, paragraph 53.

So if that's what we expect, then let's look at what actually happens. If we go to figure 1 of the Harbeson declaration, that's Exhibit 2001, we see the specific data that occurred.

JUDGE HULSE: Counsel, do you have slides on this? It's a little easier, if you have a slide, for us to go to the slide.

MR. WIESEN: I apologize. For this one, I did not make a slide with this figure on it.

JUDGE HULSE: Okay. No problem. So, repeat that cite again.

MR. WIESEN: It is on the Harbeson declaration, Exhibit 2002, Figure 1, which is on page 10.

JUDGE HULSE: Got it. Thanks.

MR. WIESEN: And what we see here, as Dr. Harbeson relayed -- and again Dr. Thisted, their statistician, confirmed the numbers are crunched correctly. This line is not flat. It's sloped downward, and it's statistically significantly sloped downward.

Now, what does that mean? That means that the people on the left-hand side metabolize ruxolitinib more quickly. That means that the dose is going to get pushed through their body and they're less likely to have an efficacious effect. But when we deuterate the compound, it will create the octadeuterated compound CTP-543.

Surprisingly, there is a greater slowdown for those people than there are for the people who metabolize quickly. That evens out the dose, which is beneficial to doctors because it's easier to dose a drug that's similar across patients. And it also means it's more likely to be efficacious for those fast metabolizers where ruxolitinib may not have been efficacious. And that is a surprising result.

If we go to slide 153. Dr. Mackay-Wiggan, who is our M.D. who treats our alopecia areata patients, explains that as a clinician that would be seen as a benefit. Dr. Baillie says the same thing. And then Dr. Harbeson, on slide 155, explains why that would be unexpected. And as we saw from what Dr. Ortiz de Montellano set out as the expectation, of course it's unexpected that we see that downward slope.

JUDGE FRANKLIN: And so then are you saying, I guess contrary to what I heard from Petitioner, is that is a difference in kind?

MR. WIESEN: We are, your Honor, saying it is a difference in kind. This is something that would -- people would -- if you would expect that similar treatment. I noticed Mr. Feldstein pointed out that -- or claimed that Dr. Shapiro said the .4 hour change in half-life and clearance rate, he pointed to it for this argument.

This argument doesn't have anything to do with that .4 hours. That .4 hours is an average. And this argument looks at the individual patients and says we see this trend across patients, not as an overall average.

I don't think they've got any evidence to suggest that this, if it really occurs, is not a difference in kind from drugs and significantly different as Dr. Mackay-Wiggan explained on slide 153.

And so with this different -- this unexpected result, let's look at what Petitioner has argued is a reason that this should be rejected.

They point to other examples and say there are examples that yielded the same result.

If we go to slide 164, they start with Dr. Thisted, who's their statistician, talking about the data that we've generated. Dr. Thisted, however, is not a person of ordinary skill in the art. He didn't talk to any people of ordinary skill in the art. They didn't provide his analysis to any people of ordinary skill in the art.

So when he says what he would or would not expect, that doesn't give us a lot of insight. It gives us no relevant insight for the question that's presented here, what would be expected to a person of ordinary skill in the art?

Instead what we get is that Petitioner points to a series of other examples that they claim show the same trend. But, in fact, none of those are helpful to Petitioner. First, even if they could find a handful of examples, that wouldn't actually tell us what the answer is about what would or wouldn't be expected. But if we look at each of the examples they point to, in fact, they don't help.

So the first one they point to is deutetrabenazine. And if we go to slide 155. Dr. Harbeson explains that we need to look at, as Ms. Hardman was discussing, which CYP enzyme does the metabolism to understand this argument.

CYP3A4 is different than CYP2D6, which is what impacts deutetrabenazine because CYP2D6 is subject to genetic polymorphism.

That is, you'd expect differences across the population. That's not true for CYP3A4, which is what metabolizes what affects CTP-543.

And if we go to slide 157, we see that Dr. Harbeson explained that Austedo, or deutetrabenazine, is a CYP2D6 example; i.e., it does not go to the same question. Moreover, there's no establishment when Dr. Harbeson was aware of this. And if it wasn't in the prior art, you can't set the expectation for anything.

If we look at venlafaxine, that was the next example they talked about. And if we look at slide 158. Venlafaxine, again, is a CYP2D6 example. And there's no evidence, in fact, I think, that it was a statistically significant trend that they saw.

The last one they talked about was atazanavir. And if we look at slide 160, we actually asked Dr. Thisted about the data that they put up on that slide, is that trend statistically significant? Remember that it is statistically significant for CTP-543. And he had to admit, no, it's not statistically significant. So, although you see that slight downward trend in the data with atazanvir, that's not statistically significant, and we think is therefore different than what we demonstrated with CTP-543.

Finally, the atazanavir data, as well, was not public. That was an analysis they did of internal Concert data that was generated just as part of this litigation and so can't set the expectation for unexpected results.

I want to turn, then, your Honors, if I can, to the second unexpected result, which correlates to the therapeutic window. For that argument, your Honors, I think it's important to note that we are not arguing that one particular pharmacokinetic result is an unexpected result. We're not talking about the half-life. We're not talking about the AUC. We're not talking about any one piece of it. What we're talking about is what we discovered, as a whole, for CTP-543 was that the pharmacokinetics were unexpectedly better than the pharmacokinetics for ruxolitinib. That when you combined -- that you have the slowdown in the clearance, the Cmax not being statistically significantly higher, combined with the thresholds for efficacy and toxicity in alopecia areata, in AA, you surprisingly and unexpectedly got a longer time than the therapeutic window.

Most of what Petitioner's argument is, is to pick at one piece of that or another piece or a piece here or a piece there and challenge each one. But they haven't put together any reason that a person of ordinary skill in the art would've expected that entire combination that we lay out in the papers that provides an unexpected benefit.

If you can put up Incyte's slide 17 for a minute. We heard about this slide from Mr. Feldstein. This slide is actually flawed in two ways.

The first is that Dr. Shapiro does what I just said. He picks out one of the pharmacokinetic parameters and talks about it alone. But the

second is that the comparison that Incyte is doing here is 16 milligram to 16 milligram doses of ruxolitinib and CTP-543.

And as we explained in the petition, what you have to do is actually create dose-normalized doses that have similar efficacy and then compare toxicity. Because, as you said, Judge Franklin, you have to look at efficacy and toxicity together. And that's what the therapeutic window argument is about.

And when we look at them together, that is when we see an unexpected benefit that comes from deuterating, because we see the Cmax stay statistically the same, the AUC get longer. And when that happens, we stay longer in the therapeutic window. And I didn't hear any argument that suggests that that's not what occurs here, and no challenge to whether the dose analysis that we did is the correct one.

And as Dr. Mackay-Wiggan explained, that's an important difference. If we go to slide 144. Dr. Mackay-Wiggan explained that that advantage that we see with CTP-543 will be an important to adopt there.

Now the evidence in the record is that previously Concert was considering giving this dose, this drug twice a day. And it's outside the record. I admit they have now made public that they're going to move forward with a once-a-day clinical study because they believe that the pharmacokinetics here are truly advantageous.

MR. FELDSTEIN: Your Honor, I'm going to object to going beyond the record and ask that testimony by counsel be stricken.

JUDGE FRANKLIN: Thank you.

MR. WIESEN: I apologize, your Honor. One of the issues here is when Incyte chose to bring this challenge during the clinical development, which is not yet completed on the product. We've got other data that, just because of timing, hasn't been able to put into the record. And I won't --

MR. FELDSTEIN: Your Honor, I would object to that too and ask that be stricken.

JUDGE FRANKLIN: It's not being considered. You can continue. And just to watch your time, because I know you want to get into the motion to amend, you have just over ten minutes left.

MR. WIESEN: Understood, your Honor. Dr. Mackay-Wiggan did note that it would be possible to give the drug less frequently. Unclear whether that's possible, but that is certainly in the record, as well as at a lower dose which would be likely to lead to lower side effects.

Let me turn briefly to the long-felt need issue before I turn to the motion to amend. There's no question that alopecia areata is a serious disease. It's a chronic disease. There is no FDA approval for it. Before you were asking Petitioner about the FDA fast track. That confirms that the FDA at least believes there is no drug that is appropriate for treating that disease.

What I'd ask is if you look at what Dr. Shapiro has cited and what Petitioner is relying on to try and establish that any need for

treatment is fulfilled. Look at the data that he cites. The answer is, there is no data.

In the prior art, before 2012, the only actual evidence established by Dr. Shapiro is anecdotal evidence that he purports to provide. He points to a patent application on ruxolitinib that has no actual efficacy data in human beings. He points to the fact that people use tofacitinib or other drugs. Again, nothing but anecdotal evidence on that subject.

The first drug to get FDA fast track approval from the FDA to move forward for alopecia areata is CTP-543, that being Concert's product. And that product is the one that we think will fulfill the long-felt need, as Dr. Mackay-Wiggan explained as we just looked at.

JUDGE FRANKLIN: So this is -- I'm sorry to interrupt. So this is more of a prospective argument? Because I think Petitioner's point also was that you cannot yet establish a long-felt need has been met.

MR. WIESEN: Correct, your Honor. We do not yet have FDA approval. That is true. What we have is the analysis that we've done of the likely efficacy from the modeling based on the pharmacokinetic profiles and the therapeutic window. And Dr. Mackay-Wiggan has explained that, based on that data, it's likely that there will be FDA approval.

So it's not there yet. But in terms of between the FDA fast track and the data we've presented, which is all the data we have to date

given the timing of the IPR, we think that's sufficient to establish a high likelihood we will fulfill the long-felt need and meet the secondary consideration, because it puts us well ahead of the prior art.

JUDGE FRANKLIN: But is that something we can consider now?

MR. WIESEN: I think it is, in light of the therapeutic window analysis that's been done and Dr. Mackay-Wiggan's analysis of that data where she concludes and gives the expert opinion that it's likely to become available. That suggests that that data is sufficient to fulfill the technical need of a drug that would be sufficient to treat alopecia areata.

I want to turn to the motion to amend, if I can. And I'll deal with the commensurate in scope issues a little bit more in that context as well. It's a contingent motion to amend. And, at times, Petitioner sort of points to the fact that there's an inconsistency. Of course, with a contingent motion to amend, we hope you never get to this issue. But if you do, the Valeo decision is sort of right on point from the PTAB. That's a case in which the original claims were found invalid as obvious. The secondary considerations didn't match the -- were not commensurate in scope. The amended claims were there and were found valid because they were commensurate in scope.

There's really two issues I want to deal with for the motion to amend. The first is claim construction. The second is the commensurate in scope issue.

If we put up slide 191, that's the first proposed amended claim. And let's go back to slide 192 because it's the same, although it adds a deuterium substitution level at the bottom, 95 percent. And there's no dispute that this claim goes to one single compound, the octadeuterated compound.

There's also no dispute in the claim construction issue that the patent itself provides a construction of the particular limitations. If we look at slide 227, we get the patent's definition of deuterium, D, which means that you have to have at least 45 percent. Any place you see a D, it's at least 45 percent D. And the definition of compound.

Compound here is not what we think of as a single molecule. Compound is specifically defined as a mixture of molecules where at least 50.1 percent of the molecules have deuterium at the identified location, and 49.9 percent of them can be what are called isotopologues which means that instead of the D, there's an H at one of the claimed and identified locations.

And if we look at the claimed element by element, then, we can simply see what the scope of claims are. If we go to slide 240, we can see that on slide 240 has Claim 16 and 17. To meet the compound limitation, you would need to have at least 50.1 percent of the molecules or more, have D at all eight of the positions that are identified. And to meet the Hy2 is deuterium or Hy3 is deuterium, you have to have at least 45 percent D at each position.

And then we just look and see, all right, do we meet this construction? Well, since 50.1 percent is bigger than 45 percent, for this claim, you have to have at least 50.1 percent of the molecules have D at all eight locations. We got to the next slide. Actually, let's skip to slide 243.

If we look at Claim 18, here we've got three different limitations we have to look at. We've got compound, which is 50.1 percent. We've got each D -- 95 percent of each D. And then you can figure out as Petitioner actually points out what percentage of the molecules must have at least D in all of the positions if 95 percent of them have Ds. And that's 66 percent.

And we do the same analysis again. And we say, all right, for a compound to meet this limitation, here it's got to be at least 66 percent of the molecules are octadeuterated. And it's as simple as that.

Petitioner's argument is that we were trying to claim an octadeuterated molecule and instead managed to claim less than one percent of an octadeuterated molecule. Even when we wrote 95 percent into the claim limitation, we still didn't manage to claim anywhere near 95 percent. We think that's an unreasonable construction, and the right construction is what we put forward in our paper.

I'll note, if we go to slide 247, you can see the inconsistency explicitly between Petitioner's construction and the specification. If you look at their sur-reply on the motion to amend, they explained that

they have what they call non-isotopologues having hydrogen atoms at the positions identified in deuterium. That's on the bottom of slide 247.

But the patent specifically says it is an isotopologue if it has an H there. Therefore, it can't be an non-isotopologue and the logic simply doesn't hold together.

If I could turn then, briefly, to the commensurate and scope issue. If we look at slide 256, starting with a little bit of the case log on commensurate in scope. There's really no dispute that you don't have to test every specific example. All that you need to do is show a reasonable basis to believe that the data that's presented is commensurate in scope with the claims.

I've got the Genetics Institute case on 256. We turn to 257, we have the Takeda case. And, sorry, if we go to 259, I think I need. The In re Huai-Hung Kao case. Evidence of secondary considerations must be reasonably commensurate. This does not mean an applicant is required to test every embodiment.

So then the question is, what do we have for evidence and is it reasonably commensurate? If we look at the Cowden declaration, it's on slide 261. This is the Concert employee tested the deuterium level, or reported on it. And he reports there's at least 98 percent deuterium incorporation at each of the eight deuterated positions. So that's 98 percent. It is a little bit higher than the 95 percent, to be sure. But 98 percent is the data that we have for the batch that's in CTP-543.

And what Incyte has admitted, if we look at slide 265, is that isotopic purity is what's called a known result-effective variable. What does that mean? We're going to see the same effect but to a slightly different amount when you reduce the amount of deuterium. So whatever you see at 98 percent you'll see at 95 percent, just a little bit less. You won't see some massive change in the kind of result that you get. And that's a admission that Petitioner gave based on the testimony of Patent Owner's expert, if we look at slide 264.

JUDGE FRANKLIN: You have two seconds.

MR. WIESEN: I'll go a little bit over, if that's okay.

JUDGE FRANKLIN: Sure.

MR. WIESEN: Just to finish this point. Dr. Baillie explained the same thing, that you would expect the degree of enrichment to be a result-effective variable. And so you'd be able to expect, once you have the data at 98 percent, you'd expect a similar result, maybe a tiny bit less at 95 percent and a little bit less than that at 66 percent.

We'll know, and if we go to slide 266, Petitioner doesn't present any evidence that there is some big change, some big difference. And in the Cephalon case, the court held that against a challenger to a patent. They said if you think there's going to be a difference in the commensurateness in scope once we know we have sort of a result-effective variable, bring forward the evidence. Show us why this

different. The court held that against them, and I think you can hold that against Petitioner here.

If we look, finally, at Incyte slide 34. This is a slide that Incyte has made to show what's supposedly not commensurate in scope. The problem is this slide is misleading. The 98.7 percent that we looked at, the 98 percent, is the amount of D at each of the eight positions. We know for Claim 18 that that should be a 95 percent line, not a 66 percent line or a 33 percent line. The 66 percent line is the molecules that have D at all eight positions rather than the percent of Ds that are identified.

And so if you want to make this chart accurate for Claims 18 and 19, you have to draw a line at 95 percent. And if you draw that line, it becomes pretty clear that the unexpected results are commensurate in scope.

With that, we'll reserve the rest of our time, if there are any questions.

JUDGE FRANKLIN: Okay. Thank you.

Before you begin, by my count, you have 26 minutes. Does that sound right?

MR. FELDSTEIN: I'm going to take your word for it, your Honor.

JUDGE FRANKLIN: I think it's right.

MR. FELDSTEIN: I'm sure it is.

JUDGE FRANKLIN: You may begin.

MR. FELDSTEIN: We worked backwards -- actually, can you put up the slide that they just had of ours up? It's slide 142.

So, I take issue with this being called misleading. And we cite for the -- well, first of all, let me explain this slide.

So, the blue line at the bottom is our expert's, Dr. Reider's, determination of what happens if you apply two constructions, which apparently they don't disagree with the individual construction of compound and the individual construction of deuterium. They currently don't disagree with the individual terms, at least that's what counsel said.

And if you apply them, there are two separate terms. The math works out to be the math. Claims 16 and 17 have as little as .08 percent required amount of compound 111. And Claims 18 and 19 have a minimum required amount of compound 111 of 33 percent.

I heard something about -- from Concert just now that their claims and their views carry some -- are limited to something like 95 percent. In paper 79, Patent Owner's -- or actually paper 84, their amended reply on the motion to amend, they say on page 6 that Claims 18 and 19 would be at least 66 percent. And they say on page 5 that Claims 16 and 17 would be 50.1 percent. It's exactly what we've illustrated here.

So even in their view, prior to today at least, what they're talking about is a single data point, 90.7, when they agreed that as you change the amount of deuterium in a compound, you're going to change the

properties. Their unexpected results are slim at best. They're expected, but the difference is slim at best. A .4 hour difference in time of half-life. Nobody knows what it's going to do at lower time than that.

Their idea that there's no evidence in the record to indicate that a single data point is not commensurate in scope. Well, they put up Dr. Baillie's testimony themselves. They argue in paper 8 that there's significant PK differentiation between ruxolitinib and octadeuterated ruxolitinib.

And the remainder, the amount of the claim that isn't required to become compound 111 here, could be ruxolitinib. The way they claim it, it can cover a mixture of ruxolitinib and deuterated ruxolitinib. And so their claim covers the prior art or a mixture of the prior art.

JUDGE HULSE: Could you explain to us why your construction, the .085 percent number, why that's not inconsistent with the spec's definition of the compound and 49.9 percent of them, those compounds -- or the relative amount of such isotopologues in toto will be less than 49.9 percent of the compound?

MR. FELDSTEIN: I'll do my best, your Honor. Can we go to slide 149? Or -- the numbers are too small on the paper -- 139. So, these are the construction. There are two different terms. There's a term deuterium, and each deuterium means at least 45 percent deuterium. So it can be the majority hydrogen, majority protium, as in the original ruxolitinib.

In a separate term, a compound of Formula X. And there's a definition. By that definition, a compound allows for 49.9 percent of isotopologues. So we tried to illustrate it on slide 140. There's a first step you do. You look at what compound means, it's the first term in the claim. And compound allows you 49.9 percent of isotopologues. That's the left-hand side of slide 140. That's 49.9 percent of isotopologues separate and apart from the claimed formula.

And then you look at the claimed formula, what we call A2, the 50.1 percent. And you can calculate. They don't dispute our math that if you have 45 percent deuterium -- at least 45 percent deuterium in each of eight locations, the math just works out that you can have as little -- the question of how often do you have deuterium at all eight locations works out to be a small number, .17 percent of the time. And then now you combine. You have 49.9 percent of isotopologues from the meaning of compound. And you have all the variability in deuterium from within the formula. And you put those together, and you end up with a very small amount of required compound 111 in the claim.

It's similar on slide 141 for Claims 18 and 19. Again, you've got a compound term that splits them up immediately into 49.9 percent versus 50.1 percent. And then you apply the 95 percent limitation on the right-hand side, which works out to be 66 percent, which is what they said in their reply. And then you have to put the two together to end up with 33 percent.

If that answers your Honor's question, I'd move to slide 144 and point out what's inconsistent about what Concert is doing. And, again, Concert doesn't have any expert testimony on how a person would understand the claim. They don't dispute apparently the individual constructions.

But what they do, at least in paper 84, until today, their view was that Claim 16 covers 50.1 percent. And the way they get that is they look at just compound meaning in the preamble of things, 16, and ignore the effect of deuterium within the body. And then on Claims 18 and 19, to get to the 66 percent, they ignore the meaning of compound, which allows 49.9 percent isotopologues, and only use the meaning of deuterium.

If that answers your Honor's question, I would move back to slide 63, please, and address their idea of a therapeutic window. And their therapeutic window is, again, no surprise. What they do is they take a dose of CTP-543. This is a single dose study, I believe. It's not really critical, but it's non-patient study. And they then scale up the ruxolitinib dose, not to 16 milligrams to match what the CTP does; they don't normalize on dose. They scale up the Incyte does to 27 milligrams and say, wow, surprise, if you scale up the ruxolitinib dose to 27 milligrams, the Cmax goes up and you're above the threshold for what may lead to side effects more.

So Dr. Baillie agreed that you're just multiplying by a constant factor. The expected multiplication is pretty predictable. It's math.

And so, if you turn to slide 65. What we do on the left-hand side is the model show that they're comparing 27 milligrams, an elevated dose of ruxolitinib that wasn't actually tested, to the 16 milligrams of CTP-543 that was tested.

And so they say, oh, you got to compare. Now they say, oh, you've got to compare it to 27 milligrams. In their press release, Exhibit 1015 again, they said that 16 milligrams of 543 appears comparable to the reported exposure of 20 milligrams of ruxolitinib twice daily.

And then they say, also in Exhibit 1136, they say that 16 milligrams BID of, what I believe is the compound for 543 appears -- it's comparable to exposure for 20 milligrams BID ruxolitinib.

So the comparison they're making is inflated for the purpose of inflating it. They talk about whether it's going to be for the same efficacy or not. Their expert, Dr. Mackay-Wiggan, they introduced Exhibit 2009. That's a study that she did showing that ruxolitinib -- not deuterated ruxolitinib, but ruxolitinib -- has efficacy in treating alopecia at 20 milligrams.

And so Concert was right in its public statements that the right dose is 20 milligrams, or seems right at least at 20 milligrams, is the right dose. And what they're comparing to now is elevated solely for the purpose of this IPR.

If I can move to slide 73. This is their therapeutic window. They're saying, we don't consider all the PK parameters together.

Well, that's not true. Their point, I believe, is that there's something magic about being able to stay between the two blue lines here, the lower floor of activity and the upper floor they say is side effects.

Exhibit 2009, another prior art ruxolitinib paper, shows that if you get 15 milligrams of ruxolitinib you stay within that range always. Cmax is within that range. Cmin is within that range. And unlike 15 milligrams of ruxolitinib, their 16 milligrams of CTP-543 actually exceeds this. And so to say that we don't address their combination of properties as a whole is not accurate.

If I can go back to slide 69 for a moment. Incyte says there's something significant about the half-life in the slope, the inverse relationship. Again, the average difference is .4 hours. There's no clinical benefit to .4 hours, 24 minutes extended.

I don't believe even their experts, Dr. Mackay-Wiggan and Dr. Montellano, had testified that a 24-minute increase, even proportional to the linear fast metabolizer, slow metabolizer, has any clinical significance whatsoever.

And if you go to slide 75, this is Concert's argument. Concert argues -- and this was similar to what they had on a slide earlier -- that POSITA would have expected that if the deuteration results in increased half-life the amount of increase would be similar across subjects.

They then go on to say, for example, it could be five percent constant for all metabolizers. So that's one example, and not a limiting

example, of what similar means according to the declaration of their expert, Dr. Montellano. It's not limited similar to being five percent or even a constant percent. Similar would also, I believe, be similar absolute amount, which, as Dr. Thisted explains, is that the data is consistent with an average shift that does not vary across the ruxolitinib T1/2.

And so you can look at it. Our statistician looked at it and finds that essentially it's 24 minutes across everybody. It's a similar increase across all subjects. And that what's important, I think, is that while Dr. Montellano does give the example of a hypothetical five percent increase as being the example, there's no evidence whatsoever of that ever happening before.

So we don't know where Dr. Ortiz de Montellano got his five percent from. It's not clear that it's from the prior art. There's certainly nothing in the evidence to show a different relationship between half-life and deuteration than the evidence that we've shown. The evidence that we've shown is Dr. Harbeson admitted that he's seen this trend before. And his own data from other products and other products in the literature also show the trend.

I think they tried to cut things much too fine by arguing, well, this was one p-450 subtype versus another p-450 subtype. That's not what they said in their papers. They said that it's p-450. And even if they had, it doesn't seem material on which subtype, especially since

they've got no evidence of any example in the prior art with the three or four subtypes showing any different effect.

JUDGE HULSE: I'm sorry to interrupt. Could you please respond to Patent Owner's argument that Dr. Thisted is not a person of ordinary skill in the art and that we should disregard his testimony?

MR. FELDSTEIN: A testifying witness doesn't need to be a person of ordinary skill to provide helpful information to the court. Dr. Thisted is an expert statistician. He's a biostatistician. This is meaningful. This is what he does. His testimony on the statistical significance of Concert's data is more relevant than Dr. Thisted's. It doesn't matter -- no, he's not a chemist or a pharmaceutical pharmacist. That's not relevant to whether or not he provides helpful testimony. He's probably the ideal person and the only person to explain statistics to the court.

JUDGE HULSE: And Patent Owner's definition of a person of ordinary skill in the art is slightly different than Petitioner's. Is that a difference that makes a difference? Or should that make a difference in our opinion?

MR. FELDSTEIN: You know, I don't think it matters for how it comes out. I found their definition to be a little strange because it sort of has an optionally language in it. Optionally, we can consult someone else. I don't know what that actually means for whether a person of ordinary -- what a person of ordinary skill in the art is. I believe it's language to the effect of a person of ordinary skill can

optionally consult a clinician. And that is not a limitation when you say it's optional. And consulting with a third person isn't the person of ordinary skill themselves. But, at the end of the day, in terms of the obviousness here, I don't think it matters.

Let me turn, if I can, to slide 87, please. So, there's plenty of evidence of an expectation of improved metabolic stability. And we argued in the petition that the purpose of deuterating 4uxolitinib would be to improve its safety, tolerability, and efficacy. That's in the petition, paper 1 at page 31, that you would apply the motivation in the background to improve safety, tolerability, and efficacy and obtain superior ADME properties. You'd be motivated to provide superior ADME properties to ruxolitinib.

So we do address the motivation to improve, and the expectation of improvement is pretty clear. Slide 87 has a number of Concert references where the whole purpose of deuteration is to improve metabolic stability.

Whether it results in a commercially viable product, that's a different question. Whether it's enough of an improvement that you then go compete head-to-head with a product that's already on the market, that's really irrelevant to the obviousness and the motivation to improve its properties and go in that direction. The commercial considerations are something else entirely.

Concert has an argument, of course, about -- oh, yeah, thank you. Concert pointed to one case, Anacor Pharmaceuticals. I'm not

sure why they think supports their position in terms of structural obviousness. But Anacor says, at page 1385, our cases have held that the greater the structural similarity between compounds, the greater the motivation to combine and reasonable expectation of success. And so there is no greater structural similarity than a compound and its deuterated analog. Exhibit 1041 says it's a small structural difference.

So, the idea that dose limiting toxicities would prevent one from moving forward, well, those are addressed in the case law already. That dose adjustment is well known. Dose adjustment is taught for ruxolitinib specifically. It's within the skill of the art to do dose adjustment. Part of the point of deuteration is to reduce the dose. So you have to use less dose. And so the argument is also belied by the fact, and you can look in the petition, they literally have dozens of patents taking pharmaceutical FDA approved drugs and deuterating them.

It's a well-oiled machine of taking approved FDA drugs and putting on deuteration. It sets up a pattern. It shows the obviousness of doing what they did for the next drug in line, ruxolitinib.

JUDGE HULSE: Can you respond to Patent Owner's point that your expert didn't consider the toxicity issue when rendering his opinion?

MR. FELDSTEIN: So, that was raised by Concert in their Patent Owner reply. They raised arguments that there would be an affirmative teaching away. And they raised that the toxicity would

teach away. That wasn't an issue that we addressed in the petition. That's a counter-argument that Concert was referring to teaching away, which we responded to. And so there was no need for Dr. Guengerich to address specific toxicities of ruxolitinib to establish that there's motivation to deuterate similar properties. There's motivation to deuterate to get improved ADME properties.

So, in terms of the expectation of improvement, they don't like our data. But this is data in the case for roughly 160 or so compounds that Dr. Reider went through one by one and looked at. If you deuterated it, was there a KIE? Was there a slowing of metabolism? In 79 percent of the time, just the data in the record, there was. What he testified to on cross-examination was that it's conservative analysis, in my experience, it's a percentage greater than 79.

And so the expectation that you're going to get an improvement by slowing metabolism is borne out by all the evidence in the record. And it's especially relevant with slide 93, something we talked about earlier, for Dr. Reider's analysis showing the 79 percent wasn't limited to the type of deuteration or the type of metabolism specifically.

But we know that ruxolitinib -- it was known from Shilling in the prior art that ruxolitinib is primarily metabolized by hydroxylation of the cyclopentyl ring, i.e., an alkyl deuterate -- an aliphatic oxidation, which is the most likely, most significant type of -- it's the most impactful reaction.

That's on slide 95. We've got three prior references all confirming the fact that for aliphatic compounds, the deuterium isotope, a DIE or a KIE, would be expected, and generally speaking, ultimately large.

If there are no other questions, your Honor, I'll reserve my last few minutes.

JUDGE FRANKLIN: Okay. One moment. Let me check with Judge Hulse. Do you have any other questions?

JUDGE HULSE: None for me, thanks.

JUDGE FRANKLIN: Okay. Judge Smith?

JUDGE SMITH: None for me, thanks.

JUDGE FRANKLIN: All right. Thank you.

MR. FELDSTEIN: Thank you.

JUDGE FRANKLIN: By my account, you have 23 minutes remaining. Does that sound correct?

MS. HARDMAN: That does sound correct, your Honor.

JUDGE FRANKLIN: Okay. You may begin.

MS. HARDMAN: Thank you. I'll just make two quick points and then turn it over to Mr. Wiesen. If we could have Patent Owner slide 66, please.

Counsel made a point again about the dose-limiting toxicity issue. He said it's addressed in the case law. I think the case that is probably most on point is the Takeda case. That case, we pointed out that it requires a specific motivation to make the specific molecular

modifications that are proposed. And here, in Takeda itself, when it did that very specific analysis, it found no motivation because the proposed new drug would be used for a chronic disease. And the court found that researchers would've been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity or other adverse effects, particularly where you're going to be using it in a product situation.

Counsel again raised the issue of Dr. Reider's analysis. And he also showed some references he says support the concept of the KIE is expected and large for aliphatic compounds. In the petition, they were talking about methylenes. They sort of shifted that to aliphatic compounds in the successive papers. I'm not sure why that changed.

But, in any event, the important point there is that Dr. Reider's analysis, and also the general references that counsel cited, those are relating to CYP enzymes generally. And, of course, here we have the specific CYP that's at issue, 3A4, is something that Dr. Guengerich himself has identified as a special case.

And, with that, I'll turn it over to Mr. Wiesen, unless there are questions.

JUDGE FRANKLIN: Okay. Thank you. You may begin.

MR. WIESEN: Thank you. I want to start, Judge Franklin, actually with an answer to the question you asked me. My partner pointed out a slightly pivoted answer from what I was thinking about

when you asked whether we had a case that should just focus on the obviousness of the three compounds that Petitioner chooses to focus on.

I think the answer to that actually was in SAS from the Supreme Court, where they say that an IPR proceeding is the Petitioner's petition, not the director's discretion and is not an agency-led inquisitorial process.

In other words, if they chose to focus on those three compounds, the focus should be on those three compounds. And when they bring up a series of other compounds later, the way the process works here, to bring up that new argument further into the petition is simply something that, if they wanted to show those compounds had a prima facie obviousness, they could've tried. They didn't. And so what we're really focused on are the three compounds that Petitioner chose to look at.

JUDGE FRANKLIN: Okay. And I guess what is more important is whether you argue that in your brief.

MR. WIESEN: I'm not arguing which point in the brief? I don't think we are. We --

JUDGE FRANKLIN: You're citing stats for a proposition that you're making regarding --

MR. WIESEN: I don't believe we cited SAS for that proposition in the brief, your Honor.

JUDGE FRANKLIN: Okay.

MR. WIESEN: Let me turn to the claim construction and the motion to amend, if I can. Mr. Feldstein, if we could have our slide 192 just so we have Claims 18 and 19.

We heard from Mr. Feldstein that we don't have any expert testimony on how this would be read. That's true. I don't think claim construction requires an expert. Here the definitions of the limitations are provided specifically in the specification. And the question is how they get applied. And I don't think it requires an expert to apply the grammar of a claim construction.

Fundamentally, the Petitioner's argument is that you have to somehow multiply the compound and the deuterium numbers together to reduce the number. And there's simply no language in the claim that suggests that true.

There's two limitations. Each requires more than or no less than certain amounts of deuterium. And one is going to go down each limitation and see if it's met. There's simply no suggestion that any sort of multiplication is necessary in this analysis to apply this point.

If we could look at Petitioner's slide 34. It appears somewhere else in the deck as well, but this is the one we looked at previously. The issue we take with this slide is that the 98.7 -- we don't disagree that we advocated that on one interpretation you would have 50.1 percent of the molecules would have D in all eight locations for Claims 16 and 17, and 66 percent would have D in all eight locations for Claims 16 and 17.

What we disagree with is that compares to the 98.7. Because the 98.7, from what we saw in the Cowden declaration, refers to what percentage of the Ds have a -- or what percentage of those locations have a D. And in Claim 19, that is explicitly a 95 percent.

So if you want to use that 98 or 98.7, 95 would be the proper comparison. And our contention is that if it's 95 that it's clearly commensurate in scope. I didn't hear Petitioner --

MR. FELDSTEIN: Your Honor, I apologize. I just want to object. This new argument about whether it's commensurate at 95 percent. That's not an argument, I believe, anywhere in Patent Owner's briefs.

MR. WIESEN: Your Honor, we objected to the slide as misleading because of that comparison. They continue to insist on putting it in.

JUDGE FRANKLIN: Okay. We will consider and scrutinize the record as to what has been argued and what is new argument. And I think we're all aware that we're not going to consider new arguments presented today. So you can continue.

MR. WIESEN: Absolutely, your Honor. What I don't think I heard Petitioner contest, that the deuterium substitution levels, whatever the numbers are, are result-effective. And that means what you would get is not a change in the kind of effect that you have, but just a change in the amount.

And we think in the commensurate in scope case law that's exactly the type of relationship that's properly supported. In fact, it's worth noting that, in the petition, there was no argument made about the percentages for commensurate in scope analysis. It was only after we had -- the initial analysis was that we multiple compounds claimed. Only after we filed a contingent motion to amend and narrow down to the single compound did we get this commensurate in scope argument about the levels of deuterium substitution.

If we look at Incyte slide 140, please. Again, this just highlights the problem and inconsistency, I think, that you asked about, Judge Hulse, between the specification's definition of isotopologue and the construction that's proffered by Petitioner. Because on the right-hand box here on Incyte slide 140, they label things as non-isotopologues even though 99 percent-plus of those compounds are by definition isotopologues. And that's simply inconsistent with the specification and suggests that the construction offered by Petitioner is unreasonable.

If there are no other questions on that subject, I want to turn to the therapeutic window and expected results. And if we could have Patent Owner slide 139. I want to talk for a minute about the appropriate dose for the comparison in the therapeutic window analysis. This is the data that's provided in Dr. Harbeson's declaration, Exhibit 2001. It's table 5, paragraph 16 and 17.

And what Dr. Harbeson explained, if you look at the first line, the IFN gamma pSTAT1 row. You see that if you get 16 milligrams of CTP-543 and 16 milligrams of ruxolitinib and you calculate how long is that above the line for efficacy in the therapeutic window, you get 14.9 hours for CTP-543 and just 12.7 for ruxolitinib.

Those are not the same number, obviously. And so the appropriate way to do the analysis is to dose-normalize and get a number that is comparable for the same amount of time for efficacy. And that's what's on the right-hand side of Figure 5. You can determine that a 27-milligram dose of ruxolitinib will have the same period of time for efficacy as a 16-milligram dose of CTP-543.

Then, Judge Franklin, to the point you made, you have to balance that efficacy against toxicity. So we look down to the next line, the EPO pSTAT5 line. That's known to be the pathway that causes hematological toxicity. And we take those same doses. If we did 16 to 16, we did the same dose head-to-head, we'd see a difference as well in toxicity. But that's a little bit hard to compare. You've got differences in efficacy and toxicity.

So we take the same dose for efficacy, apply the toxicity analysis, and see that the result is that negative 1.4. And that's why this analysis makes sense, because what we've done is taken two doses that are head-to-head comparable on efficacy and see that we see more time above the line, more toxicity for ruxolitinib compared to CTP-543.

That's the analysis we did. That's the analysis our experts say is appropriate and yield the unexpected result of a longer period of time in the therapeutic window.

Petitioner talked about some prior statements we made and suggested that they were inconsistent with the statements we've been making here. If you look at Exhibit 2002, it's Dr. Baillie's declaration, paragraphs 47 and 48. I apologize, I don't have a pre-made slide on these.

Dr. Baillie explains that the difference is previously we were looking at two different studies and two different populations. And when you look at these pharmacokinetic studies in different populations, because of interpatient variability it's very difficult to compare data across these studies.

But here in this case, the data we're relying on is head-to-head. It's a crossover study where the same patients received CTP-543 and ruxolitinib. So they control for themselves. If you get one person who's a fast metabolizer, they're fast for both drugs, we saw and we'll get to -- not exactly the same fast, but they control for themselves. And in that way, that's the right comparison.

What Dr. Baillie explains in paragraph 47 and 48 of his declaration, Exhibit 2002, is that the prior statements are not inconsistent. They're from two studies. They're made based on studies that weren't head-to-head. But the right data for you to analyze to look at is the head-to-head data that takes out that problem of

different populations. And when you take it out, you see the results that we've shown, the longer time in the therapeutic window, the conclusion that Dr. Mackay-Wiggan came to that this data is sufficient to give a belief that we will have a safe and efficacious treatment for alopecia areata, and with the FDA fast track designation, likely to be the first one.

If we can go to -- I think it is Petitioner slide 73, if I typed my notes correctly. Let's see if I got it. Thank you. This is a slide that Petitioner talked about on the therapeutic window. And they pointed to the box and said if you get 15 milligrams of ruxolitinib, you're going to stay in that range.

Now, for the first time, we heard Petitioner say that you get a higher result for CTP-543, because if you look at the slide, CTP-543 doesn't appear there. There's a reason for that. This is not data from the head-to-head study. This is data from a separate study that was done with ruxolitinib. So you can't compare this data head-to-head to the CTP-543 data because it's a different population.

And so what we've got here is a Cmax of 649, they report. And the Cmax, the threshold for toxicity, was I think 677 in the other analysis. So they say it's below that. But this is an average. And as we explained in the papers, because it's an average, half the people, approximately, if we assume a normal distribution, will be above that 649 and half will be below it. And the half that are above it are going to be above the toxicity threshold.

So the argument that the average ends up within the therapeutic window doesn't actually solve the problem when you're this close to the number. And then this data is not comparable to CTP-543 because it's not a crossover study. And you notice this one is 15 milligrams of ruxolitinib when previously it was 16. I haven't done the math, but I'm curious where that comes from and why it's that number.

I want to turn, then, to the rapid metabolizers' unexpected results just briefly. We've had some discussion about what Dr. Thisted is and isn't an expert in. There's no question he is an expert in statistics and a statistician. But he provides opinions about what would be expected versus unexpected.

And for that issue you must look at what a person of ordinary skill in the art would expect or not expect and whether one can -- and there is no question Dr. Thisted is not a person of ordinary skill in the art. And they didn't provide his analysis to anyone who's a person of ordinary skill in the art.

Often what you see is a statistician will run the numbers and then a technical expert, a doctor or a chemist, will then give you the opinion, do those numbers make a difference? Are they important? That's what we've had here. Dr. Harbeson does some calculations. Dr. Mackay-Wiggan tells you want the conclusions you should draw from that.

But Dr. Thisted's data was given to no one. He ran the numbers by himself. He did an expert declaration. It wasn't shared

with anybody. And he rendered opinions, which are fine for what they are but we think don't establish that -- don't raise questions concerning the unexpected results that have been demonstrated.

Dr. Thisted, by the way, never disagrees with the underlying data itself. He simply runs different analyses of it. But, quite frankly, even if we had a constant 24-minute change, that even would be unexpected. Because if you think about biology, there's no argument or evidence or logic for why you would get a constant change across patients from a biological effect.

You would expect it to be relevant. After all, a KIE is a ratio. And that ratio is going to change relative for different patients. That is, if you look at what Dr. Ortiz de Montellano and Dr. Baillie said, just to try to suggest there's some ambiguity of the declaration which suggests there isn't. And if there was some ambiguity, they wouldn't have brought out an expert to explain why the expectation would have been otherwise.

We see nothing but the uncontested explanation of what would be expected in the papers. And we think that the result we see here is unexpected.

JUDGE HULSE: I apologize if you've spoken to this already, but could you address their -- is there any evidence in the record that says that 24 minutes is a significant amount of time for a patient?

MR. WIESEN: Sure, Judge Hulse. I think the -- thinking of it as -- so, let me take it first for the rapid metabolizers and then for the therapeutic window.

For the rapid metabolizers, it's not 24 minutes. It's a different amount of time for each of the patients. And what we're seeing here is when we've got a 12- to 14-hour clearance rate, or half-life, then I think that there's reason to -- there's no evidence that that is insignificant and it varies by patient.

And so what Dr. Mackay-Wiggan has explained is that smoothing out across patients that having a greater effect on the fast metabolizers is likely to make it more -- create an improved likelihood of efficacy for those patients who would not have seen an efficacious result from ruxolitinib. And that's her interpretation of the data. And I don't have the paragraph, I think, but that's the Mackay-Wiggan declaration and explanation on the fast metabolizer data.

The 24 minutes is the artificial number that Dr. Thisted comes up with. It's that dotted line in his graph. But that number has got nothing to do with any actual biological result. There's no evidence from any person of ordinary skill in the art or technical expert that that's what would be expected. It's just a mathematical construct that he comes up with.

As for the therapeutic window argument, it's not a question of 24 minutes in the therapeutic window because the therapeutic window depends on the Tmax and the AUC and the threshold for efficacy and

the threshold for toxicity. And so, it's much longer that a comparable efficacious dose of CTP-543 is in the therapeutic window than the dose of ruxolitinib.

I'm told it's the Mackay-Wiggan declaration, paragraph 41. And if we go to slide 144, is where that language is. And so she's looking here at the actual data that we've provided, because we gave her the data to look at and provide an opinion. And she concludes that it is sufficient.

Oh, sorry. I'm told paragraph 41 is not on the slide. But it's paragraph 41 of Exhibit 2048 that has the discussion of the rapid metabolizers for Dr. Mackay-Wiggan.

Your Honors, if you have no other questions, I will cede my last three minutes.

JUDGE FRANKLIN: Judge Hulse?

JUDGE HULSE: None from me, thank you.

JUDGE FRANKLIN: Okay. Judge Smith?

JUDGE SMITH: None from me, thank you.

JUDGE FRANKLIN: Okay. None from me either. Thank you.

MR. WIESEN: Thank you.

JUDGE FRANKLIN: Well, we want to thank both parties for your presentations today. And it's very apparent to me that you all have spent a great deal of time preparing and that we appreciate. And we appreciate how you've answered all of our questions today.

A decision will be forthcoming. And with that, we stand adjourned.

(Whereupon, the above-entitled matter went off the record at 3:30 p.m.)

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