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The Collaborative and Strategic Benefits of Exploring Drug Models in Clinical Development

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These notes were adapted from the transcript of the 6/03 DIA presentation by Bob Korsan of Pharsight Corporation and Lilliam Kingsbury of Cephalon, Inc. Except where indicated otherwise, quotes from Dr. Kingsbury are verbatim. Quotes from Bob Korsan have been edited for readability by Bob Korsan.

[Bob Korsan, Pharsight Corporation]

Thank you for attending this last session of the meeting. You have amazing perseverance [staying for the last session of the meeting], for which I am very grateful.

My name is Bob Korsan. I'm the Director of Decision Services for Pharsight Corporation. Today you're here to hear about the collaborative and strategic benefits of exploring drug models in clinical development. And if you're not here for that, stay here anyway.

We do modeling because we have difficult decisions that have to be made, and have to be made well. I'll present an example first. Would somebody like to come up and take this \$5 bill? [Person stands, comes to the front and takes the bill.] Thank you. Sit down, please.

Decision-making is not always hard. A phrase that I like to use is: "when you know what to do, do it." We just had an example of somebody doing what they knew was a good thing to do. So that was an easy decision.

The Collaborative and Strategic Benefits of Exploring Drug Models in Clinical Development

Lilliam Kingsbury, PhD
Vice President, Biometrics
Cephalon, Inc.

Robert Korsan
Senior Scientist
Pharsight Corporation

[Bob Korsan, Pharsight Corporation – continued from previous slide.]

How many people here find that in drug development easy decisions are the only kind of decision that they face? ... If that's the only kind of decision that you face, raise your hand. [Nobody raises their hand.] Good – that's my experience as well. The reason we do some of these other things – modeling and simulation and collaboration – is that we don't face easy decisions. And since they're not just no-brainers, what we need to do is find a way to make clear and transparent what the right decision is – or at least, make it clear as best we can, in the face of our uncertainty.

Contents

- **Background & Introduction**
- **Overview of Cephalon-Pharsight Collaboration**
- **Collaboration Case Studies: Cephalon Modeling and Simulation Experience Developing Provigil™**
- **Conclusions and Closing Comments**



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[Bob Korsan, Pharsight Corporation]

This presentation will show you some of the things that we think you can get out of using these approaches, and demonstrate what you can do through some case studies that we've done jointly with clients over the years.

This is also a story of how consultants can go from being hired guns to collaborators. I think we've established that relationship with several of our clients, and I think it's been beneficial for us and for our clients.

Once we've established a collaboration, we work to create a critical mass of credibility in the eyes of management for these techniques by illustrating how modeling and simulation are useful in the context of their specific development needs. Then we can build excitement over these techniques within drug development teams so that they start wanting to adopt them. The next step is to develop a group of people inside the development company to take these tools from being what they're usually viewed as – the bleeding edge of technology – to a core competency. And we're going to talk about all of those things today.

During the talk please ask questions any time, including now.

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[Bob Korsan, Pharsight Corporation - continued from previous slide.]

Next, I'd like to introduce my co-presenter, Dr. Lilliam Kingsbury, who's Vice President of Biometrics at Cephalon. She's been involved in the Cephalon-Pharsight relationship from its inception. She and I are going to talk about some of the things that we've done and some of the benefits that have accrued.

So with that, Lilliam –

[Lilliam Kingsbury, Cephalon, Inc.]

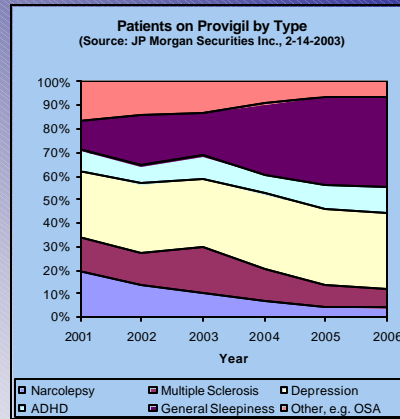
Good morning again. Thank you for attending this last session, as Bob indicated. I hope you can hear me and can get through the slight accent. It is my pleasure to be here today, first of all, to go over a little bit of background about our relationship with Pharsight and how we are using, have used, and continue to use that collaboration to try to streamline our drug development efforts.

Bob will provide you some details of two case studies, two major efforts that we have undertaken together. Then we'll move along the lines of the topics that he indicated.

Cephalon is an exciting mid-tier pharmaceutical company. Provigil™ is its leading drug.

- Cephalon had total product sales of \$506M in 2002 and is projected[‡] to have total sales of almost \$1,500M in 2006.
- Provigil™ is Cephalon's most important product contributing over 50% of revenue in this time frame.
- There were approximately 125K patients treated with Provigil in 2001 and this is expected to grow to approximately 1,000K (1M) patients by 2006.

[‡] Source: JP Morgan Securities, Inc.



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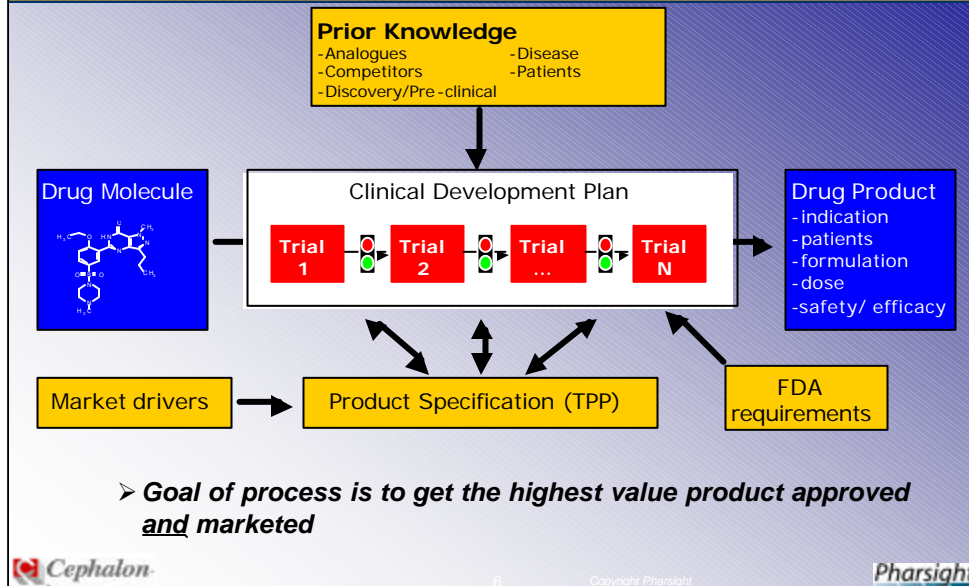
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[Lilliam Kingsbury, Cephalon, Inc.]

You may or may not have heard of Cephalon. We're classified as a biotech company, but in reality we're a small-molecule, mid-sized pharma company. Our flagship product is PROVIGIL, which is approved for use in narcolepsy as a wake-promoting agent. PROVIGIL, as I mentioned, is our flagship and contributes a great proportion to our revenue, to our bottom line. So in the process of protecting that franchise, one of the efforts we have undertaken is to expand the label. And so in the context of that label expansion program we have collaborated and continue to collaborate with Pharsight.

Drug development is complicated, requiring use of knowledge from many different sources



[Lilliam Kingsbury, Cephalon, Inc.]

You know what drug development is like. You know what the market drivers are. You design a clinical development plan that meets the FDA requirements to achieve the goal that you have. But this is a lengthy process, so we have to execute it as quickly as possible because of the constraints we all face regarding patent expiry, exclusivity considerations and so on. So we're always fighting against time.

Modeling and simulation maximizes the value of drug development decision making.

- **Maximize value of prior information**
 - All available data within company, literature, previous trials, related compounds/analogues, competitors
 - Models are updated whenever new information is available
- **Models allow exploration and quantitative evaluation of ...**
 - Current knowledge of product performance
 - Competing strategies/ downstream options
 - Novel (adaptive) trial strategies
 - Sensitivities to key assumptions and uncertainties
- **Integrates knowledge and provides a common platform for communication and collaboration**
 - Across drug development disciplines (Scientific, Clinical, Commercial, Financial)
 - Between development team and decision making bodies
 - Across time



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[Lilliam Kingsbury, Cephalon, Inc.]

And in many instances, for us in this particular program, there is also the scarcity of patients. So our task was [to determine]: how can we utilize the information that we accumulated, what we know about this compound, in order to streamline and create an efficient development program in this label expansion context?

Integrated modeling and simulation is the basis of quantitative decision making.

“What’s the best dose and schedule?”

“Is it worth developing a new dosage form?”

“Should we continue this development program?”

“What is the optimal patient population for this drug?”

“Is there a clinical trial design that will show PoC and find the best dose?”

“Is this treatment likely to be as good as the competitors?”

“What’s the probability of success in Phase III?”

“Should we in-license this compound?”

“Which indication should we go into first?”

“What are the most important attributes of a 2nd generation compound?”



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[Lilliam Kingsbury, Cephalon, Inc.]

So we had the usual questions. If we were going to do trials, what would be the best dose to use and the schedule? What would be the best clinical trial design? At what point should we even continue [or discontinue] it? Do we have a chance in this indication? And this is all in the context of: what is the probability of success? It's just too expensive to undertake if we don't have a reasonable level of confidence that we will have a successful program.

Clinical development is expensive, time consuming and uncertain. The industry challenge is to make good decisions.

- Companies have a difficult time understanding the value of new treatments. New treatments do not achieve the level of use expected by their developers.
- There is a vast array of development uncertainties and decisions. Since only 10-20% of all new NCEs reach patients, development decision making has to be structured as a **learning process** and designed for speed.
- Trials buy information and then development teams learn. Currently, about 30% of all trials provide no useful information. Adaptive development programs with formal learning mechanisms can speed decision making about dose, regimen, target population, etc.

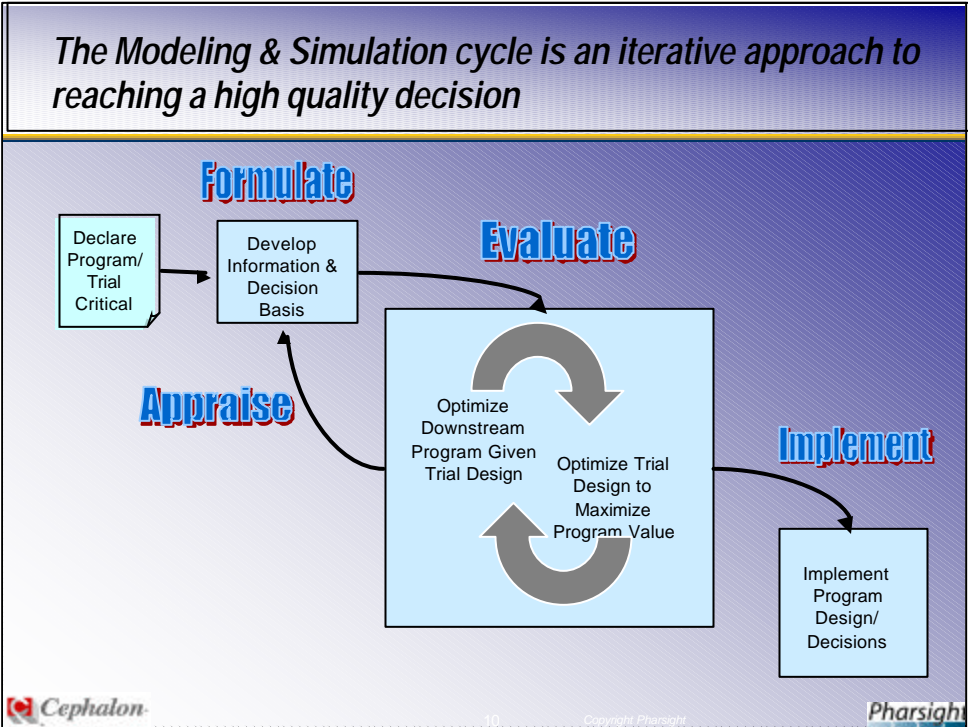


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[Lilliam Kingsbury, Cephalon, Inc.]

So as I said, we wanted to use modeling and simulation to try to maximize the value of this prior information, to then explore and evaluate what we know and develop some trial strategies. And ultimately, we also wanted to integrate what we know across multiple disciplines, including even our commercial people, because we wanted to design a trial that would also allow us to interpret this resource in terms that will support the product even through its commercial development.



[Lilliam Kingsbury, Cephalon, Inc.]

So the point in this slide I think we all share in common – understanding you need to do a fair amount of selling internally. You need to go through this learning process, which is part of development, and you want to anticipate as much as possible. And even although the trials really buy you information, we have too many trials that are neutral or that don't provide the information that we need.

“Quantitative Decision Making” leads to enhanced productivity and reduces risk

A systematic, quantitative, model-based decision making method

- **Increase drug development productivity**
 - Decrease late stage attrition
 - Decrease time to market
 - Increase # of drugs reaching market / \$ invested
- **Improve clinical quality and commercial performance of final product**



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[Lilliam Kingsbury, Cephalon, Inc.]

Now I'm going to introduce the two examples that we are going to discuss in detail of our interaction. Along this continuum in the modeling and simulation cycle, we have done this. We have a program, we know that the trial is critical, and now we want to see how we can inform it so that we can evaluate and optimize what the trial design will be, implement the program, and hopefully reach the conclusions that we want.

Cephalon-Pharsight Collaboration



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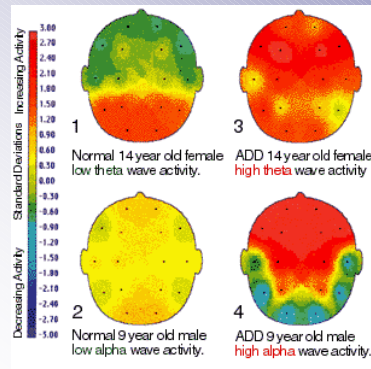


[Lilliam Kingsbury, Cephalon, Inc.]

The Cephalon-Pharsight collaboration, the period we're describing here, has gone on for just two years – which, in terms of drug development, is not that long. Just almost exactly two years ago in late 2001, as I told you PROVIGIL – that is actually marketed [unintelligible] for narcolepsy – we were undertaking this label expansion program. And the objective was to label PROVIGIL as a wake-promoting agent in disorders of sleep and wakefulness. We knew we had a model of disrupted sleep in narcolepsy and we wanted to evaluate a circadian misalignment model, and that was shiftwork sleep disorder.

Collaboration Case Studies

ADHD



Shift Work Sleep Disorder



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[Lilliam Kingsbury, Cephalon, Inc.]

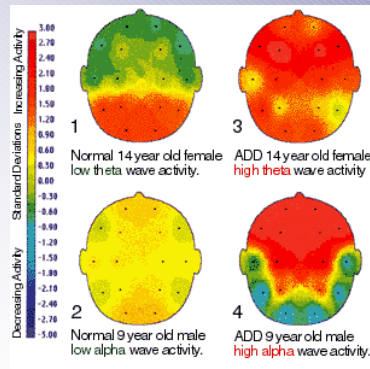
Even though it seems trivial, shift work [sleep disorder] is very hard to evaluate. [Not] all shiftworkers have shift work sleep disorder. And in fact, what we faced was that the literature is filled with just simulation experiments [that only simulate shift work sleep disorder], really sleep deprivation studies where normal volunteers are taken, they are sleep deprived, and the condition called shiftwork sleep disorder is simulated.

Why is that the history of shiftwork sleep disorder? Because most researchers consider shift work very difficult to study in the workplace, as you can imagine – because you have real working situations, you have to allow for evaluation at sleep labs to an objective measure of sleepiness, screening the population. And actually, at the sleep meetings this year, when we presented the results of this study [on] shift work [it] was standing room only. Why? Because again, there is a paucity of data – or there was prior to this study – in the real work space.

Since we know that we need to do a trial, we can't afford to waste anything. So what we're trying to do is to come up with a trial design that's based on PK-PD properties of our compound in other indications, the literature, which - as I mentioned, was based primarily on [normal volunteers] in sleep-deprived conditions – and our narcolepsy data and then [a] simulation of [results in] shift work. One important thing that we needed to decide was how many arms we needed for this trial because, patients are scarce.

Collaboration Case Studies

ADHD



Shift Work Sleep Disorder



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[Lilliam Kingsbury, Cephalon, Inc. – continued from previous page.]

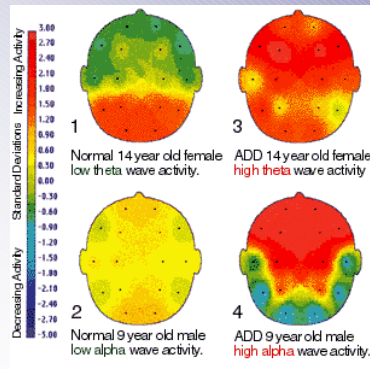
So it was actually through the simulation effort that we undertook, with Pharsight, that we were able to finalize that trial design, know that it took two months. [We] incorporated that and took the risk of going just with the two-arm study – which turned out to be just right. But the value of the simulation then of course will speak for itself.

An additional area in which our compound has been theorized to have potential effects is the area of Attention Deficit Disorder. And Cephalon had conducted studies in the area with adult ADHD that had not been positive. They had not been able to differentiate from placebo. But we had a very limited amount of information in the pediatric population. [On] the basis of what we [had], we felt encouraged to go on but we were not really confident that we could invest either financially or [take] the risk of going into a pediatric population without knowing more than what we had.

We decided to do a dose-ranging study in the pediatric population. It was a well-controlled study, but it was only 300 children and it explored a wide range of doses. And we also collected pharmacokinetic data. So our interaction with Pharsight when we completed this trial in August of last year was: let's look at the data from this dose-ranging study and see how we can evaluate it, incorporating what we know about pharmacokinetics, and see what level of control we have and how we would design a Phase III program with this indication, and [determine whether] we even want to [proceed with Phase III].

Collaboration Case Studies

ADHD



Shift Work Sleep Disorder



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[Lilliam Kingsbury, Cephalon, Inc. – continued from previous page.]

So again, in a relatively short period of time – [a] two-month period -- we completed the modeling exercise with dosing recommendations delivered and we are in fact in the process of presenting these conclusions to the regulatory agencies to get their agreement on pursuing the Phase III program that we've designed on this basis.

So we have from this an effort that led to success in trial design. We have from this an approach to designing a Phase III program that will now go through regulatory scrutiny as to whether they will accept the incorporation of this modeling data with our clinical data to allow us to pursue this Phase III program.

And finally, [due to] the success in these products, we are studying some follow-on compounds, which is part of the development program from its inception and will include a modeling exercise.

So – we're sold! Having said this, I will let Bob take you through the details of those two examples – the information we had and how the models were developed that we have been able to use.

Pharsight's model assists decision makers by predicting all relevant clinical dimensions.

- The clinical outcomes for a population of healthy normals.
- The clinical outcomes for an untreated population in the indication.
- The pharmacokinetics of the drug with all appropriate covariates.
- The pharmacodynamics of the drug in the indication.
- The side effect profile of the drug.



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[Bob Korsan, Pharsight Corporation]

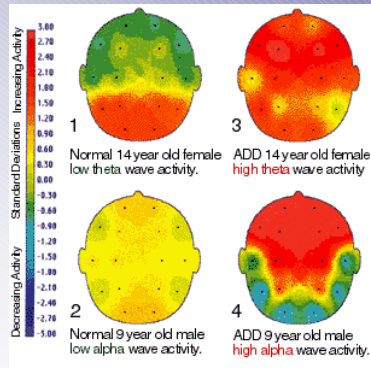
As I said, questions are welcome any time. And if there are any questions for Lilliam now before I start, please raise them. If not.....

As Lilliam outlined, we worked primarily with PROVIGIL and in these two areas, ADHD and shift work sleep disorder.

When we're developing models, we try to focus on the decisions that need to be made by the decision-makers, and to make clear the important relevant clinical dimensions. So we want to know what's going to happen in healthy normals. We want to know what's going to happen in an untreated population. We need to understand what the body does to the drug. We need to understand what the drug does to the body, and we need to understand the side-effect profile. We try to establish a vision of a program, looking for the most valuable part of the efficacy side-effect space -- not the most efficacious part.

We value understanding the tradeoffs between side effects and efficacy, and modeling those simultaneously. We may include both clinical tradeoffs and market tradeoffs, and our understanding of the prescribing physician's perceptions of these tradeoffs, in building our model.

Case Study #1: Attention Deficit Hyperactivity Disorder



[Bob Korsan, Pharsight Corporation]

Let me first talk about Attention Deficit Hyperactivity. I'm doing this in reverse chronological order.

Pediatric patients have a significantly different PK and PD response to Provigil than adults.

- PK is affected by age, weight, dose and time of administration.
- Maximum efficacy lags Tmax differentially.
- Increased nighttime alertness is a transient side-effect.
- Careful design of a QD Provigil™ dose will demonstrate significance in phase III trials.



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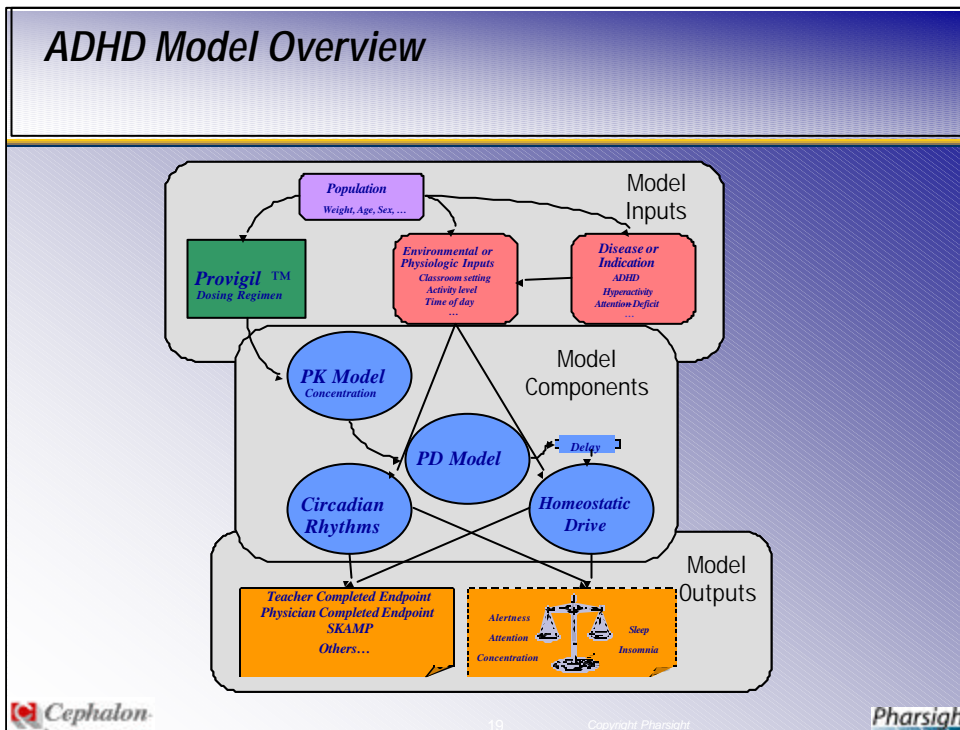
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[Bob Korsan, Pharsight Corporation]

One of the things that we found out about the drug PROVIGIL — is that the PK in adults is not affected by a lot of different things. The reverse is true in pediatrics. So in children, age, weight, dose, and timing of administration matter. It's true both in pediatrics and in adults that maximum efficacy of PROVIGIL is delayed from the time of maximum concentration.

One of the things that was good about the modeling effort that we had done previously on shiftwork sleep disorder was that we could take parts of that model and use it as a side-effect model within the ADHD population. The most significant side effect in children from PROVIGIL was in fact that they would not be able to fall asleep after they had done their homework. Developing the dosing regimen for this population was a very delicate balance, with all the covariance that existed, and with getting enough efficacy to keep the children attentive during the day at school, able to do their homework, and yet not awake at bedtime.



[Bob Korsan, Pharsight Corporation]

This is an overview of the elements of the model. There are a significant number of inputs to the model. Obviously, the decision that is most important is the dosing regimen. There is the information, though, here about the population – weight, age, sex, etc. There are all the environmental or physiological inputs – what the classroom setting is like, the time of day and activity levels that they'll be going through, and there is of course indication – ADHD is sometimes treated as a couple of different indications. It's not always treated as a single indication.

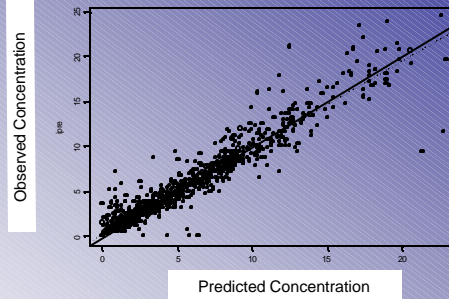
Within the model itself, once you've described all of the environment in which the subjects are taking the drug you have the PK model. In the PD model, there is the delay between drug concentration and effects, there is a circadian component and the homeostatic drive for sleep, and there is also a prediction of values for different kinds of end points that could be measured in various trials, including teacher-completed end points, and physician-completed end points – those are usually done jointly with the parents. Both are interview questionnaires. SKAMP is a scale that's been developed in some simulation laboratories for children, and there are other possibilities. Some of the other outputs, which we use as side effects, are alertness and whether or not the child was going to fall asleep.

PK modeling was able to account for all covariates across a range of trials.

Patient

- weight,
- age,
- sex,
- dose and
- time post-dose

are important linear covariates



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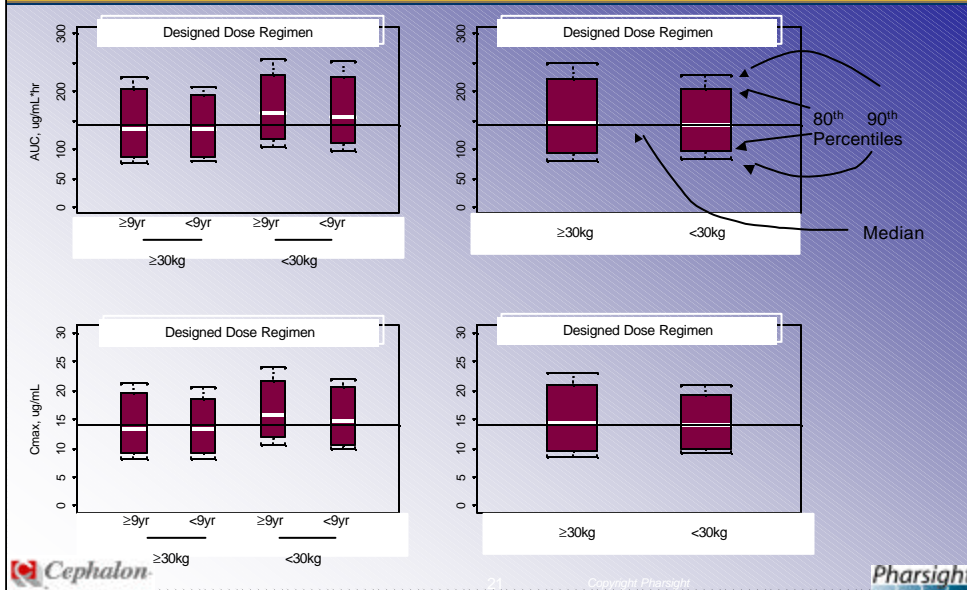
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[Bob Korsan, Pharsight Corporation]

We had done an extensive amount of modeling work for PROVIGIL prior to this in adults. However, when we looked at the PK modeling in children, it differed from that in adults in that it was highly sensitive to the weight, age, sex, dose and time post-dose. -
- This slide shows the predicted concentration versus the observed concentration for the data that we have. You can see that, once we had all the covariates taken into account, the model was able to predict concentrations very well.

We could use those simulations to show the amount of exposure and then in the next slide I'll show you some of the responses.

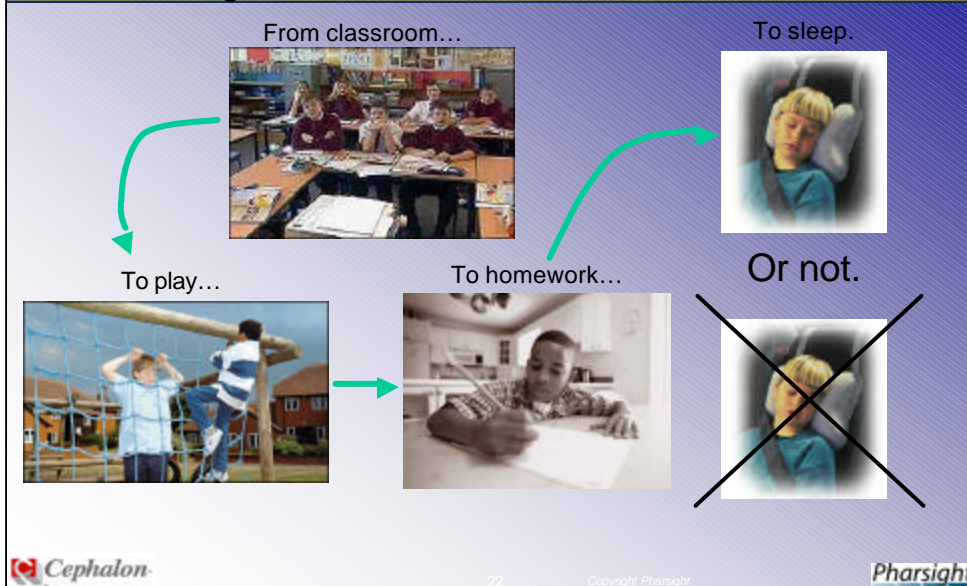
Simulations show maximal efficacy for equivalent PK exposure following the designed dosing regimen.



[Bob Korsan, Pharsight Corporation]

We developed a PD model which predicted, as I said, the various questionnaire responses that you would be seeing. We were able to design a dose regimen that took into account two primary influences on PK – how old the children were and how heavy they were. Although there was a lot of variability, due to other influences on PK, we could get acceptable exposure with a few doses that would cover all of the major variability, only taking into account those two aspects.

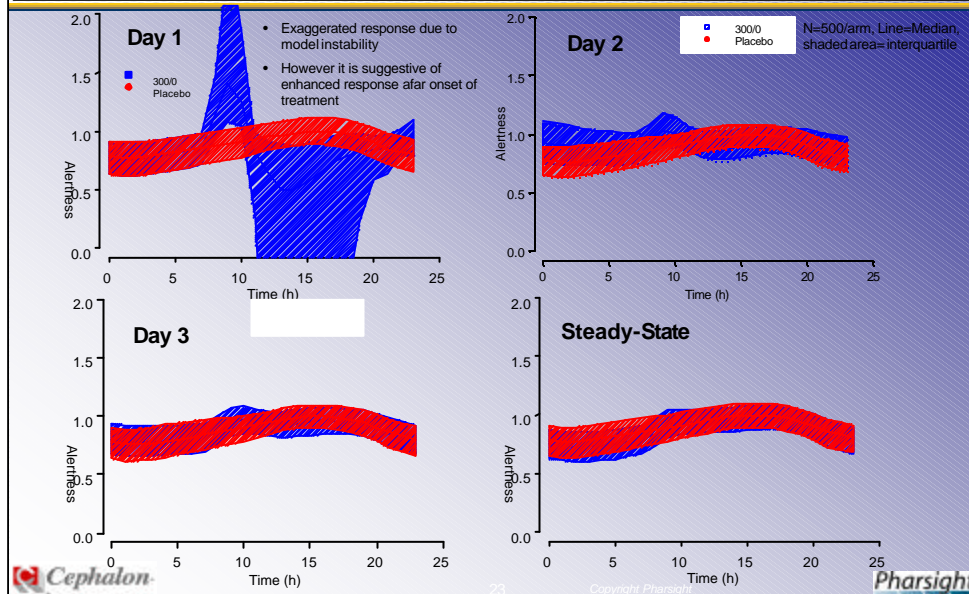
In ADHD, the model used to design trials for excessive sleepiness becomes a side effect model predicting increased nighttime alertness.



[Bob Korsan, Pharsight Corporation]

We had a sleepiness model that we could use, with slight modification, from the previous work that we had done in adults. We needed modifications to deal with the environments that the children go through from classroom to play to homework to sleep. What you don't want to do is have kids be awake at night.

The only transient AE is increased nighttime alertness early on, however steady-state profiles are indistinguishable from placebo.



[Bob Korsan, Pharsight Corporation]

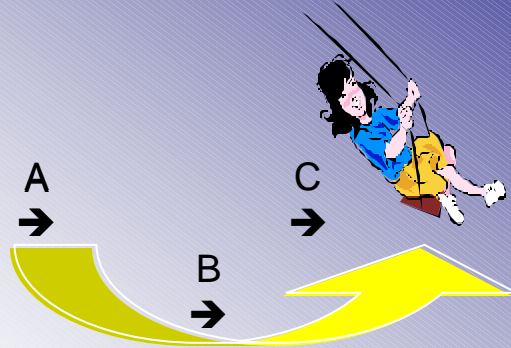
Our modeling showed that, with the chosen dose regimen, there would be some increased alertness at nighttime, and some inability to stay awake during the day, but it was a transient phenomenon. Basically, you'd only see it in the first week and by the end of the first week it should not appear anymore. The trial data actually supported this as well.

Both the trial data and the models that we had put together show this distinction.

Circadian biology and trial data indicates a relationship between the timing of the Provigil™ dose and efficacy.

- Trial data indicates that Modafinil dosing has an AM/PM time-dependency.
- AM dosing is aligned with the daytime needs of ADHD children and corresponds to natural circadian rhythms.

The force and the timing of the push must be accounted for to predict the magnitude of the effect



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[Bob Korsan, Pharsight Corporation]

This cartoon illustrates dosing issues. PROVIGIL dosing is sometimes a little bit of a problem due to the delay in PD compared to the peak concentration. So the effects do not parallel concentrations. With kids it's important to get the timing of the dose right, so that they'll have maximum drug effects (wakefulness and concentration) during their classroom period.

An effective QD regimen can be determined.

Findings:

- A very significant portion of the PK variability can be attributed to body weight and age. PK contributes understanding to the efficacy findings in Cephalon trials.
- Equivalent Exposure to Modafinil across age and body weight strata can be assured with the proposed dosing table:

Body Weight<30kg		Body Weight>=30kg	
Age<9yr	Age>=9yr	Age<9yr	Age>=9yr
XXXmg	YYYmg	YYYmg	ZZZmg

- QD morning dosing demonstrates advantages as compared to divided dosing regimens.



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[Bob Korsan, Pharsight Corporation]

In the end we were able to, break the key issues down into two areas – body weight and choosing the appropriate once-a-day dosing to enable best benefit in terms of classroom attention and homework for the kids.

Phase III trials are next! The trials are extremely likely to be successful.

Research published in the Feb. 2001 edition of the Journal of the American Academy of Child and Adolescent Psychiatry reports that Provigil (generic name: modafinil), a medication already approved for the treatment of narcolepsy, may also have potential as a once-daily treatment for AD/HD.

The most recent - and most promising - research compared results on three different AD/HD assessments, without and with medication, in children with AD/HD. Eleven children with AD/HD, ranging in age from 5 to 15 years, took modafinil for an average of 4.6 weeks. The children were then evaluated using the Conners Parent and Teacher Rating Scale-Revised (L) (CPRS, CTRS), the ADHD Rating Scale-IV, and the Test of Variables of Attention (TOVA). Improvement was shown on all three indicators.



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[Bob Korsan, Pharsight Corporation]

Phase III trials are next step. The Phase II results showed significant benefit and we fully expect the Phase III to be significant as well.

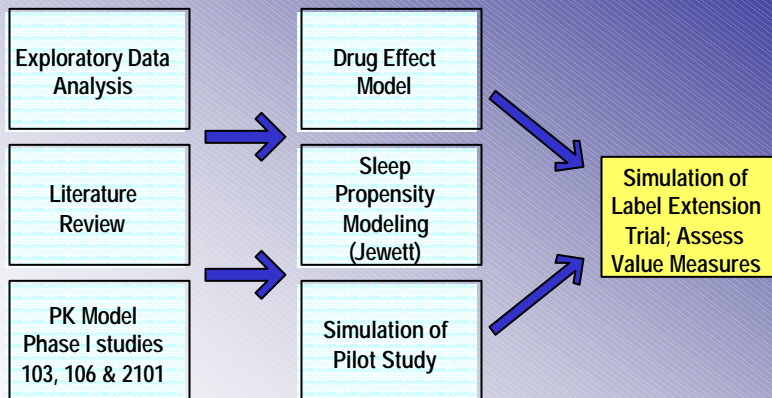
*Case Study #2:
Shift Work Sleep Disorder*



[Bob Korsan, Pharsight Corporation]

We now go back in time to the first work that we did with PROVIGIL. The focus was on shiftwork sleep disorder.

Pharsight built an "excessive sleepiness" model using the literature, public data and Cephalon study data.



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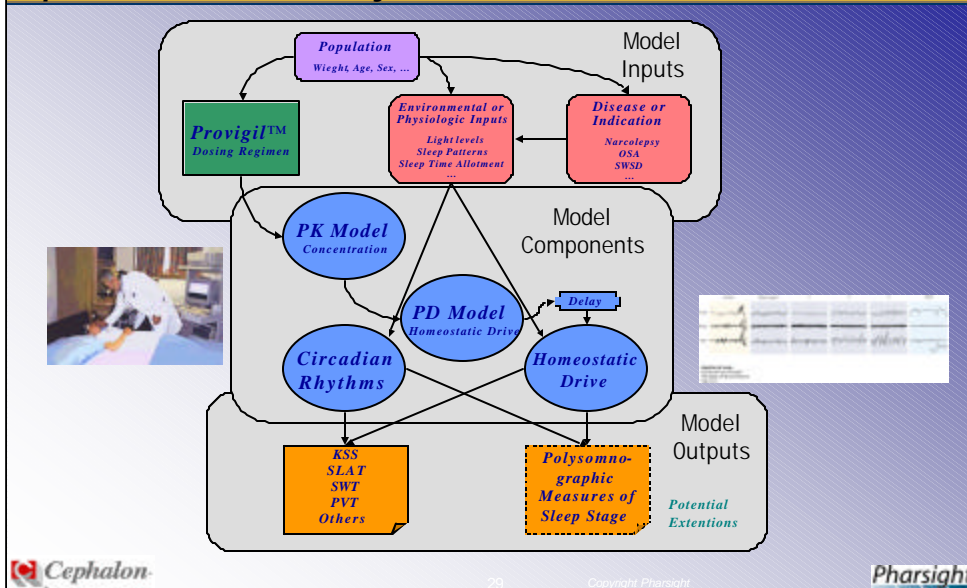
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[Bob Korsan, Pharsight Corporation]

We went through quite a bit of effort in pulling together all of the information that was available about this disorder. We did a literature review. We worked with the internal clinical data, including both PK and a simulation or pilot study of shiftwork that Cephalon had done. We used sleep propensity modeling that Jewett and a whole bunch of collaborators had worked on. We first did an exploratory data analysis to convince ourselves that we could use these models to build a drug-effect model and to simulate what was going to happen in shiftwork. I'll have to say it was one of the most intense periods of modeling that I've ever been involved with in my 40 years of experience. It was pretty amazing.

The “excessive sleepiness” model incorporates disease & population characteristics, PK and PD effect models giving predictions for a variety of clinical measures.

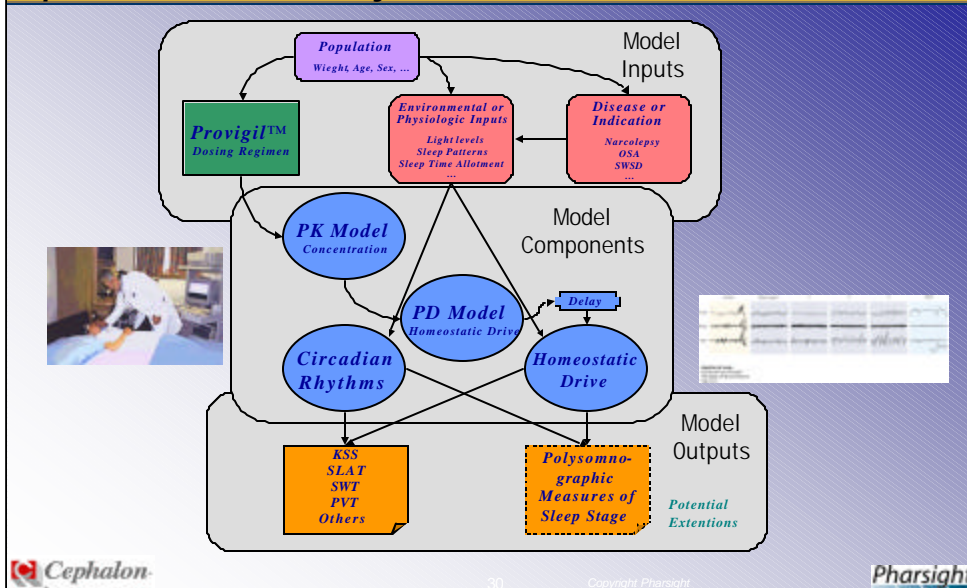


[Bob Korsan, Pharsight Corporation]

This model looks very similar to the one that we showed you in ADHD. The green box is the dosing regimen that you have to choose. One of the things that's not shown is the decisions that we faced for the trial design, which would be yet another box. The lavender rectangle is the population that you are treating. In pink, at the center, are the environmental or physiological effects that you have to worry about. These can actually be significant. There's a difference between shiftworkers in San Diego and in Washington. When it rains you have different responses in your body to alertness. Sleep patterns are important, the light patterns are important, whether or not you give yourself a full eight hours of sleep – most shiftworkers tend to get only six hours – all of these issues have to be modeled in the design of the trials that you're going to be using. And the model itself has to be responsive to all of these factors.

There is also a question of what is causing the sleepiness that you're facing (right-most pink rectangle). Certainly, the dosing and the outcomes may be different if the problem is due to shiftwork, as opposed to narcolepsy, obstructive sleep apnea, or some other cause.

The “excessive sleepiness” model incorporates disease & population characteristics, PK and PD effect models giving predictions for a variety of clinical measures.

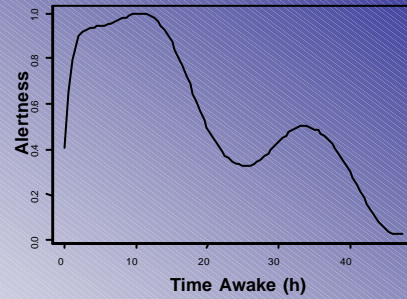
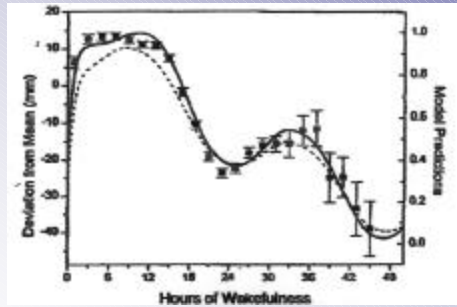


[Bob Korsan, Pharsight Corporation – continued from previous slide]

The internal model components – except for the trial components, which are not shown – are the same as those for the ADHD model. They include a PK model, a PD model, a delay between drug concentration and effect, circadian rhythms, and homeostatic drive. There are a variety of sleep measures. KSS is a self-reporting score. SLAT is sleep latency. SWT is wakefulness. PVT is a psychomotor vigilance test measuring how well subjects follow dots on a screen. Alertness is measured that way also.

One extension that could be added onto this model is polysomnographic measurement of sleep stage. At present the model is focused primarily on alertness and daytime functioning. Generally once subjects go to sleep we don't worry about stage of sleep they're in or other things like that because PROVIGIL is a drug to promote alertness, not to alter sleep patterns. Still, the model could be extended to deal with the stage of sleep that patients are in and to model what's happening to the architecture of their sleep – whether or not they're getting very restful sleep or they're waking up a lot and those kinds of issues. Depending what the pipeline looks like, we could do that in future modeling of PROVIGIL.

Based on the work of Jewett, et al., a model of alertness was implemented in Trial Simulator™.

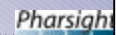


- This model has been implemented in Pharsight Trial Simulator 2.
- This graph duplicates Figure 2 from Jewett and Kronauer, *J. Biol. Rhythms*, 14:588-597 (1999).



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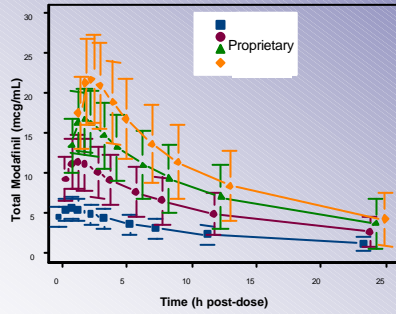
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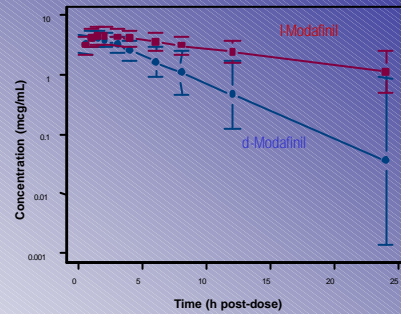
[Bob Korsan, Pharsight Corporation]

I said, the literature provided a tremendous amount of previous work. We used that. We based our model on the work of [Jewett]. This slide compares a figure in her paper to the results of our model for the same set of inputs.

The Provigil™ PK model accurately reproduces the observed population drug response.



- Graph shows simulated Day 7 PK for various doses
- Appropriate covariate effects in PK model



- Graph shows simulated PK for each enantiomer after single XXX mg dose
- Total concentration is the sum of l- and d- isomers

The Modafinil PK model is based on Phase I studies



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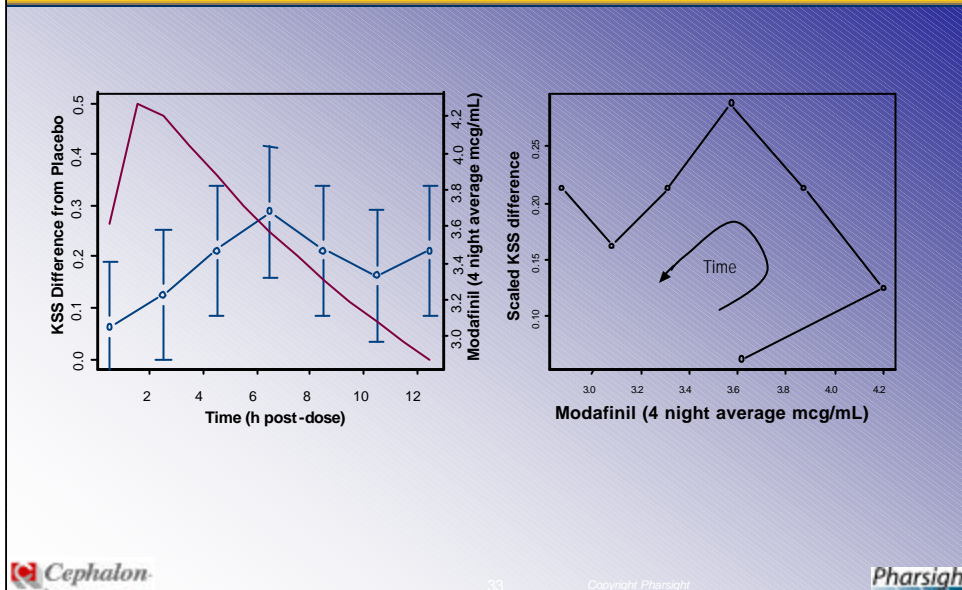
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[Bob Korsan, Pharsight Corporation]

PROVIGIL is a combination of two enantiomers. There are different PK properties for the two enantiomers. We were able to deal with them separately, and modeled the PK over a seven-day period for various doses. There are far fewer important covariates in the adult population than in the pediatric population.

The pharmacodynamics of Provigil in SWSD patients is similar to narcolepsy and ADHD.

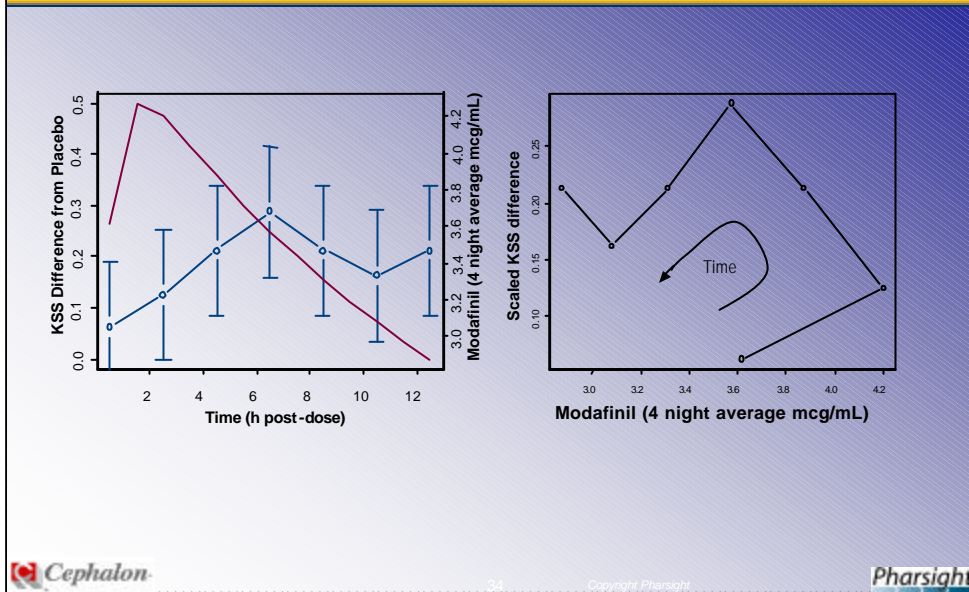


[Bob Korsan, Pharsight Corporation]

This shows some of the pharmacodynamics for PROVIGIL. KSS is a self-reported sleepiness scale that ranges from 1-9. If you say 1 it means you're very awake. If you say 9 it means you are barely able to keep your eyes open. The left graph here shows the difference between the concentration, which is in red, as a function of time post-dose, and the efficacy (KSS difference from placebo). You can see the delay that I was talking about: the concentration peaks at about two hours; the alertness peaks at about six and a half hours, so there's a considerable delay. This has been seen in ADHD, shiftwork sleep disorder, and narcolepsy. We haven't gotten around to looking at obstructive sleep apnea yet but we're going to do that as well.

The second graph on the right shows the same data, plotted as drug effect against drug concentration. It shows you that there's a pretty significant delay between concentration and effect here. Time, instead of being along the bottom axis, follows the shape of the curve, as shown by the inner arrow. You can see that for a given concentration, the effect is very different at different times post-dosing.

The pharmacodynamics of Provigil in SWSD patients is similar to narcolepsy and ADHD.



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[Bob Korsan, Pharsight Corporation – continued from previous slide.]

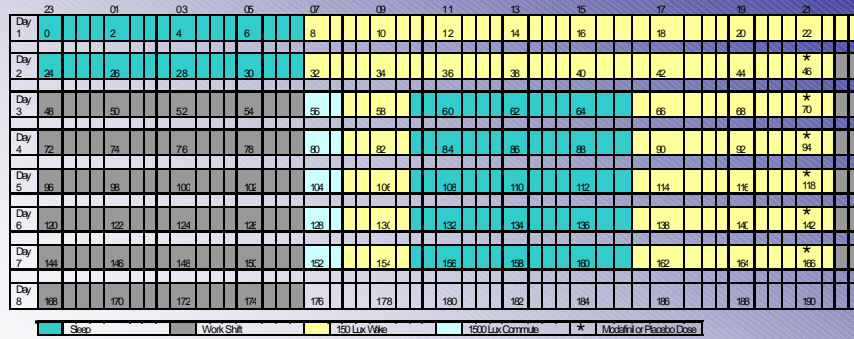
[Lilliam Kingsbury, Cephalon, Inc.]

In the first graph on the left – that rise that you see approximately 10-12 hours post-dosing – in case you're wondering why that doesn't fit the concentration it's because of the circadian effect. Dose was given at 10:00 at night. So that's the effect that you see. But of course, once daylight hits, wakefulness will increase again. So if you see the disparity in the curves 10-12 hours post-dose, it's because of this external factor.

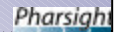
[Bob Korsan, Pharsight Corporation]

Earlier, people are getting some rest and after 10 hours post-dose, they start waking up because the light environment has changed. Thank you.

The model simulated patients over 2 nights of normal sleep followed by 6 nights of shift work.



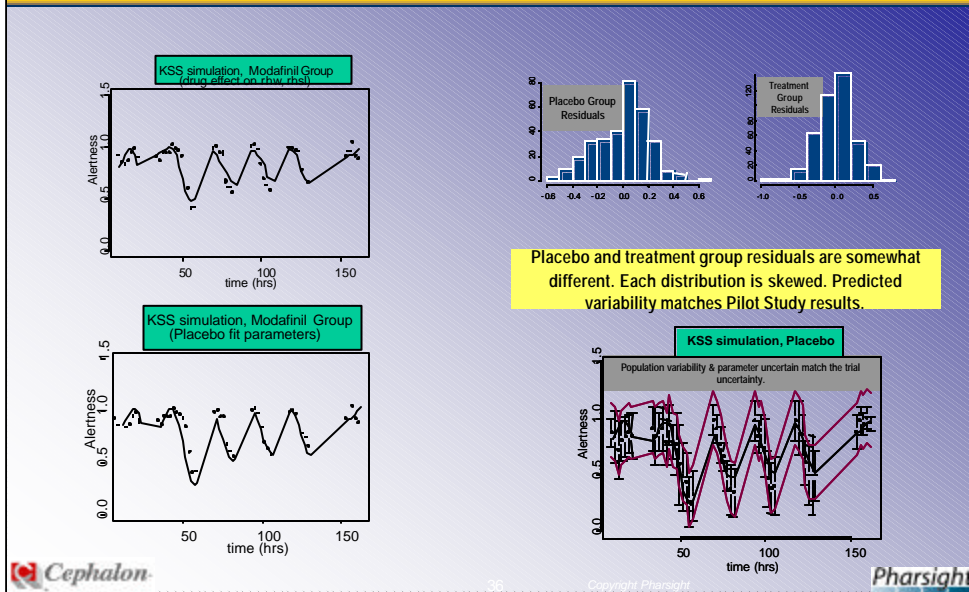
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[Bob Korsan, Pharsight Corporation]

We modeled the sleep behavior of patients in a particular geographic region this way: on weekends they follow normal sleep patterns, but during the week their sleep is shifted considerably later in the day. We had confirmatory simulation runs in which we had modeled out to at least three weeks worth of sleep. We say no difference in the patients after the first week, so we could just take a look at one.

The model provided good fits of the pilot study population means. Side effects were negligible.



[Bob Korsan, Pharsight Corporation]

The model itself was fitted to the data from the pilot study. As you can see here, the top-left plot is the Modafinil group or PROVIGIL. The mean effect is quite well-represented. The placebo group, on the lower plot, is also quite well-represented, although there is some as yet unexplained residual variability. This is actually old data. We were under a tremendous amount of time pressure in order to get the trials designed. These are the results that we had at the time we made decisions on the trials. Subsequent to that we were able to go back and look at the data and to correct some of the problems that are in there. And we're going to do an update of the model based on the shiftwork sleep disorder trials that we got so that we have a better model yet, and we expect all of the unexplained residuals to go away.

There were several critical design decisions to address to optimize the study.

1. How many nights of shift work need to be observed?
 - Are 6 nights required, or are fewer sufficient
2. Are the two drug arms sufficiently different to provide informative results?
3. How likely is the proposed trial to yield a positive result?
 - Is sample size sufficient?



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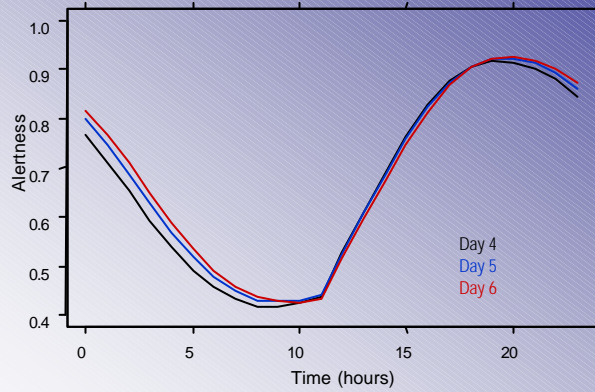
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[Bob Korsan, Pharsight Corporation]

In designing the trials we asked ourselves: what are the critical elements in order to make this a more valuable trial? First of all, how long would the shiftworkers have to be observed? The original design when we got involved was that six nights of observation of the patients would be necessary. Second, as Lilliam already alluded to, it was planned to have two different dosing arms of PROVIGIL in the trial as well as placebo. And last, was the trial properly powered in order to produce the results that we wanted?

Shift work nights 4, 5 and 6 appear to be indistinguishable



- Graph shows typical Placebo Alertness on Days 4, 5, and 6
- Can observe patients for 4 nights rather than 6

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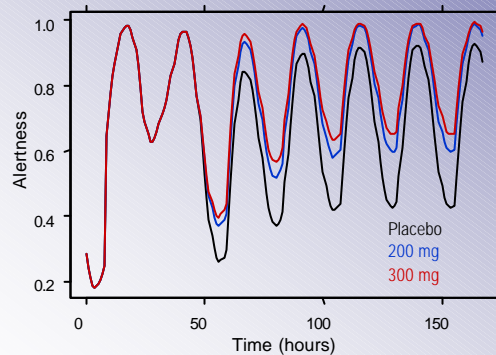
Pharsight

[Bob Korsan, Pharsight Corporation]

The first thing we did was look at the alertness of the shiftworkers during the course of the day over days 4, 5 and 6. As you can see, although they are distinguishable in the population average, they're in essence not enough different to make a difference in terms of the observations that you're going to see. So, the first thing that we recommended was to observe the patients for four nights instead of six.

The 200 and 300 mg arms are quite close in their expected effect

Typical Alertness Profiles vs. Time



In simulated trials:

- The 200 mg arm yielded significant result vs. placebo 98% of the time
- The 300 mg arm was always significantly better than placebo
- 200 and 300 mg arms could be distinguished only 3% of the time

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[Bob Korsan, Pharsight Corporation]

The second thing that we looked at was the number of dose arms. There was a proposal to use a 200mg and a 300mg arm. In simulations, there was clearly a difference in both arms from placebo but, except over small regions of time, there was not enough of a difference in the behavior of the 200mg arm from the 300mg arm to justify putting the 300mg arm in. So, our second recommendation was to remove the 300mg arm.

We saved 25% of the trial costs by eliminating a 300mg arm when the model predicted that 200mg was enough.

- These results led to decision to eliminate 300 mg arm from trial
- Evaluation of 4 nights instead of 6
- Savings of 25% in direct clinical costs on a multi-million dollar trial
 - Time savings for smaller trial probably substantial, and much higher value
- Trial was a success as predicted.



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[Bob Korsan, Pharsight Corporation]

These two recommendations resulted in direct clinical cost savings of 25%. Also, of course, the trial was smaller. You could use the same patient population that you had available when you were enrolling them, so the trial could be completed more quickly. Initially, we also looked at the trial power and decided it was more than adequate. The original plan included an interim look at the data during the course of the trial. That was dropped so we even saved a little bit of alpha in that.

The bottom line was that the trial was a success as predicted.

Case Study #2: Shift Work Sleep Disorder



October 23, 2002

Cephalon, Inc. announced that results of its clinical study evaluating PROVIGIL (modafinil) C-IV in patients with shift work sleep disorder (SWSD) showed statistical significance on both primary endpoints of the study. The 12-week randomized double-blind placebo-controlled study included 209 patients with a ICSD-confirmed diagnosis of shift work sleep disorder randomized to either 200 mg PROVIGIL or placebo.

Patients in the study received PROVIGIL or placebo as a single dose given prior to the start of their night shift. The study showed that PROVIGIL significantly improved wakefulness compared to placebo, as measured by the Multiple Sleep Latency Test (MSLT), an objective measure of sleepiness ($p < 0.01$). In addition, patients treated with PROVIGIL showed significant improvement in their clinical condition as measured by the Clinical Global Impression of Change (CGI-C) when compared to patients treated with placebo ($p < 0.0001$).

[Bob Korsan, Pharsight Corporation]

This is the announcement of the trial results that were obtained. And I've got to say – this has been a wonderful collaboration. This has been some of the most exciting work that I've ever done. It's also been some of the most grueling. Also, Cephalon has really put a tremendous amount of trust in our results. I'll tell you a little story, which I probably shouldn't tell, but I will anyway.

At one point I worked with several other people on the team in putting these results together, and I was giving the final presentation for some of this work. We happened to be doing it by teleconference with the Cephalon folks in Pennsylvania, my colleague in Boston, and myself in California. I'm going through the slide presentation and I get to the last slide that is labeled "Conclusions." This project was so tightly done, timewise, that I literally had to say, "You know why this slide is blank? I don't know the answer. Kevin, did you finish the calculations?" And Kevin said, "Yep – I did." "Good! Would you tell us what the answer is?"

Cephalon has trusted our integrity enough to be able to take that kind of close result and turn it around within a couple of days in terms of changing trial designs and letters to the FDA, etc. So this has been a wonderful collaboration from our side. We have a relationship where we can produce the results that are really important and trust that they're going to be turned into action within a matter of hours. It's an amazing relationship. I have no relationship like that with any other client, and I'm really amazed.

So with that, I'm going to turn it back over to Lilliam.

Cephalon and Pharsight have worked together enabling better quantitative drug development decision making, accelerated trials and reduced costs.

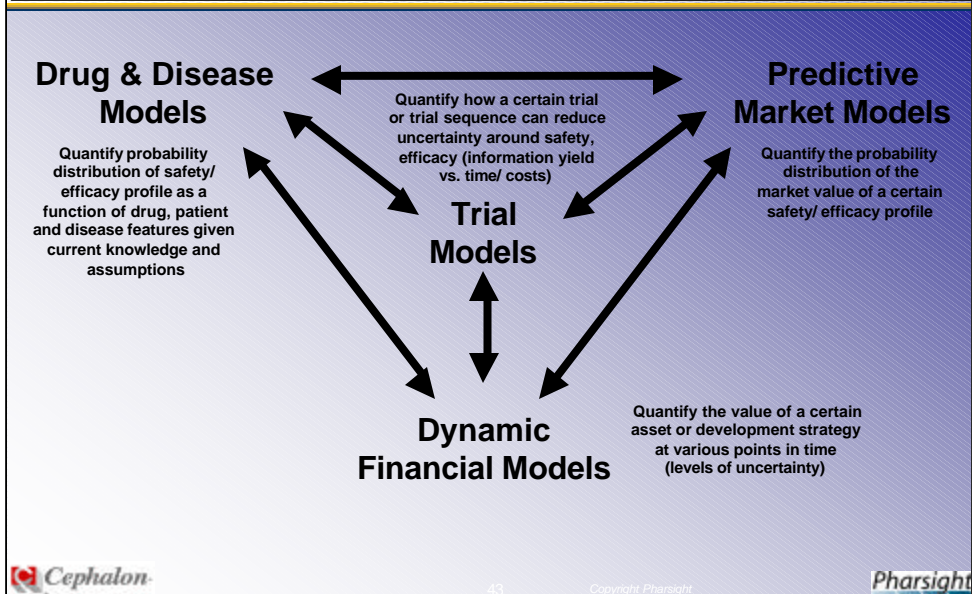
[Lilliam Kingsbury, Cephalon, Inc.]

Well, I think it merits that I say a couple of things after the statement you have made. It is a very good collaboration, but we have gone through an evolution. In terms of that shiftwork effort, we know the drug. So in essence after you've worked with the drug, you know how it behaves. You have this gut feeling you need one dose. This dose is what's going to work. You need to do this. But you don't have support for that. So we wanted to have a separate party that would take into account data that were available from multiple sources, both internal and the literature, and would make a recommendation. So we were thinking maybe four nights instead of six, but we weren't sure. Well, now we have more level of comfort that we could cut it down to three. Everybody was banking on this 200 – we just had this gut feeling that 200 and 300 are not going to be that different. But then you did the model, as I said, in that first effort. There was a lot of comfort that the clinical sense – what we knew in my department, which is statistics, matched what the models had suggested we should do to modify that trial.

It also helped us with, believe it or not, our internal customers which are, of course, our commercial [group], that, yes, we did this study and we will have measured that we will be able to communicate some potentially-marketable advantage. So it was very useful.

This collaboration – again, I'm putting it really in the chronological context – changed however now. Now we're moving to this ADHD model and we don't know yet whether the FDA will or will not accept what we have from our relatively limited Phase II experience, Phase I experience, and the modeling to agree to the Phase III program we're proposing in ADHD. We don't know that yet. But it's a different use of this modeling information because instead of being essentially confirmatory of what our thought was, it's truly now an addition.

Everyone makes models ... Cephalon just writes them down for later use.



[Lilliam Kingsbury, Cephalon, Inc.]

[unintelligible] to shorten development and also allows us to increase our prediction but it is an additive effect. It is something that truly we could not derive purely from the previous clinical experience.

I think that even in the presentation by our new Commissioner at dinner last night there is the sense that we must all work together to try to reduce the cost of drug development. There are too many failed trials. The cost is staggering.

Cephalon has taken advantage of the amount and type of prior information possessed to accelerate development.

Amount of information	Example	Number of assumptions	Uncertainty in predictions	Goals of modeling & simulation	Trial designs	Role of pre-clinical and in silico data
High	Pre-clinical models Known MOA n th indication n th in class	Few	Low Intermediate	Shorten and focus development	Fixed-dose dose finding Skip PoC & dose finding?	Quantitative prediction Rescales existing clinical models
Intermediate	Mixture	Intermediate	Intermediate	Robust strategy	Fixed-dose PoC & dose finding Adaptive stopping?	Semi-quantitative Mechanistic rationale
Low	No pre-clinical models Unknown MOA 1st in indication 1st in class	Many	High	Manage risk	Adaptive stopping Adaptive dose assignment?	Limited Qualitative



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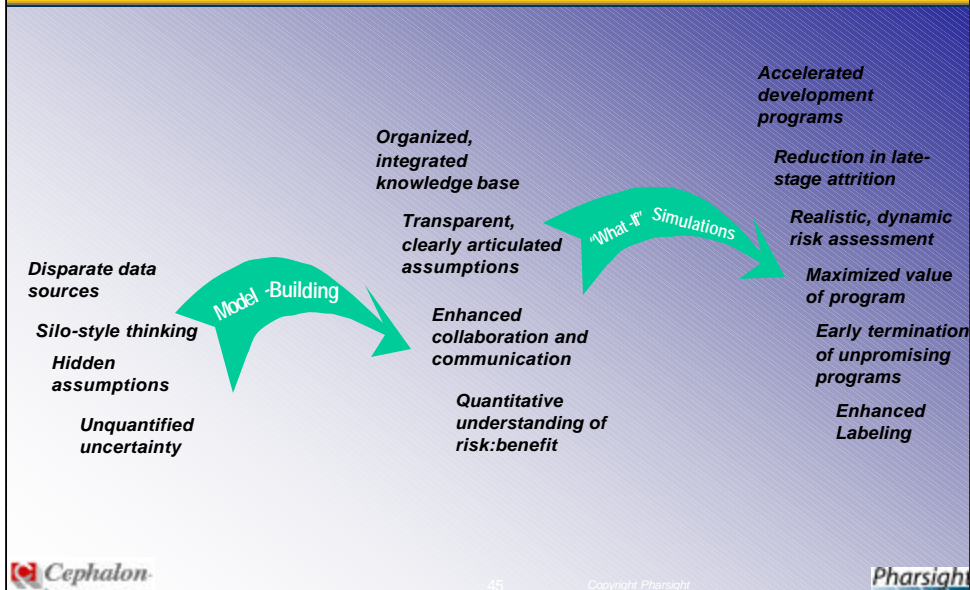


[Lilliam Kingsbury, Cephalon, Inc.]

We have technology now – clinical trial simulation, the ability to create sophisticated models – that we are willing to say at Cephalon we want to use this to try to in fact choose better trial designs and decide on programs that would be more focused. We don't know yet what the regulatory response to that will be, but we have been encouraged in initial interaction that this approach will be viewed positively.

So we will have more to know once we meet within six weeks or so with the agency in this ADHD program. But again, it is new technology. It's an approach that should be able to enable us to take advantage of the prior information that we have to accelerate development, not by reducing the amount of information that we have from subjects and patients but really by targeting better how we design our trials and how we present that evidence.

Cephalon integrates literature, prior data and modeling to improve development decision making.



[Lilliam Kingsbury, Cephalon, Inc.]

We do believe that integrating disparate data sources, literature and all quantified [uncertainty] through model-building can bring us a more integrated knowledge base. We can improve our communication of what we have and have a better understanding of the risk benefit of some of our programs. This is what Bob alluded to. You know, you work sometimes with these children to get risk benefit [things] that I think everybody can appreciate. You want to improve their performance during the day – you don't want to keep them awake at night. So we have a better way of understanding risk benefit and that hopefully will lead to an accelerated development more and a reduction in late-stage attrition and ultimately leading to [unintelligible] to enhance labeling.

And frankly, this is also important. If we don't have something that is successful we would like to know as soon as possible so that we can put our efforts [elsewhere].

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Lilliam Kingsbury, Cephalon, Inc.]

So I should close by saying that we are now – Cephalon is small, relatively small. We have relied heavily on consultants, namely Pharsight, in this effort. We are in the practice now of a training effort and moving to that next level where we can incorporate these skills as one of our core competencies. And I think this slide that you chose to close could not be more appropriate. We would like to be as simple as possible but no simpler, so that we take account of all the factors that are relevant to the effort. Thank you for your attention.

[Question and answer session]

Q: Is this methodology useful in animal testing and early phase trials?

Bob Korsan: Well, the answer depends on the situation, obviously. I'm going to turn myself into a two-handed economist – on the one hand and on the other hand. If you've got a drug that is nth in class, it's got a similar mechanism to things that you've done before, this kind of work can be used in the animal modeling side just as well. And what you want to do is to find out that your predictions are verified by the animal tests that you do – not necessarily start from scratch each time.

“A [simulation] model should be as simple as possible and no simpler.” – Albert Einstein

Finis

[Question and answer session - continued]

But on the other hand if it is a new compound that is not something that you can do. So if there is a sufficient information base from previous work that you've done or work that you're aware of in the literature or some other reason, I'd say yes. On the other hand, I'd still rather do work in animals than in humans. So if it would increase your risk – and that's only a question that can be answered by the level of uncertainty that you have when scaling the models from animals to humans – then you may or may not gain much benefit. So far we haven't applied it in that realm. We've for the most part used almost all of our work with the traditional animal models and then tried to develop either seamless Phase I/Phase IIs, collapsing Phase IIA and IIB together, adaptive dose-ranging, better trial designs – those are the issues that we've applied it to first. So I don't have a lot of experience in there. I don't doubt that it can be used to effect, but I don't want to make a blanket statement.

Other questions? Yes?

Q: I wonder if your models are just regression analysis or what, but I'm not sure I understand the mechanics of how your model works.

“A [simulation] model should be as simple as possible and no simpler.” – Albert Einstein

Finis

[Question and answer session - continued]

Bob Korsan: Well, part of our models are also statistical models – because when we do trial designs you have to model whatever the statistical tests are going to show. PK models – what the body does to the drug – are typically really just chemical mixing models. You have a couple of vats with chemicals in them and you want to understand how the concentration of the drug is going to evolve over time. PD models are somewhat different. They strongly depend upon whether or not you understand the physiology of the PD effect or you're just dealing with things from an observational point of view. An awful lot of what we wind up doing unfortunately – there is no understanding of how the drug has the effect that it does. So if you take a look at the effect, say, in schizophrenics you know that you give them these drugs but there's no understanding of why people get better. All you know is that if you observe patients before they take the drug and you get them evaluated by a doctor on a scale for 30 questions or whatever PANNS is you're going to wind up with a score. And then if you look at them over time that score is going to change. So you have a longitudinal model of what's happening to that score over time and it depends upon many different things. It can depend upon the dose that you have. It'll depend upon time. But over all, the effect that you're going to see can usually be captured in – depending upon whether you need to take the concentration into account or whether you can just deal with dose in some type of a curve, which is usually [monotonic] increasing. It's just an abstraction that's fit with the usual regression tools.

In other cases you do understand the physiology of what's going on, in which case then you can build much more complex models that actually track the physiology of what's going on.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

So again, I'm not trying to avoid your answer. I'm trying to say that the question has to be in the context of whatever particular indication you're dealing with and what your state of knowledge is. Here we have a lot of information in sleep about the physiology – temperature changes in the body, what's happening to the EKGs over the course of the night. There's a tremendous physiologically-based amount of information that's available to you from the research that's been going on in the last 30 years. In something like, as I said, schizophrenia it's just not the case. So it's totally – you know, I've got a curve and it does this. And that's my model.

Q: Do you predict trial results as well?

Bob Korsan: Yes.

Q: Do you only deal with conceptual models?

Bob Korsan: Well, no. It's both a conceptual model but if we can express it in a computer program that actually will predict what's going to happen under different trial circumstances then we haven't done our job.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

Lilliam Kingsbury: Bob, I'm a statistician also. So it is really a high order. We start our model in this separate – I'm trying to give you an oversimplified [unintelligible] but like a statistician thinks of it. We really have – there is a PK model and a PD model. And then essentially those two are correlated. And then you have previous trial data that [feed] the model as well as, as Bob indicated, in the context of sleep in particular there are [circadian phase] parameters. So it is really a very high-order, nonlinear model that we use to predict response into a set of equations that we then predict the response that we want to observe in the trials.

Bob Korsan: In this particular case, just for completeness, the circadian and homeostatic components of the sleep model – there is a series of differential equations that are used to model the behavior of what's happening inside the body of the patient. And in this particular case it turned out that there was no significant feedback from the PD to the PK. So we could separate the PK model and the PD model and deal with them sequentially inside the model that we had of the patient.

But that's not always true. In many cases, there is a feedback between PK and PD in an indication and you do need to work with the two simultaneously and take that feedback into account.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

So again, I'm not trying to avoid your answer. I'm trying to be complete. And I hope I haven't muddied the water in that....

I am sorry I am so long winded, I just want you to have a good clear answer.

Any other questions?

Q: It seems that the validity of your model depends on the amount of data that pre-exists. Is that true? In this case study you have, as you said, a lot of data that you could plug into your model. [Unintelligible]

But you don't have much data, hardcore data from many new mechanisms.

Bob Korsan: Usually, as one mentioned, you have at least animal data that you can scale up.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

Q: You have used animal data?

Bob Korsan: Yeah. I have also built models based totally on somebody's gut feel but that's very dangerous. There is optimism and strong biases on the part of the investigators. They couldn't do their job if that wasn't so.

Q: How do you work with clients in later phase engagements? How do you get clients to patients sooner?

Bob Korsan: Right. As I said, what we do with a client is a series of modeling engagements primarily focused on either doing a seamless Phase I/Phase II or a Phase IIA/IIB, which might be adaptive or group sequential in order to reduce the amount of time that you take to do your dose-ranging kind of information.

In Phase III you're usually not able to do a whole lot of savings in terms of the actual trial design because you have to fill out your safety database. And so if you make your trial shorter it really doesn't help you a whole lot in terms of the time you get to market. So most of our work tends to be on the design of Phase I/Phase II kinds of things.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

As I said, you can also apply these to the design of animal studies. I do recommend at least having animal data but if you're not a novel mechanism but yet a different – you know, the nth in class where you've got a different chemical but you've got the same basic physiological mechanism, then you can use the information that's available in the FDA Summary Bases of Approval from other drugs as your database. And we regularly grab information from literature or from summary bases of approval of other drugs and use that as a basis of building the model, understanding the difference in the [ED50] or the [EMAX] effect, etc. based on what we understand from the animal data.

So it's not a black and white question, but there needs to be some level of understanding of how things work. If it's novel mechanism and you haven't got any data whatsoever it's a gleam in somebody's eye -- I can build equations but I wouldn't trust them.

Q: What is the fundamental difference between your approach and Entelos?

Bob Korsan: The fundamental difference – well –

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

Q: If there is one.

Bob Korsan: I was originally trained as a physicist so I'll – if you're going to be building an airplane you don't want quantum mechanics as the set of equations that is your starting point. Engineers develop short cuts. They develop tools that will allow them to design airplanes, not to understand the basic underlying physics of the situation.

The same is true between us and Entelos. Entelos is trying to model the physiology through a long chain of what's happening inside the human body. And although that can be very useful – and I don't want to in any way denigrate the work that they're doing; I happen to know the guy who founded the company. He was a colleague of mine previously and he's very bright and the work that they're doing is very important. But it's different in philosophy. I would say that they are basic researchers and we are engineers. Our job is to engineer a drug development program to be the most successful one you can get, just like you want to engineer an airplane to carry as many passengers as cheaply as possible.

But if you want to understand the underlying molecules and what that does to create stress cracks in the wind and other things like that, that's more the level at which Entelos is working. And it's simply a matter of – we don't have enough computer cycles yet, no matter how fast computers have gotten to do the level of modeling that Entelos is doing when you want to understand what's happening in a population or you want to understand what's going to happen in a trial or in a sequence of trials.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

Q: How come pharma is not doing this already?

Bob Korsan: Well, part of it is simply a tremendous amount of inertia. I mean, there are 50 major pharmaceutical companies around the world. We have relationships with about six or seven – deep relationships where these companies have decided to adopt our techniques and to develop them as core competencies. These are things that take time. These programs – when we talk about bringing these in as core competencies within corporations, this is a multimillion-dollar, multi-year – we're talking 5-6-7-year programs to develop a large group of people within an organization who have these kinds of skills. You're talking about organizational change. If you have a small group of smart people who are doing some of these kinds of things they're not going to be that effective unless they're able to talk to a lot of different people. We advocate and try to have people develop processes within their organizations that are cross-functional. So we want PK talking to the clinical director talking to the project director talking to the people who are trial design talking with the statisticians talking with the commercial folks and understanding what are the preference shares out in the marketplace among physicians for prescribing this. We want them talking to the folks who are doing economic analyses and talking with third-party payers and trying to get the drug on the formulary. We want them talking with the regulatory folks.

"A [simulation] model should be as simple as possible and no simpler." – Albert Einstein

Finis

[Question and answer session - continued]

This is not just about building models. This is about changing the way you do business. And you don't take a big boat and turn it on a dime. So – it's happening but it's happening slowly.

Well, unless there are any other questions, you've been a great audience. Thank you very much for attending. As I said, I'm amazed that there's anybody in the audience considering how long you've been around here. This has been a lot of fun for me and I hope it's been valuable to you.