



# **INSYS Therapeutics, Inc.**

NasdaqGM:INSY

*Analyst/Investor Day*

*Thursday, December 03, 2015 1:30 PM GMT*

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## Call Participants

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Executive Vice President

**Dennis J. Dlugos**

**Douglas Glenn Brust**

**Jeff Gudin**

**John N. Kapoor**  
Executive Chairman, Chief  
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**Lisa Wilson**

**Santosh Vetticaden**

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**Douglas Glenn Brust**

**Jeff Gudin**

## Presentation

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### **Lisa Wilson**

Good morning, everyone. I am Lisa Wilson, Investor Relations for Insys Therapeutics. Welcome to the company's Investor Day. I'd like to kick off with the standard and customary forward-looking statements. The company will be making forward-looking statements during the course of this morning's presentation.

So thank you again for coming. And without further ado, I'd like to introduce Dr. John Kapoor.

### **John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

Thanks, Lisa. And good morning, everyone. I want to take this opportunity to welcome you all to our first Analyst Day and Investor Day, Analyst Investor Day.

The reason for us to hold this meeting today is primarily driven by the fact that we feel Insys, although we've been public for the last several years, is still not well understood. We get associated with one product, Subsys, which we've been very successful in. Since launch, we have captured the major market share in the product and we just feel like that's all investors think we are about. So we want to take this opportunity today to introduce you to our pipeline primarily, and also introduce you to some of our management people, some are here today. Starting with Dan, who joined us recently as the Executive VP, Chief Operating Officer; Dr. Santosh, next to him is our Head of Clinical Program, he's been with us for about a year now; and also recently joined in audience somewhere is Sanga Emmanuel, is Sanga here? Anyway, Sanga came to us as our Chief Compliance Officer from Biogen Idec. And he's been here also very recently.

There are many other people that you will see, their bios that are behind the scene working, of course, Darryl is also here. I know the reason I didn't say Darryl -- everybody knows Darryl. And we have lot more people that you will see their bios that are working back in Phoenix and Austin, Texas plant on different projects, trying to build what we think we can have an opportunity to build a great company. As I say, to build a great company, you need great people and we are gathering a team of great people. A lot of them are already in place, some of them will come onboard as we move forward. But we have this objective to really build a great company.

Also it's my privilege to have with us some experts in the field of pain, Dr. Gudin; in the field of epilepsy, Dr. Dlugosz; and in the field of THC, Dr. Brust. And they will be making presentation later on in the program to give you some idea about the areas of interest to Insys, and how these experts feel those fields are. And we're really honored to have them here and be working with them in projects that we are pursuing.

So with that introduction, I want to turn it over to Dan to talk about the company and other things. And again, I look forward to our session all morning and getting your feedback, your input that's very important to us, hopefully, answering your questions that you might have about the company. And we very much appreciate you taking out your time today and joining us this morning.

So with that, Dan?

### **Daniel Brennan**

*Chief Operating Officer and Executive Vice President*

Thank you, John. Good morning. I'm Dan Brennan and I recently joined Insys Therapeutics as the Executive Vice President and Chief Operating Officer. It's interesting to have the new guy up here giving an overview of the company, but I have a different perspective having looked at the company from a different angle than most of you, perhaps in the audience. In fact, I kind of looked at it from the pipeline back. I was part of a group from one deck that visited Insys about 9 months ago with specific interest to meet John Kapoor and the company about some exciting developments that they had related to epilepsy. I didn't know anymore about the company, all I knew about was the cannabinoid and cannabidiol program.

Soon I became aware of the full pipeline and commercial presence with Subsys and beyond. While those partnership discussions didn't progress, fortunately, for me John called several months later with the opportunity for this role. And now, I get to share with you a bit about what I've learned in my due diligence and what I found so attractive in coming here.

Insys is a fully-pledged integrated pharmaceutical company. Vertically integrated, profitable, no debt. And an ongoing sales model that allows us to fund our own research and development. There are 2 key proprietary drug platforms, the sublingual spray technology and the pharmaceutical grades synthetically manufactured cannabinoid program. Of course, there's also Subsys, the market leader in breakthrough cancer pain treatment market. And an important near-term growth driver is Syndros, our synthetic THC and an aqueous oral solution that we hope to launch in Q2 2016.

There are also multiple clinical programs initiating in 2016 related to our marketed products, Subsys, and our pipeline, which will be the focus of today's discussion.

One of our important and relatively unknown clinical activities includes our synthetically manufactured, cannabidiol. And we have studies both underway as well as about to begin with this important program. Again this is the program that first introduced me to the company.

So the overall strategy for Insys is to: First, continue to optimize the commercial plans and strategies to grow Subsys; second, leverage the proprietary platform technologies into multiple products and disease areas that you will hear and learn about today; third, ensure that we develop and commercialize cannabidiol, which I believe can be a pipeline in a single molecule; and finally, we have the opportunity and the resources over a time to be acquisitive, although this is not part of our corporate strategy right now. We can be opportunistic, but we do not need to rely on external arrangements with all we have in our own house.

First, let's briefly talk about Subsys. It's the most prescribed product in the transmucosal immediate-release fentanyl class. We launched it in 2012. It has meaningful patient value differentiation from the other products in the class, with a 5-minute onset of action and a very simple process to administer that only take seconds. We promoted for a syndicated population of breakthrough pain in opioid tolerance cancer patients. The TIRF class is currently about \$700 million in sales and it is flattened basically, plus or minus 2% or 3% from this level over the past few years. With Subsys, we have stable market share, orange book listed patents expiring in the late 2020s, and it is my initial priority to ensure that we optimize the performance of Subsys in the near term through sales and marketing activities.

And I do think that there are interesting strategic commercial opportunities coming in the next 12 to 18 months that can stabilize and grow scripts for Subsys. But I'm very excited about the prospect of new clinical data being generated for Subsys in the coming months and years. In my experience, the best way to break out of an existing script performance trend is to bring out new clinical data and indications. And you'll hear about those studies from Santosh later on this morning.

So we have 2 major drug development platforms. First, the sublingual spray technology platform. This is a deceptively simple looking device and approach, but the beauty is in its simplicity. It has hidden complexity and technological know-how and IP behind it. Our formulators and research scientists understand the dynamics of bioavailability and how to get as much drug as possible concentrated into a small amount of liquid that then gets dispersed evenly across the mucosal area. Additionally, we have other experts to identify the appropriate accelerators allowing the drug to rapidly move into the bloodstream so that it can do its work.

We also have the manufacturing know-how to put all of these elements together into a regulatory GMP process. For this, we target many supportive care markets for the technology where ease-of-use and fast speed of clinical onset are valued by patients. And finally, we have a great deal of IP protection for both the device and the formulation.

Next, our pharmaceutical cannabinoid platform upon which the company was originally built. My new boss, Dr. Kapoor's previous venture Unimed, is a company that initially developed and commercialized Marinol, a soft gelatin capsule based THC product. But there were, and still are, drawbacks of Marinol, which is

generically known as dronabinol. Here our team has designed improvements in the way to synthesize cannabinoids, not only THC, but also the important and pharmaceutically active cannabidiol. We have the only active drug master file for pharmaceutical grade cannabidiol.

And we're fortunate to have many talented experts with a broad and long range of experiences within big pharma, small pharma, start-ups. And many of these folks have had actually the experience among all 3. Ramesh, our EVP of Scientific Affairs, has 40 years of experience, including AztraZeneca, Watson, Elicon and many others. Santosh is our Senior VP of Clinical Development, and you'll hear from him in a few moments.

We have Steve Sherman, who has not only worked in regulatory at Novartis, Abbott and Shire, but he's an ex-FDA guy who knows the in and outs of this fine government organization.

L.L. is our Senior VP of Manufacturing and Supply Chain. And he just joined us from years at Baxter. And you can see, we have a large group of experienced and capable experts in their respective fields.

Dr. Dan Tuck in Quality Control just joined the company a month ago. Lou Ferdan and I have been building out a medical science liaison team that I believe will help not only Subsys, but also other products. And Dr. Robert Brown joins us in Clinical Development as an oncologist with palliative care experience as well.

I should mention that Deborah Lee here was a colleague of mine at Lundbeck. We had a great epilepsy franchise their with Sabril for infantile spasms and Onfi for Lennox-Gastaut syndrome, and Deborah was in charge of the clinical trial development there. And I'm happy that she and I get to work again together here at Insys.

You'll see a few of these people in an upcoming video. Bryan Waltrip is very much involved and perhaps responsible for our manufacturing technical ability to develop our cannabinoids in the Round Rock Austin, Texas facility. Venkat, Ashok, they were instrumental in the development of Syndros and Subsys. And Brent, recently was hired from Merck to head up our inhaled THC program.

Ankara is in our sublingual formulation group. And finally, I would be remiss if I didn't highlight our most recent hire here, Sanga Emmanuel, who has great experience and has immediately been a great partner with me. He is our Chief Compliance Officer most recently from Biogen, but also spent years at a small growing company called Organogenesis. He also spent years at Nixon Peabody in their litigation practice. Sanga is here with us today.

We'd like to share a short video now showcasing our state-of-the-art facilities where these fine folks work. Let me roll the video for you.

[Presentation]

**Daniel Brennan**

*Chief Operating Officer and Executive Vice President*

So now let me switch to a high-level overview of the tremendous commercial opportunities that we have that our targeted platforms are addressing. We've already gone over Subsys, let me walk you through the other areas.

Starting with naloxone. Naloxone can be used to help address accidental drug overdose, oftentimes coming from opioids or heroine. Our program utilizes the sublingual spray technology and it has a fast track designation. There are 3 different approved forms of naloxone on the market with the Narcan injectable being the first approved in 1971, but recently NGO approved in 2014 and finally, Adept Pharma's Narcan nasal spray was approved this year for treating emergency opioid overdose. This is a small, but growing market. And while we don't expect this to be a significant contributor to top line growth, it will provide key benefits to patients, complement our suite of pain management products and solidify our reputation in the pain management space.

Buprenorphine. This can be used as an opioid analgesic in both acute and chronic pain. It's used extensively in Europe for pain and is one of the only few opioids that has the lower scheduled free classification by the DEA. Again, we believe this is an a optimal product for development as a sublingual

spray in both acute and chronic pain indications. The market had originally been dominated by buprenex, an injectable product by Reckitt, but Purdue and their Butrans Patch has since grown the market and dominated and moved it to over \$200 million in sales.

Of course, this has opened the door for a nice opportunity for Belbuca to launch. And quite honestly, we hope that Belbuca is successful in growing the market because we believe our formulation and delivery has potential for certain advantages over Belbuca.

By adding naloxone into the spray with buprenorphine, we have a great candidate to compete with Suboxone in the very large opioid dependence market. This market continues to grow as Reckitt now in the wire has successfully switched the market from tablets to their Suboxone film. This is a large and growing market with Suboxone garnering well over \$1 billion in annual sales.

Dronabinol, Syndros here for us at Insys, is an interesting opportunity. And this has been a product that's been available since the 1980s and now generic for years. But with the recent interest and craze in medical marijuana and physicians challenged in dosing and prescribing marijuana, this product has actually been growing in units without any promotion. We believe our formulation addresses limitations in Marinol. The current market is dominated by generics, with about 96% of the market sales coming from generics and about 4% going to the branded Marinol. At those primarily generic prices, this is still a \$150 million market. We hope to convert the market to Syndros with our improved patient valued features.

The call points are interesting because Marinol over the years has grown and with this recent medical marijuana interest, quite a bit of use is coming from the internal medicine community. But still 30% or more of its use are coming from oncologists and pain management specialists. And as I mentioned on Tuesday, as part of our brief presentation at a recent conference, much of the use of current Marinol is concentrated into a manageable group of physicians. So we'll be more deeply analyzing to prescribing targets and patterns in the coming weeks and months and developing that into our launch strategies.

Finally cannabidiol. This is a unique new chemical entity. And our pharmaceutical-grade cannabidiol is not derived from the marijuana plant. And therefore, we're not restricted to the manufacturing challenges or the political challenges as a result. In fact, we recently filed a Citizen's Petition to reclassify our cannabidiol formulation from Schedule I in order to more easily facilitate research for the physicians and ultimately, the patients. Our synthetic formulation of cannabidiol has no alcohol, no sesame oil and is 100% THC free. We have 6 orphan drug designations and we're initially focused on pediatric epilepsy as Santosh and others will discuss with you shortly.

I could go on and on about the market opportunity for this in epilepsy as I've spent the last 6 years at Lundbeck with 2 products, Sabril and Onfi that are both used in infantile spasms and Lennox-Gastaut syndrome. Needless to say, with these products out there, there is still a high unmet need. And there's high patient and caregiver demand for a cannabidiol for a medical marijuana-like product and treatment.

The graph on the sales here is a little bit misleading. The large growth that you see here on Ektar [ph] sales includes their sales for MS and other indications that we weren't able to parse out from IMS. Yet we do know that it is a large player in this market. And it is one that has significant downside that patients are trying to avoid by finding another good treatment. The same goes for Sabril.

So this would be a new call point, but one that is very familiar to me, and I look forward to remaining in the epilepsy space. And in fact, I plan on leaving this conference to go to Philadelphia for the American Epilepsy Society meeting to meet with our investigators as well as patient advocacy groups there.

So we have multiple opportunities, multiple shots on goal for the future just within these 2 platforms. I'm excited about the future here for Insys. We have Subsys, currently market leader in generating great value for the company and patients, and I'm excited about the new potential for new studies in the opioid naive patients.

We have the other sublingual spray technology opportunities in chronic and acute pain, opioid overdose rescue, and treating opioid addiction along with Suboxone. Then we have our cannabinoid platform, starting with the launch of Syndros next year. And the lifecycle management opportunities that Syndros

has that Santosh will share, including potential in agitation associated with Alzheimer's disease. And a very new and exciting inhaled delivery approach with our partner in Senzer.

And finally, we have the opportunity to enter into the epilepsy space with cannabidiol. And then branch out with this pipeline in a molecule into a variety of other areas that have good pilot data, given the interest and use of medical marijuana and cannabinoid -- cannabidiol oil in the academic setting.

So thank you for allowing me to share our robust opportunities with you. The rest of the morning is dedicated to a clinical review of the products and the diseases that they address.

Santosh, you're on.

### **Santosh Vetticaden**

Thank you, Dan. Good morning, everyone. I'm Santosh Vetticaden, Senior Vice President for Clinical Development at Insys. It's a pleasure for me to be here with you today to review our product pipeline. Dan provided you with the high-level overview of our pipeline. As you can see, we have multiple opportunities for growth. These represent the most advanced candidates in our pipeline.

As we go through the presentation, I will provide you greater details regarding each of these products in development. Take this high level slide for example. You see dronabinol oral solution on the top, there's a PDUFA date of April 1. And we plan to have it on the market in 2016.

We are developing our buprenorphine sublingual spray, both for acute pain and for chronic pain indications. And we plan on initiating these trials in 2016.

We are currently conducting bioavailability studies for the buprenorphine-naloxone combination sublingual spray. Another exciting opportunity that Dan mentioned is our naloxone sublingual spray, which is in development to antagonize opioid toxicity. Clearly, a significant unmet medical need.

Cannabidiol, or the cannabidiol is one of our platforms, we are focusing initially on the epilepsy indications, infantile spasms, Lennox-Gastaut syndrome and Dravet syndrome. We currently have an ongoing study in refractory pediatric epilepsy.

We have significant label expansion initiatives with regards to Subsys, both in the opioid naive population and the opioid experience population. Additionally, you will notice on this slide, we have a liposomal encapsulated paclitaxel for which we'll be conducting Phase II trials in multiple oncology indications.

We also have the ondansetron sublingual spray, which is currently in development.

Let me walk you through each of these products to give you a bit more flavor regarding our products in development, I will begin with Subsys. With regards to Subsys, we have numerous life cycle opportunities. You will notice that these range from the opioid naive setting to the cancer settings, bone marrow biopsy, emergency department, for example, Subsys could potentially be utilized where there's pain experienced in the shoulder reductions or patients presenting with sickle cell crisis. Clearly, we don't have the time to cover all of these today, but I'll walk you through a few of the representative life cycle opportunities.

So just to recap when you look at the indication expansion opportunity, for simplicity, we can bucket them into the opioid naive population indications and the opioid tolerant. Clearly today, we are not in the opioid naive setting. So our first responsibility we see is to characterize both the safety and the PK in the opioid naive population. With that in mind, we have completed a single-ascending dose study, evaluating both the PK and the safety of Subsys in an opioid naive population. Subsequent to that, we'll be conducting a multiple-ascending dose study, which we'll initiate in the first half of 2016. With that information in mind, we'll be in a position to embark on our indication-specific clinical trials in this population.

I mentioned we conducted a single-ascending dose study, we took doses of -- single doses of Subsys, 100 micrograms, 200, 400, 600 and 800 micrograms. The comparator we used was fentanyl IV 50 micrograms, because this is a dose that lot of pain physicians anesthesiologists, et cetera, are fairly comfortable using in patients that are opioid naive. We completed the study, Subsys was well tolerated and we hope to share the results with you in the first quarter of 2016.

As I mentioned, we are building on the study because physicians after they use 1 dose may feel the need to dose more frequently. Then the question that remains is, how frequently can I give this dose and at what intervals? So with that in mind, we're conducting a multiple-ascending dose study, looking at Subsys doses of 100, 200 and 400 micrograms given every 4 hours, every 2 hours, every hour and if tolerated, every 30 minutes. The comparator again will be IV fentanyl. So with this data in mind, as I mentioned, we can now embark on our life cycle opportunities in an opioid naive setting.

These represent 2 such opportunities, bone marrow biopsy. This is a procedure, as you can see from the slide where you essentially go through skin into the bone and aspirate the bone marrow, and perhaps even take a core biopsy. A painful procedure. 70% of the patients complain of pain, because typically this is done using local anesthetics. 35% report severe pain. What we hope to study is to give Subsys prior to the bone marrow procedure and evaluate a patient's pain through the course of the procedure and upon completion of the procedure.

Similarly, take patients with burns. There are about burn injuries that -- close to 500,000 that are admitted for bone injuries or get treatment for burn injuries, of which the hospitalized population is about 30,000 to 40,000. As you can tell by the picture of the denuded skin, that dressing changes in this population is extremely painful. Patients get premedicated for -- when prior to undergoing those dressing changes. This if they are in a hospital could involve IV fentanyl.

We'll be evaluating Subsys to see how well their pain can be managed by using Subsys as the treatment for their pain. This will be given during the -- prior to the dressing change, but also through the course of the dressing change. The endpoints that they'll be looking at are, of course, the pain rating scores because that's what they currently receive IV fentanyl for.

So these are 2 representative indications. Clearly, there are a number of other indications I highlighted earlier, and will be embarking on those files in 2016.

Let me now switch gears from Subsys to our second platform, which is the cannabinoid platform. In the cannabinoid platform, we have Syndros, which Dan mentioned earlier. And we've very excited about this data. This is our data from our 52-patient crossover bioavailability study. You'll notice in the slide, and some of you may have seen this slide before, that with our product, with Syndros, subjects -- 100% of the subjects achieved detectable plasma levels at 15 minutes compared to less than 25% of the subjects achieving detectable levels in 15 minutes with the reference or Marinol.

In addition, equally important is that we have low intra-patient variability with Syndros. The intra-patient variability with Syndros, 60% lower compared to the reference drug, Marinol.

We also looked at safety. Syndros was well tolerated and the safety profile was comparable to what is currently known for Marinol. What's exciting is that we have additional lifecycle opportunities for Syndros. We have new indications in planning. We are looking at using Syndros for the treatment of agitation in patients with Alzheimer's dementia.

Another indication that we're looking at is the treatment of anorexic ataxia and chemosensory impairment in cancer patients. Take Alzheimer's agitation, the significant economic and social burden in patients with Alzheimer's disease. There are no approved treatments currently. And as we know, an increased focus on the comorbidities in Alzheimer's disease.

Why do we think Syndros could be effective in this setting? This is one piece of data on the Y-axis, what's depicted is the CM -- CMAI score, which stands for the Cohen-Mansfield Agitation Inventory, a measure of the agitation experienced by patients with Alzheimer's. On the X-axis is the number of weeks of therapy. You'll notice that the agitation score declines over time when treated with dronabinol. Clearly, this is one piece of information, there's other pieces of the data and other literature available to support the use of dronabinol in patients with Alzheimer's dementia and agitation.

Our next drug in the cannabinoid platform is cannabidiol. We manufacture synthetic cannabidiol, which is the non-psychoactive component of cannabis. And we are leveraging this to address significant unmet medical needs.

On the left upper corner of the slide, you'll see that we are targeting epilepsy as one of our first indications. We have orphan drug designations that have been granted for Dravet syndrome, a rare catastrophic form of intractable epilepsy that begins in infancy. We will be studying cannabidiol in the treatment of epilepsy in Lennox-Gastaut syndrome, another severe form of epilepsy with a typical onset of 2 to 6 years of age.

In addition, we'll be looking at cannabidiol for the treatment of infantile spasms, also known as West syndrome, for which there are inadequate treatments currently available.

On the right-hand side, you'll see that we've been granted other orphan drug indications for glioblastoma multiforme, for pontine glioma, for pediatric schizophrenia. We have other potential indications they'll be considering and these include chemotherapy-induced peripheral neuropathy and PTSD or post traumatic stress disorder.

Since we have the synthetic cannabidiol, this has sparked a lot of interest in the research community. We have received requests to conduct, investigate the initiative trials in a variety of settings. Some of these we fund, and these include assessing CBD effects or cannabidiol effects in dependents such as cocaine, amphetamine and opioid.

We are also supporting trials of cannabidiol evaluating its effects on anxiety and analgesia.

So as you can see we have a broad development program with cannabidiol. And our initial focus will be the epilepsy setting.

So where are we with epilepsy program? As I indicated, we currently have an ongoing trial in pediatric refractory epilepsy. And we intend to conduct our Phase III trials in Dravet syndrome and Lennox-Gastaut syndrome in 2016. We are also initiating a trial in the infantile spasms in early 2016.

I also mentioned the additional indications we are considering, chemotherapy-induced peripheral neuropathy and post traumatic stress syndrome.

With regards to the ongoing trial, this is the Phase I/II trial to assess the PK and safety of multiple doses of our product, cannabidiol oral solution, in pediatric subjects with treatment resistant fissure disorders. We've completed the first cohort of 20 subjects at the dose of 10 milligrams per kilogram per day. The Safety Review Committee has looked at this data and has recommended that we advance to the next cohort. So fairly soon, we'll be dosing the 20 milligrams per kilogram per day dose.

Then indication I mentioned was infantile spasms. This is a new indication that we will be considering and developing. The graph on the right and Dr. Dlugosz will get into a bit more detail on this. It shows a normal EEG in an infant. The one at the bottom is the chaotic EEG that you see in an infant with infantile spasms, a very devastating disease. Orphan drug status was granted to us in July of 2015, and we'll be initiating a study with cannabidiol in this setting in the first half of 2016.

Thus far I've covered Subsys and our cannabidiol platform. Let me now turn to our sublingual spray product candidates. We have over 20 potential molecules being evaluated as sublingual spray product candidates. We prioritize this based on unmet medical need and the market need. Differentiation is clearly a key element of these sublingual products as we've demonstrated with Subsys. And we leverage to 505B2 regulatory pathway and our clinical regulatory and commercial experience from our Subsys development.

We have a thorough product development process for our sublingual spray candidates. In this 9-step process we carefully study all of the approved products for a molecule that we're considering. We thoroughly review the literature and the summary bases of approval of the approved products to learn from their development. From these approved products, we pick the appropriate reference listed drug or RLD. Based on this data, we assess, we conduct a limited proof-of-concept study in a limited number of subjects to assess how our spray compares to the reference listed drug, or the RLD. Based on the data from the proof-of-concept study, we fine tune our formulation to match the Cmax, AUC or both. We then submit to the FDA the data and plan or subsequent pivotal and additional studies that may be needed.

This is a pictorial view of that process. You'll notice on the left that in the idea stage, we are screening a large number of approved products as potential sublingual candidates. We screen these molecules in R&D based on a number of factors such as solubility, the need to utilize permeation in answers, taste masking if needed, to arrive at our new potential formulation candidates. As we develop formulations for these molecules, you'll notice in the middle of the slide, we utilize sophisticated in vitro and in vivo models for further screening. These may include artificial membranes or human skin models or in vivo animal models as appropriate. These methodologies then result in our short list of sublingual spray formulations, which can be carried forward into the clinic for our initial clinical proof-of-concept study. As I mentioned previously, based on the results of our proof-of-concept study, we fine tune the formulation and finalize the formulation, which we will then take forward into our pivotal clinical studies.

This systematic and thoughtful development process has successfully yielded our extensive portfolio of sublingual sprays in development, including buprenorphine, buprenorphine-naloxone combination, naloxone and a number of other products that are listed on that slide, which I will mention further in a few minutes.

For greater granularity, let me walk you through a few of these representative sublingual sprays. Buprenorphine is a very exciting sublingual spray. As Dan mentioned, it's a partial new agonist and so it differentiates from some of the other full new agonist that are currently available. The indications we're developing are both for acute pain and for chronic pain.

You can look at the development strategy in sort of 2 buckets, one is the acute pain development and the chronic pain development. In the chronic pain development is a bit more extensive and that involves studies in the opioid naive setting and the opioid experience populations.

For development in the acute pain setting, we intend to conduct a Phase III randomized double-blind, parallel group, placebo-controlled study evaluating our buprenorphine sublingual spray for the treatment of moderate to severe pain. The doses that we're considering are 0.5 milligrams 3x a day, 0.25 3x a day, 0.125 3x a day compared to placebo. The endpoints that we'll been looking at are the pain scores or the pain intensity difference, which is known as the SPID scores for 48 hours. The model that we are using is the post op pain [indiscernible] model, which is a well accepted model for developing pain products.

When it comes to developing in the chronic pain setting, the model that we use is the chronic lower back pain setting. There will be 2 studies, one in the opioid experience population and one in the opioid naive population. In the opioid experience population, we have in this setting we have a precedent, as Dan mentioned, Belbuca was approved and so it provides us a great deal of insight into the development pathways, the clinical trial study designs and a path to consider as we consider our own development.

So the study involves an open-label titration period of 8 weeks, followed by a randomization to various doses of our sublingual spray product. The doses of 1 milligram BID, 0.5 BID, 0.25 BID, 0.125 BID compared to placebo. The endpoint will be the pain assessments over a course of 12 weeks.

So this was in the opioid experience population. We have a companion trial in the opioid naive population. The doses, as you can see, are lower in the opioid naive population, but it's a fairly similar design.

Another sublingual spray in development is the buprenorphine-naloxone combination product. Currently, multiple agents are available. Dan shared the market opportunity here. And clearly, we see the advantages of our sublingual spray. The indications that we are pursuing would be the maintenance treatment of opioid dependents. And our development program includes bioavailability studies relative to the reference listed drug, dose proportionality studies, pH temperature study and a local tolerability study. The RLD, or the reference listed drug, would be the Suboxone film.

We currently have an ongoing bioavailability study for this product. The current study looks at the 2.2 milligrams of buprenorphine and 0.55 milligrams of naloxone sublingual spray compared to the reference listed drug, Suboxone, at 4 milligrams of buprenorphine and 1 milligram of naloxone. We'll be looking at bioavailability comparisons. This study is currently ongoing, and we'll be sharing the results with you in January of 2016. Subsequent to that study, we'll be conducting some of the other studies that I mentioned earlier.

Another sublingual spray product is naloxone. Naloxone sublingual spray is a significant opportunity. As you can see from this slide that the number of deaths due to overdose of opioids has dramatically increased from 2001 to 2013. It's currently estimated that there are over 14,000 deaths per year, the recent numbers are slightly higher, it's close to 16,000. So we believe developing a naloxone product that could potentially reverse this toxicity would be an extremely useful product to have, not only for patients, but also for caregivers and for first responders.

There's logic and support for placing these time-critical medications in the hands of nonmedical personnel. And this is currently being utilized by EMTs, law enforcement officers and even the general public for a number of state laws. Naloxone sublingual spray has the potential to address the ease of administration when compared to the currently available IM or IV products. In fact, first responders often take the IM and IV products, use an atomizer and utilize it as a nasal spray, they are patching it together, a product that is not currently approved. So we believe providing a tested sublingual spray would be of advantage for all of these folks that are currently using it.

With that in mind, our development path will be to compare our product against the currently available products. So we are studying our sublingual spray and naloxone sublingual spray 8 milligrams versus the currently available naloxone IV, 0.4 milligrams, or the IM, 0.4 milligrams. This study is currently ongoing, so we are well advanced in our development and will plan on sharing the results with you in January.

Once we have the results of those studies, we'll be reaching out to the FDA to discuss what a development path might look like leading to a potential NDA.

As I mentioned, we have 20-plus projects in the sublingual spray area. This is not a comprehensive slide, but this slide gives you a sense of the representative products that we are considering. So we'll notice that the formulation development is currently ongoing for hydromorphone, for epinephrine, diclofenac, ketorolac, sildenafil, ondansetron, rizatriptan, lorazepam and others.

We also have, as Dan mentioned, an inhaled platform and we're looking at inhaled delivery for both THC and cannabidiol, providing us another route to deliver these potentially important drugs that are part of our portfolio.

Another compound that we have in our portfolio targeted -- targets the oncology setting and is the Liposomal Encapsulated Paclitaxel Easy to Use. This product, or this -- the LEP-ETU was initially developed by Neopharm and was acquired by Insys. Preclinical studies that were conducted by Neopharm suggests superior activity and less toxicity in the preclinical studies. There have also been clinical studies conducted in advance cancer and metastatic breast cancer. So we are leveraging all of this information as we embark on our clinical studies.

The potential advantages of this product is that there's no cremophor needed, which as you know is associated with significant infusion-related reactions. It's easier to reconstitute. And based on the preclinical data that we have, it may have the potential for a reduced side effects and therefore, allow increased dosage.

With regards to clinical development we're looking at conducting Phase II studies in multiple settings in gastric cancer, in cervical cancer and in cholangiocarcinoma. These Phase II studies will begin in 2016 and subsequent development plan be dictated by the findings in these studies.

I've covered a lot of information. What I'd like to talk to takeaway is that we have a solid product platform with an extensive pipeline. It's diverse and we have multiple clinical programs that will be launched in 2016 across various product candidates. We feel confident about this because we have a management team that has a proven track record in the clinical and regulatory setting, as well as in commercializing our products.

That covers the portfolio review and I'll thank you for your attention. As you know, we have 3 honored and esteemed guests here, who -- external guests who will be speaking about various disease states and as it relates to our development portfolio.

So let me first introduce our first speaker today, which is Dr. Jeffrey Gudin. Dr. Gudin has been the Director of Pain Management and Palliative Care at Englewood Hospital and Medical Center. He's also a Clinical Instructor of Anesthesiology at the Icahn School of Medicine at Mount Sinai University School of Medicine.

Dr. Gudin is a nationally recognized leader in pain management. He completed his anesthesiology at Yale University School of Medicine, his fellowship at the Yale Center for Pain Management. In addition, Dr. Gudin is also trained in addiction medicine and has directed a substance abuse treatment center. He remains very active in teaching and research and has lectured internationally on a variety of topics on pain management, palliative care and addiction medicine. Dr. Gudin has dedicated his career to promoting education on pain management, and he has attended and presented at American Pain Society and various other venues.

Needless to say, he's an expert in pain management, and he also serves as a consultant to state medical boards on challenging cases as well as for the industry on novel analgesic development and risk management associated with opioids. So please join me in welcoming Dr. Gudin.

### **Jeff Gudin**

Thank you for your welcome. I didn't expect the applause. I always say it's always better to get it in the beginning because you'll never know if you'll get it in the end. So that was nice. Thank you.

So what the Insys folks have asked me to do today is something relatively simple, talk about what I do. This is -- I'm not sure about my colleagues, but relatively new to us the kind of business with the analyst side of the industry is what we call it, but my goal today is to just give you an idea of what it's like on the front lines of pain management. I direct a pain and palliative care unit over at Englewood Hospital just across the bridge, maybe 15 miles from here, yet an hour and 45 minutes in traffic last night to come in. So you all know if you're local, you know what I'm talking about.

So I thought what I might do is just kind of put this in the light of what's really the unmet need in pain management. If I think about what I do each and every day from a pain and a palliative care standpoint, I've probably told patients and their family members 10,000 times in my career, "Look, we have Tylenol. We have anti-inflammatory drugs, whether they're aspirin or steroids or NSAIDs, and we have opioids." We don't have a whole lot of choices for pain medicines. We have some muscle relaxants. And if you have nerve pain, neuropathic pain, of course, we use some of the Cymbalta or duloxetine-like medicines, the antidepressants, some of the anticonvulsants. But for basic nociceptive bone, muscle, joint, low back pain, we're pretty limited for our choices of analgesics. And if you think about putting those into categories of how do we choose which kind of drug for what kind of pain. Well, if you were to come into our emergency room with a kidney stone, and I came up to the bedside and said, "Hey, welcome to Englewood. Here we have a free of little IV Tylenol and a little IV ibuprofen." And your pain was 10 over 10, and you're sweating and screaming. You think to yourself, "Hey, that's not going to do anything for this level of pain." But we think something very similar in the clinical setting. The only category or class of medicines that works for severe pain are the opioids. And we're not going to get into today, even though I wish we could, the whole new recommendations for lowering opioid-dosing guidelines and things that the government in certain states have come out with. There's a big pushback from some of my colleagues as to limiting dosing of opioids, knowing that as of now, they're the only class of medicine that works for severe pain. What we do have to learn is how to use them more safely and more appropriately. So I put on my list here for the unmet needs. We certainly could use newer drugs, and I'll mention in a few minutes what some of those in the pipeline are to improve efficacy. But along those lines, we have Santos Benson [ph] the recent number of 16,000 deaths a year related to opioids. If any know the number of deaths per year related to NSAIDs, 16,000, right? That's just an ER study of people who developed GI bleeding and died that admission where they blame the NSAID for the GI bleed. But nobody talks about a prescription or prescription NSAID drug crisis with an equal number of death. And acetaminophen, the #1 cause of liver failure in the country, #1 cause of liver transplantation. Nobody talks about that as being a lethal or a dangerous drug. So we clearly need drugs with better safety.

Unless you've been living in a closet, you recognize that we have a whole new kind of realm of opioids coming with abuse-deterrent formulations. Notice they're called deterrent. They're not resistant because

where there's a will, there's a way. People will do whatever they can to get controlled substances, including oral overconsumption, just taking more pills than they're supposed to. I evaluated a technology recently, which may be able to hamper that. So the more you take, the less you get. So some neat things on the horizon from abuse deterrent.

And you heard a bit this morning about cannabinoids. I'll speak just briefly about that because one of my colleagues is going to speak more about it in his field, but I'll talk about it related to pain. You've seen some of the publicly held companies that have nerve growth factor inhibitors on the horizon, which I hear are very promising, some newer ion channel modulators, and clearly, next-generation molecules of drugs that we already have. So it's kind of where we are in the pain space.

But I just want to remind you all that medication management of pain is just one tool in the toolbox, and opioids are just one small portion of medication management. When you come to the pain center, you get things like behavioral intervention, complementary therapies. We do all the spinal and epidurals and implanted analgesic devices if patients make it there. We offer all of the adjuvants and the non-opioid therapies. So often times, people are critical of us prescribing these controlled substances, but they don't recognize they're just one small portion of the patient's overall treatment regimen.

And when we do prescribe opioids, this concept was introduced probably 10 or 15 years ago by 2 colleagues of mine. We take these universal precautions. Well, how do you know who is at risk for overdose, abuse, misuse and diversion? Well, we don't really know who is at risk. We have some factors that we consider. So we treat everybody like there's some kind of risk. We now have prescription drug monitoring programs. You've probably heard about urine drug testing companies that every patient gets put through the same risk management strategies for making sure that they're "behaving" or using their medications appropriately. We've learned over the years how to discuss with our patients, not just the risks, but also the benefits of taking controlled substances like opioids, and we have them signed what's called an opioid treatment agreement or a medication treatment agreement. Almost every pain management center in the country has one. It's a one page written outline of rules and responsibilities associated with taking controlled substances.

The most critical times for opioids are initiation, especially for opioid-naïve patients. That's when you could experience the greatest degree of side effect, changing the dose titration and with discontinuation of therapy. And clearly, we won't have time to talk about today, but there is a role in the pain management space for high-dose opioid therapy. That's why many of the pain societies disagree with these arbitrary dosing guidelines. We have genetic evidence that some of us are poor responders to opioids. If you are poor responder to opioids, it's going to take you a higher dose of opioids than it would take someone like your neighbor, who is a high responder to opioid. We have that data. So we can't just arbitrarily set these lower dosage limits. And sometimes, patients genetically respond to one class of drug, where they haven't responded to others. So some are morphine responders, some are oxycodone responders, some are fentanyl responders, which is why you'll see my colleagues do something we call opioid rotation from one drug to another to see if a different type of opioid might be beneficial for that patient.

And there's one thing I teach the primary care clinicians, is that you have to know how to get a patient from the immediate-release opioids, like hydrocodone, you know Vicodin or Lortab products, or oxycodone like Percocet products, over to other immediate-release agents if one isn't working. Or how to get them if they're appropriate over to long-acting medication, the all-day long medicines, whether it's a transdermal fentanyl patch or controlled-release oxycodone or even methadone, they need to be familiar with how to convert from the immediate release to the extended release. And now within the last decade or even more, the addition of the TIRF products. How do complement your opioid regimen using the TIRF products if patients have what we call breakthrough pain.

So this is really basic or the different kind of opioids, well, of course, they are. I just mentioned the 3 of them. There's immediate-release opioids, or what we call short-acting opioids. They used to be called -- and I guess, they still are kind of termed IR, immediate release. But as you know, if you're familiar with Subsys, the medicines like oxycodone and morphine immediate-release tablets are anything but immediate release. 30 to 60 minutes for these drugs to have peak effect. If you're a patient in pain,

especially a patient that gets hit with a lightning bolt of pain that you need release now, you don't want to wait 30 to 60 minutes for your medicines to reach their maximum effect.

We have the long-acting opioids. I mentioned a few of them before. A lot of people ask, "How do you know who is a candidate for the long-acting opioids?" Well, for me it's been relatively simple. I talk to patients, and I say tell me about your pain. If you have pain all-day long, then you are a candidate for all-day long analgesic. If you only have 1 or 2 episodes of pain a day, I'm probably not going to put you on a 12-, 24-, 36-, 72-hour or 7-day preparation. But if you fall into this category of patients who have an all-day long type of pain, but on top of your all-day long pain, you get hit with these flares, these intermittent paresthesias, these rapid bouts of uncontrollable pain, what we call breakthrough pain, then you are an optimal candidate to get what we call the rapid-onset opioids. Used to be called the ROOs, what you guys know of as the TIRFs, the transmucosal immediate-release fentanyl products. This is used for what call breakthrough pain. So we indeed have 3 classes of analgesics: Short acting, which sometimes called immediate release, but again aren't immediate release; controlled release or long acting, that's also for the patients that have pain all day long; and then the TIRF products for that rapid, unpredictable type of pain.

When you look at the literature for cancer patients, breakthrough pain, obviously, varies from patient to patient, but there are some commonalities. The patients rated usually a severe or excruciating. This is not mild-to-moderate pain. Breakthrough pain is severe or excruciating. You can imagine, it stops them in their tracks. It affects their function. They say it comes on in minutes. This is not your typical osteoarthritis flare where as the day goes on, their knee hurts a little bit more. This is within minutes, they're at severe or excruciating pain. It usually lasts under an hour. They say it happens anywhere from 1 time a day to 7 or more times a day. So 4 was that average number that we usually talk about. And there's 2 types of breakthrough pain that patients talk about, predictable, "Hey, doc. Look, if I'm going to drive to work and I get stuck in traffic and I'm sitting for 45 minutes, I get out of the car and my compression fracture or my pain is just -- it's terrible." They could predict after a certain activity that their pain is bad. That's the easier form of breakthrough pain for us to treat.

The more difficult form is the unpredictable. Hey, I could just be sitting doing nothing and the next thing you know, my body turns on the pain and I go 0 to 10 in 60 seconds, and my pain is just terrible. I need something that works fast to control my pain. So you all know the landscape out there of the TIRF products. You see Subsys and you saw an example or a picture of it before. It's the fentanyl sublingual spray. The original version, probably 10 or 15 years ago, the Cephalon product. It was ACTIQ, also known as OTFC, oral transmucosal fentanyl citrate, and then a number of competitors that you see on the screen a variety of buccal or sublingual tablets, a nasal spray and a soluble film.

The current indication for Subsys is limited to breakthrough cancer pain in patients who are opioid tolerant. That is the current indication. I want to introduce you to one of my patients in just a second, just not live on screen and tell you about him, and let you see for yourself how sometimes clinicians look at the regulatory side of what pharmaceutical industry has to go through and think how illogical it could be. What difference does it make to me whether your compression fracture is from cancer or osteoporosis? You think the pain is any different? What difference does it make if your trigeminal neuralgia has to do with getting chemo or just getting trigeminal neuralgia for some other reason. You think the pain is any different? So it's hard for us as clinicians sometimes to know that there's a recommended regulatory or legal or FDA path of, hey, you can only use this in cancer pain. And I do a fair amount of consulting for New Jersey state medical board, and they raised a red flag when they see doctors writing these TIRF products for noncancer pain. And I said, "Look, you got to look at the patient scenario." There are times where patients need a rapid onset of pain relief. That doesn't matter what their underlying disease is.

I think, you heard Santos [ph] talked about before that Insys is looking at these acute pain or noncancer pain indications. And he asked me to think of a couple, and I thought it's painful procedures, just what my colleagues do to patients, nerve blocks with herniated discs and radiofrequency where they burn nerves and neuroablative procedures. We do painful things to patients, who often times we make suffer. When we're not in the place, where we can have nursing and anesthesia and IV. There are places where we could use a noninvasive sublingual spray to give people analgesics. You heard a little bit about their dose studies.

So I'm almost done, but I just want to tell you, I had a case yesterday that I could have presented, but this guy is a good one. Worked his whole life, builds a very large trucking business and he gives it to his kids. He's in his 70s. And he's made -- to say millions is an understatement. The guy did very well for himself. And he wants to hunt rams, so he does these helicopter hunting trips out west. All right, listen, give the guy credit. He worked his whole life and this is what he wants to do. He gets this, basically, undiagnosable pain syndrome in the back of his leg, almost behind his calf but behind the lateral aspect of his fibula. And he said, "Doc, it drops me to my knees. I've been to 3 neurologists in the city. I let 2 different orthopedists go in and do surgeries when both of them thought they'll be able to fix me, and my pain is as bad as ever. I've tried every medicine. You're the third pain doctor I've been to." And he showed me in the office. He pushes on this one spot on his leg, and it brings tears to his eyes. So listen, I can't walk. And after a couple of visits and we try some little nerve blocks and things like that, he looked at me, and this is no joke, he told me he sits at night and thinks about cutting his leg off. Not going to a doctor to have a doctor cut his leg off. That when he gets hit with these bouts of pain, that he physically wants to cut his leg off, and he's not kidding. So when you look from a clinician's standpoint, if this guy has a bout of pain that comes on in 60 seconds, 90 seconds, 5 minutes even, am I going to give him a therapy that takes 30 to 60 minutes to work. By the time it works, his pain is gone. These are short bouts of pain. He's an ideal, if you were to ask me, an off-label candidate for a medicine like the TIRF. Of course, he deserves all the possible treatment options.

I've seen my orthopedic colleague set fractures in their office and people scream. They say it was the worst experience of their life. Why do people have to suffer for short-term painful procedures if we have medicines that work rapid onset. Now they have to be safe. You have to study them in healthy volunteers to show that 25 or 50 micrograms or 100 micrograms even is safe in that population. But if we have that data, there may be a place for these medicines in noncancer pain. Think about GYN, ENT, neurology procedures, I mean, haven't had any snipping done at the urologist, but I understand it's not the most pleasant of procedures that you can have done. I hear couple of snickers out there, but I don't want to know who's laughing. One of the biggest issues that I've seen with the TIRFs, and you could find this data in the literature, is that even when the doctors sign onto the concept, "Hey, you know what doc, that makes a lot of sense." I do hear patients tell me that they have this pain that comes on really quick. I want to use the TIRFs. They write 100 micrograms, 200 micrograms, 400 micrograms, but when it doesn't work, they stop. They don't recognize that this is just a stepladder titration approach to get to the effective doses, which if you look what I circled here, more than 50% of the dose is coming the higher half of the dosage strength. You need to get these patients to the right doses. That's what we teach clinicians. But in doing so, there has to be a focus on safety. You all know about the REMS program. That's available for long-acting or extended-release opioids. There's obviously a mandatory -- but that's not mandatory, there's a mandatory REMS for this class of medicines for the TIRFs.

The other point that I'll make is I've seen this doctor say, "Well, the fentanyl products would have too much of a chance of abuse. I just don't want to use these products because of the risk of abuse." I can tell you that I am board certified on addiction medicine. I probably have 30 or 40. I call them kids at any one time in my Suboxone practice, never have I once heard any of them use the word, fentanyl. It's always oxycodone, usually immediate-release oxycodone. Sometimes hydrocodone, but usually, oxycodone. The way that doctors use these fentanyl products, the TIRFs, that patients have to fail all of the other things that we've given them. And by the time they get to a TIRF, they've already shown responsibility with Dilaudid hydromorphone, oxycodone, other fentanyl products, other controlled substances. This is not usually the first choice of opioids for patients. So in my experience, I haven't seen any data published, but in my experience, the TIRF products are not characteristically sought after by abusers. It's a comment that -- a question I get asked often. So my colleagues, the doctors, are in a key position to balance the benefits of opioids against the risks. And the risks are not just constipation and sedation and nausea, but also things like addiction and unintentional overdose and death, you heard the numbers before.

So the most important thing I do on a day-to-day basis for patients on opioids is decide whether they keep their therapy going or not. I have to be responsible. If you have good pain control, if you tell me that you're able to work around your house or function better, now you can go to church and take the kids to school and go off to dinner and you have a good side effect profile and you're compliant, you have medicines left over every month, but not only you're not running out, you have medicines left over. You're

a great candidate for opioids as long as I do your prescription drug monitoring database and you're not getting from multiple doctors. And I test your urine or your saliva every once in a while, and there's no cocaine or marijuana or illicit drugs, and the drugs that I'm giving you are in your system. And as long as I don't see any external stressors, you're a good candidate. But if you don't get pain reduction, and all you do is sleep all day on your medicines, or you can't move your bowels or you have unacceptable side effects, then we taper you off your opioids. We don't abandon your therapy, we go to all of those other treatments that we talked about.

I don't know how I got there, but I'm on the Pri-Med education circuit. Pri-Med is probably the largest primary care education provider out there. The Pri-Med opioid safe use course I did in Boston, had 4,000 doctors in the audience, my largest audience I think ever. I did one in Baltimore recently -- in Pennsylvania recently. In Philadelphia, I have one coming up in Baltimore. Doctors want to use these medicines more safely. They recognized they don't have other good choices for severe pain. They're hungry for education regarding safe use of opioids.

And before I finish, I just want to kind of expand upon something you've heard already from Dan and Santos [ph], the pipeline of technologies -- spray technologies that Insys have. Being a pain and addiction specialist, I use all 3 of the products that you see here on the screen. So I thought it might be a good idea to just give you my quick input on each of those. Buprenorphine is a Schedule III. You know they moved hydrocodone to Schedule II, so this is one of the few Schedule IIIs that we have available to us. That means we can call it in and we could put refills on the prescriptions. That's -- convenience is something that's very important to clinicians. My experience in using buprenorphine for pain and addiction is tolerable and is effective. It's got a lower reward potential. So we think there's less abuse, even though there has been reports of diversion of buprenorphine on the street. There is also some evidence in literature that has a different respiratory depression profile than pure mu-opioid agonist, which may, I say may mean less fatal adverse outcomes. You heard before it has a dual role in both the addiction space and the pain space. It is not a new molecule. It's got some novel properties. It's just not a partial mu-opioid agonist. It's also a partial kappa antagonist as well. And as I hear each and every day from my primary care doctor, we're not writing for opioids anymore, because they just can't stand the politics of it and the scrutiny of it. It might be the perfect climate to get doctors to move from the morphine-based products for their chronic pain over to buprenorphine-like medications.

Buprenorphine with naloxone, you're very familiar with Suboxone. And if you follow the space, you've certainly seen Bunavail and Zubsolv as well. To me being an addiction doctor, I could tell you that Suboxone revolutionized the way we treat addiction. Methadone was what we did for 20 years before or forever before we had Suboxone. The naloxone is added to the Suboxone to deter one thing, IV abuse. There's not appreciable absorption of the naloxone through the GI tract. We do this for detox. And when I first signed up to write Suboxone or to get the waiver to be able to prescribe Suboxone, my line of thinking was, I was just going to detox everybody. But now I have a fair number of people in my practice who are on maintenance, something I never thought I would do, but believe it or not, these patients with the disease of addiction, being on maintenance, keeps them straight. Even really low doses of Suboxone or buprenorphine keeps them on the straight and narrow and keeps them away from illicit drugs, makes them better people, keeps them employed. So I do have a fair number of patients on maintenance. And as you know, primary care docs can apply and get the waiver from the government. I don't know what percentage, but I'd assume it's a significant portion of Suboxone is now being prescribed by primary care physicians.

You heard about naloxone spray, you heard about the number of opioid-related deaths in the country, I think it's like 46 deaths a day or 2 deaths a minute or something like that related to opioids. I applaud the government's effort. This has been the SAMHSA overdose toolkit, AMA, American Society of Addiction Medicine for a while now. It's a -- if you have a patient that has an opioid-use disorder, they are perfect candidate for a take-home naloxone product. This might be the future of every patient that gets an opioid to have at home a rescue in case of an opioid-related emergency. There are a lot of issues that go along with this. And I'm glad to see that legally they've gotten around it. This is a prescription that's administered by somebody other than the patient, because usually the patient is unresponsive. So who do we write this for? Do we write it for the significant other? Do we write it for the patient? How do they administer it? But they're working out all of those logistical issues. Obviously, you heard there are other

preparations of naloxone in development. We currently have Evzio, which is the auto-injector. There's a nasal form recently approved. And clearly, if we had a sublingual spray that would complement that space. I think, this is my last slide.

My colleague is going to talk more about cannabinoids in this space. You heard here this morning something that I'm very excited about, the future of cannabinoids. I'll tell you that I was anti-cannabinoid. I'm certainly anti-recreational marijuana. I don't want more mentally impaired people driving on the roads than are already out there. I remember looking at a literature review, probably, a decade ago that said from a pain standpoint, marijuana-like products were about as efficacious as Tylenol #3, Tylenol with codeine. So I haven't been a fan. And I basically have kept my ears closed over the years where so many patients have told me. Doc, look, I know you caught me smoking, because you tested my urine, but if I just smoke a little pot, first of all, I don't run out of your pills. Second of all, let me tell you, I can take 5 of your OxyContin or whatever they say, it doesn't work the same way. My burning stops, I could sleep at night, my anxiety goes down. There's something about the cannabinoids that have an effect that I can't provide to patients. And now that it's medical marijuana program has been authorized in New Jersey, we probably have 50 or 60 patients already that have gone through, mostly cancer patients, and about half of them come back and have really changed my philosophy on this. There is something about cannabinoids that we can't provide them medicinally. And I'll tell you even from a Marinol standpoint. Because forever I would try them on Marinol as a precursor to cannabinoid. There's something that Marinol doesn't have that's the pure molecule have. Now unfortunately, the pure molecule has the side effects as well. So what I'm hoping to see is that Insys tastes pure cannabidiol through clinical trials and tells us as clinicians, hey, here is the dose that you need for pain, anorexia, nausea, whatever the indication might be. Here is how you use it. You know what happens now? You give a patient a waiver or a letter to go to dispensary. They meet some kid in the dispensary. My patients told with this. And the kid says, first patient, I ever sent to the dispensary, they called me like, "Doc, you didn't put on here an amount." I'm like, "An amount? What are my choices?" And they said like, 1, 2 or 3 ounces, or 1 ounce, 1.5 ounce or 2 ounces. I'm like, well, how does it come. And kid says, "It's pot." I'm like, well, I guess, I remember in college, but I don't know, what do you suggest? He's like, "Well, I can't tell you." So I went to the youngest girl in my office, and I said, "Listen, I got the state dispensary on the phone, how much pot do I prescribe, right?" And she's like, "I don't know. What are you asking me for?" So I said to the guy, "Give him an ounce and let's see what happens." One of the patients came back and said to me, the kid at the dispensary said, "Listen, tell me what you want. You want to be sleepy? You want to be awake? You have nausea. You have pain." I mean, you have some nonmedical personnel trying to help patients with medical decisions using an archaic plant. That's not the way medicines suppose to work. The way medicine is supposed to work is it supposed to extract the active compound, you're supposed to test it in clinical trials and you're supposed to tell us the dose and the side effects and the safety and how much to prescribe and dispense. So I like the concept of using cannabinoids in the pain space, but I think, it needs to come from industry and not necessarily from recreational or medicinal society laws.

I will stop there, and we're going to have a panel session for questions. Thank you, guys, for listening.

### **Unknown Executive**

So we're going to take a 10-minute break and then reconvene for the remaining panel speakers and then have our Q&A session at the end. Thank you.

[Break]

### **Unknown Executive**

All right. Glad to get everybody back in and get started. So we continue our distinguished speaker presentations with Dr. Douglas Brust. Dr. Brust is Chief of the Medical Staff at the Lee Memorial Health System in Fort Myers, Florida. He is an infectious disease expert and Medical Director of the HIV program. He has previously served as the Assistant Professor of Clinical Medicine and Infectious Disease Program Director at Columbia University College of Physicians and Surgeons. Dr. Brust has also served as a staff physician at the National Institute of Allergy and Infectious Disease at the NIH. He has trained at a variety of places, including the NIH, Johns Hopkins, University of Maryland, GW and has the tenures at the University of California outpatient HIV ward. Dr. Brust is a leading authority on HIV and AIDS, and is a

recipient of numerous awards and honors. I don't know where he finds spare time, but in his spare time, he is a journal reviewer for hepatology, journal of infectious disease. He is a reviewer and contributor to the Harrison's Principles of Internal Medicine, which is a textbook that all of us recognize. He is a grant reviewer for the National Cancer Institute of Canada in a volunteer position at Washington D.C. clinic. It's my pleasure to introduce Dr. Brust as a speaker today.

### **Douglas Glenn Brust**

Like my prior colleague, I've never done a talk like this before. So it will be fun to let you guys know exactly what I do during the day and as much as we're going to talk about. As John has introduced me, he said I was a chief C expert, I am not. I'm -- with a kind introduction, but I'm an HIV expert. And it's pretty appropriate that we're talking about HIV today. If you guys read The New York Times yesterday, it was actually editorial, just to remind that HIV has not gone away and that there is an article by Tom Friedman, who when I was here at Columbia, was our -- he's now the Director of the CDC, but was our Director of our Department of Health here in New York City Health Commissioner, and we worked tirelessly with him over years regarding HIV here in the New York City area. I'm a New Yorker, but I live in Florida now, and I'm glad to be back.

So I'm going to start talking about some patients, and how I really got involved in this. 35 years ago, this month, I'm looking out in the audience, who is probably older than some of you people are, but my best friend walked into my room at Cornell when I was a freshman and she had a fever, a rash, swollen glands, night sweats, we were having finals, and she was sick and got hospitalized. We didn't know at the time, but she had just met up with a lacrosse player at Cornell and had sex with him about 4 weeks before, and she was actively seroconverting to HIV. And she has seroconversion disease. And 6 months later, buried in the MMWR, which is the publication of the CDC in 1981, was the first publication of gay men in Los Angeles that had pneumocystis. And this was the first report that something was going on. And actually, it was picked up by a clerical worker because the drug used to treat pneumocystis, pentamidine, has to be obtained from the CDC. And it was a very rare type of disease to have. And this clerical worker noted that they were getting too many requests for pentamidine to treat pneumocystis, and that is how it sort of alerted the system that something was going on.

By the mid-1980s, Nancy [ph] was suffering from an HIV-associated wasting syndrome. It was very common. And what I want to do with this talk is compare and contrast what happened before and what is happening now with HIV and weight loss. Her weight had gone from 128 pounds, just down to 110 in just about a year. This is probably from uncontrolled HIV replication. Her infectious disease doctor started her on Marinol. Infectious disease doctors got very early in the game when Marinol got approved, got involved, because it had an indication for HIV wasting syndrome or HIV-related weight loss. It's an oral cannabinoid that has been recently approved for HIV-associated weight loss. So that was back in 1985. Her appetite improved and her weight increased. In 1987, she got started on AZT, which was only FDA-approved antiretroviral medication at the time. The AZT trials were conducted at University of Miami by [indiscernible] officials. It was a placebo-controlled trial where one group had AZT, which was taken off the shelf and actually the inventor of AZT never had it patented it and never made a dime of it for himself. And in a randomized trial, it was an incredible improvement in mortality, so much so that the Data and Safety Monitoring Board stopped the trial, which they -- if they had let it go on the 48 weeks, in all likelihood, there would have been no improvement in mortality just using one medication as we know. Now we have to treat with multiple medications.

At that time, the [indiscernible] dose was more than 2x of what we prescribe and is associated with severe anemia, nausea, vomiting and weight loss. Again, she needs to use Marinol to come back some of these for side effect. Since unfortunately, she died in 1994. I was in New York when she died. It was 2 years before the real advent of protease inhibitors, which really revolutionized how we treat HIV. As you can see on this pictorial, the time line of approval of new meds is incredible. In 1987, we have the approval of AZT. And most recently, we have approval of [indiscernible] as a single tablet. But there are subsequent and just actually in November, approval of multi-agent, single-dose tablets. So that in this day and age, if you're infected with HIV and you go to your doctor, you get 1 pill once a day compared to when I was -- had hair, we used to get patients up to 17 pills at a time, maybe 5 times a day.

Unfortunately, however, though, HIV has not gone away. So it hasn't been eliminated. And this is the point of The New York Times, a piece editorial and also a piece by Tom Friedman. Despite all the advances and massive public health efforts, the rate of HIV infections remained relatively constant over the past 2 decades and approximately for 50,000 cases.

This -- I want to show you, and Tom actually said in the paper yesterday that the most recent data were 45,000. Look at the top blue line here, and this is an over time. This is 1980, but this is the most recent available data. It was 2010 in this Washington Post article. And you can see here that this is the total incidents, the number of new cases per year has stayed flat over the past 2 decades and the most recent as I said was 45,000. And so that averages was about 50,000 a year. So there are cases that are occurring. This is in the United States, and worldwide, there are approximately 36 million cases. The CDC, once in a while and a bunch of other groups also wanted to know why, and it's generated by people who do not know that they're infected. So what happens is we have approximately 1.2 million people in the United States that we estimate have HIV. Only 82% of those people actually know they have HIV. Only 66% are actually in care and that means they've gone to the doctor at least once. Only 37% stayed in care, going to the doctor at least twice a year. 33% of them are actually prescribed antiretrovirals. And of those, the ultimate goal for us in HIV is if you have the buyers who want to complete the suppression and turn off this replication by using antiretrovirals, approximately 25% of people in the United States are actually suppressed at this point. So we have people that they don't know that they have HIV, and they are the ones that are actually causing most of the infections. So people that are unaware, which is about 25% of the people who are unaware, are responsible approximately for 45% of the new infections. The idea being that if you knew your HIV status, you would act responsibly, and you would not try to pass it on to someone. The other major thing that we're learning now is that treatment of HIV actually is used to prevent transmission. People that are treated successfully with antiretrovirals do not transmit virus even if they have unsafe sex. The most recent data that's come out on that, I've looked at partner studies with 4,000 couples, 1 was positive, 1 was negative. Over 4 years, the original data just released is 30,000 acts of sex, and there was no transmissions, 0, as long as the person that has HIV is taking their meds and suppresses their virus. Unfortunately, however, HIV is here to stay, and given that our life expectancy is now almost equal, given the new medications for that -- for a person of HIV negative and that we have this rate of new infection, the total number of cases still continues to grow. And with the graying, or the balding I'd like to say of HIV, our patients are getting older. Now nearly half of the patients are over at age 50 compared to -- pitting a young person disease early in the epidemic. And with that brain, people are having many more medications in addition to their HIV medications simultaneously.

So after learning my -- how Nancy [ph], I've been dedicated to my entire profession to caring people with HIV. I head up a Ryan White Clinic and I care for over 1,200 people in South Florida. And despite a significant advances we have in treating HIV, weight loss in the HIV population is common and a very frequent complaint in the clinic on a daily basis. And then an example to contrast what happened with Nancy [ph], an example what we're seeing today, is very typical, and this is MB [ph]. She's 61 years old and she was infected early in the day and she was referred to me by her -- another infectious disease doctor who doesn't treat HIV, for chronic nausea and resulting weight loss. And her weight had gone from 120 pounds down to 92. Similar to Nancy [ph] early in the day, she had a number of opportunistic infections and had been really sick using AZT. But now in this area, she only takes 2 pills to control her HIV, which is perfectly controlled, but then she has other problems that people have when they're 61. And also maybe associated -- many of them are associated with these drugs, old drugs or new HIV drugs that we have or HIV itself, but she has diabetes, hypertension, hypercholesterolemia, and she takes an additional 13 drugs on top of those 2. Because of the complex regimen, she had resulted in weight loss, and I initiated our Marinol therapy. At 1-month follow-up, she reported her weight loss has improved, but the efficacy of the Marinol was very variable. Sometimes, the small tablet that we start people on, the 2.5-milligram tablet, gave her an appetite in 30 to 60 minutes. But in another day, that had no impact at all. And she has to titrate off to go to 5 or 10 milligrams -- excuse me, or 7.5 milligrams on occasion. When she would go up, she would get more of the side effects and have -- she'll get the munchies, but she'd feel high.

Additionally, she was not keeping the Marinol refrigerated, because she was at work, unlike with many of the other HIV medicines in the early day, it has to be refrigerated. And she doesn't want her colleagues to

know that she had HIV. After about 6 months of seeing her and continuing with her dosing schedule, she bought a cooler to take it to work. Her nausea was significantly controlled. She was able to reliably take all her medicine, and she had gained 15 pounds. So there's extremely limited amount of data are available to guide clinicians for treatment of weight loss and HIV. And the current are highly effective and simpler and less toxic in antiretroviral therapy.

This last piece that I talked you about, it clearly underscores the promise of limitations of Marinol when we use to treat HIV-associated weight loss. The limitations are slow and variable release from the sesame seed oil, poor drug absorption, delayed onset of action and patient-to-patient variability and efficacy inside [indiscernible]. It also has to be kept cool. Despite the improvements in treatment of HIV, weight loss and nausea remained a common clinical problem. The nature of nausea and weight loss seen today differs from early days when treatment was extremely toxic. But with the aging of our HIV population, they are taking this -- had resulted in ever increasing need for more medications to treat their complexity of co-morbidities and resulting in residents that are clinically associated with gastrointestinal complaints including nausea, anorexia and weight loss. What we need to do in HIV doctors and ID doctors have been using the cannabinoid, Marinol, very forever, because the only thing that we had is to continue to rely on Marinol to treat weight loss and additional data are necessary to better understand the use of cannabinoids in the modern HIV treatment. Thank you.

### **Unknown Executive**

Thank you, Dr. Brust. Our final distinguished speaker this morning is Dr. Dennis Dlugos, Professor of Neurology and Pediatrics at the Perelman School of Medicine at the University of Pennsylvania. He is also the Director of the Pediatric Regional Epilepsy Program at the Children's Hospital of Philadelphia, also known as CHOP. Dr. Dlugos is an expert in the field of epilepsy, where he reporting in his -- we are considering cannabidiol and embark currently in one ongoing trial in that space. He received his MD from Columbia University College of Physicians and Surgeons in New York and went to complete his internship in pediatrics at the National Navy Medical Center in Bethesda, Maryland. He completed his residency in pediatrics at Thomas Jefferson in Philadelphia, and at the Alfred I. duPont Institute in Wilmington, Delaware. Dr. Dlugos also completed a residency in neurology and child neurology at the University of Pennsylvania Medical Center, and his fellowship in epilepsy in clinical neurophysiology also at CHOP. He is a member of the American Epilepsy Society. He serves as the Chairperson of the education and professional development committee. He also serves as the Vice President of the Epilepsy Study Consortium, which is dedicated to improving the quality of epilepsy clinical trials.

As you can imagine, his clinical research interest include epilepsy genetics, pharmacogenetics, clinical trials, epilepsy surgery, EEG monitoring, all those related to treatment of patients with epilepsy. He is well -- in a very prolific and very published author, and he's authored numerous articles in Neurology, Annals of Neurology, Lancet New England Journal Medicine many other journals. He's a very active researcher and has been NIH funded since 2001. And he is very involved in mentoring our future epileptologists and pediatric epilepsy fellows, and of course, he lectures extensively throughout U.S., the Europe and Asia. So we're very honored to have him today to share his insights. Please join me in welcoming Dr. Dlugos.

### **Dennis J. Dlugos**

Thank you very much. I'm going to continue the theme of talking about unmet medical needs this time with a focus on pediatric epilepsy. So we'll do this by first giving an overview about what epilepsy is. Part of the problem with the word epilepsy is it means so many things, it means nothing. So we have to dive a little bit into the details of how epileptic seizures are classified, then we'll focus on 3 specific pediatric epilepsy types: infantile spasms, Dravet syndrome and Lennox-Gastaut syndrome, and all along we'll be talking about the unmet needs, the burden of disease and the potential for new therapies.

So the World Health Organization defines a seizure like this. It's a transient event due to an excessive discharge of neurons, nerve cells, that can essentially do anything. It can cause symptoms that are motor, sensory, autonomic or psychic, but the key to any seizure is that it is sudden and transient. It starts, it evolves and it ends. And it was interesting to hear about predictable and unpredictable pain. There was essentially no such thing as a predictable seizure. They are unpredictable, which is one of the cruelest parts of a very cruel condition. A single seizure, at least in pediatrics, is just that. It's a single seizure. And

there are children who have a single seizure and never have a second one. They do not have epilepsy. Epilepsy is 2 or more unprovoked seizures, meaning there is no immediate reason for you to have a seizure. If that happens twice, you have epilepsy.

There are multiple types of seizures, but if we just focus on 3 general categories, generalized seizures, think of it is starting all over the brain at once or deep down at the center of the brain, such that we can't find a spot or even a size where a seizure starts. Then go way down almost to the bottom, focal seizures, start in a spot, a side, a lobe, a gyrus, starts in a spot. And then like everything with epilepsy, there is an unclear or unknown category where patients clearly having seizures -- are they generalized? Are they focal? Can't tell. And we call that unknown type of seizure onset, and a common cause of seizures with unclear forms of onset are epileptic spasms or infantile spasms, which we'll talk more about. So generalized seizures, focal seizures and then "can't tell which type" seizures.

There are multiple causes of epilepsy, and these categories outline the current epilepsy classification from the International League Against Epilepsy. In general, treatment is not based on the cause of your epilepsy. You may have focal seizures in due to a stroke, or you may have focal seizures due to head trauma. The treatment is by and large not different based on the cost. There are a few exceptions, but we base treatments on the seizure type, more than the cause. But I did want to include this for completeness. We do care a lot about the cause of seizures, but unfortunately, really, it doesn't target our treatments as much as we would like.

So this, I think, is the most helpful one slide to talk about epilepsy classification. It may look confusing, but let me walk you through it. You'll see circles going out from the center. Those are the age of onset of your seizures. So you don't have to be an epilepsy expert to figure out when a patient seizures start. The parents know that or the patients know that, and you'll see there are the neonatal seizures starting within a month; then the infant seizures, 1 month to 1 year; then childhood onset, 1 year to 10 years; and then adults, adolescent adult onset seizures. Nothing expert about figuring out the age of onset. Now age of onset is critically important for outcome in prognosis, and it also directs the search for the cause. All right. So that's the simple way to start walking you through this chart. Then look at the upper tier and the lower tier. The upper tier, you are otherwise normal, developmentally normal, and if you choose to do an MRI scan, it's normal. Again, it doesn't take an epilepsy specialist to sort out, whether someone is developmentally normal or not. The lower tier, you are not developmentally normal at the start of your epilepsy. You have developmental delay, you have cerebral palsy, you have autism. If you do an MRI scan, maybe you find an abnormality. So otherwise normal top tier, not otherwise normal bottom tier. And then the third way is the vertical axis, this is where epilepsy specialists come in. Are your seizures focal onset on the left side? Do they start in a spot in the brain? Or do they start all over at once, generalized seizures, the right side.

So the first goal of diagnosing and classifying a patient with epilepsy is what quadrant does the patient belong in, northeast, southwest, et cetera. Sometimes those little boxes are called epilepsy syndrome. Sometimes within a quadrant, you can further classify a patient as a specific epilepsy syndrome, and we'll come back to some of those in a minute, infantile spasms, Dravet syndrome and Lennox-Gastaut syndrome.

How common is epilepsy? Well, first of all, look at it by age of onset. So this is a bar graph and on the horizontal axis is the age spectrum. So notice the most common age for new onset epilepsy is 80 years plus, the far right. Now on the far left, the bar says 0 to 4 years of age. If that was subdivided into 0 to 1 year of age, that bar would essentially mimic the senior citizen peak. So it is a disease that most commonly starts in the youngest and in the oldest. It is relatively uncommon to begin in middle-aged patients. Unfortunately, if it does begin in a middle-aged patients, it may be due to a not-so-fortunate cause like a brain tumor or a vascular malformation. But in general, epilepsy is a disease in the very young and the very old.

I want to draw your attention to the blue line, the line that steadily increases across the age spectrum. That is the cumulative incidents of epilepsy. So patients who have ever had a diagnosis, it may be a lifelong diagnosis, it may be a self-limited diagnosis, because some pediatric patients grow into and then outgrow their epilepsy, and you see that blue line steadily grows across the age spectrum, such that, at

this point, focus on the third bullet: 1 in 26 people in the U.S. will develop epilepsy at some point in their life span. It is a far more common disease than it is -- that is generally appreciated. That is more than Parkinson's disease. That is more common than multiple sclerosis. It is, some say the third, fourth most common neurological disease after migraine, stroke and Alzheimer's. So epilepsy is remarkably common and that is underappreciated. The tagline for the epilepsy field to raise awareness about this point is that 1 in 26 people will develop epilepsy at some point, so it's that 1 child in every classroom. So quite a common disease.

Now let's focus on the 3 specific pediatric subtypes of epilepsy. Infantile spasms, also known as West syndrome, after Dr. West, a British neurologist and father of a child with West syndrome, who wrote the first case report in the Lancet in 1847, we're going to use the term West syndrome and infantile spasms essentially interchangeably for this talk, then Dravet Syndrome, and then Lennox-Gastaut syndrome. Now where do these fit in the pie or the dart board? Well notice all 3 syndromes are in the Southern tier, because they tend to happen in patients who are not otherwise normal at onset of their seizures, and they tend to be generalized seizures, so they're in the Southeast quadrant, you see the red circles around West syndrome, Lennox-Gastaut syndrome and Dravet syndrome. Now you'll notice that Dravet syndrome straddles the generalized and focal vertical axis because Dravet syndrome patients can have generalized seizures and focal seizures, all of the above.

Now we're going to use one slide, sometimes with an EEG, to give you a flash overview of these 3 epilepsy types. So the EEG sample in the upper part of the slide is 17 seconds of a normal EEG, most -- everybody in this room, if we were running an EEG right now, your brain waves would look like that. It's organized, it's synchronous. The bottom part is the EEG of a child with infantile spasms. There's no seizure happening during that EEG. That's their baseline waking EEG, complete chaos. Now children with infantile spasms have 10 to 20 to 100 very brief seizures a day. Quick, sort of flexion scrunches. The spasms themselves are not the real problem. They're a problem, they're unpleasant to watch, but they're not dangerous. The problem with infantile spasms is, the EEG chaos that comes with it. It is incompatible with normal development to go through your infancy in early childhood with an EEG that looks like that.

Now there are treatments that can reverse that EEG, normalize it and treat the spasm. But those treatments have limitations as we will discuss, but it is possible to convert that horrific EEG pattern to normal, stop the spasms and improve development. The trick is, doing it with acceptable side effects. So that's the flash overview of infantile spasms. Dravet syndrome, the EEG is so many things that I can't really describe Dravet syndrome by EEG, so instead, this is a patient. Now this is a very famous patient, this is Charlotte; Charlotte from Colorado, who was featured in the CNN documentary that was played over and over and over again, because CNN learned that it generated terrific ratings, I guess. So the story of Charlotte, as you may now, is she was a child -- normal child in Colorado who had a seizure with fever, a febrile seizure, happens all the time, not a big deal in the vast majority of cases, but then she developed other seizure types, some generalized, some focal. And then, her development regressed, and she was diagnosed with Dravet syndrome because that's what Dravet syndrome is, that she is typical case, and the treatments didn't work, as they always don't work. So the parents went in search of a better treatment and found online a family in California who had a child with Dravet syndrome, and they had obtained what they thought was a form of medical marijuana, not medical marijuana, that was said to be high in cannabidiol, and relatively low in THC. So Charlotte's family sought out marijuana manufacturers in Colorado, and convinced one manufacturer to try to grow a high CVD marijuana strain, and they it to Charlotte and as you've seen in the documentary, her seizures stopped. And the cannabidiol story for Dravet syndrome is ongoing, but it started with that case report.

Now of course that doesn't prove anything, but it's a very interesting hypothesis generating anecdote to test the hypothesis that cannabidiol is safe and effective for the treatment of seizures in Dravet syndrome. And you've heard about the studies that are ongoing to further test that hypothesis.

And then, Lennox-Gastaut syndrome, 2% to 5% of pediatric epilepsy, Lennox-Gastaut syndrome. You have your reference normal EEG and then, the EEG of Lennox-Gastaut. Now, it looks different from the infantile spasm's EEG, it's not complete chaos, it's actually, in a way, visually, beautifully organized, but in a profoundly abnormal way and patients with Lennox-Gastaut may not have 100s of seizures a day, although some will, they may have 5 to 10, but many of them involve sudden drops, falling, crashes

to the ground, that can cause injury and some have longer convulsions. And again, this EEG pattern is not consistent with normal development. There are multiple medications with FDA approval for Lennox-Gastaut syndrome, and we've made progress, but still the treatments are far from effective and we don't really cure, or even completely control the vast majority of patients with Lennox-Gastaut syndrome. So whatever the type of your epilepsy, adult, infant, childhood, the treatment goals remain the same: No seizures, no side effects. So that's actually not really fair. That's the buzz, that's the tagline from the epilepsy community. No seizures maybe, sometimes, no side effects is almost never achieved. So really, what we want is no seizures and tolerable side effects or acceptable side effects. We'll talk more about side effects in a second because they have really gotten a lot of well-deserved attention in the last 5 to 10 years. Another way to think of it is the life unaffected by seizures. Live a normal life. Or live the life you can otherwise live, if you didn't have epilepsy.

So medication is the basis of treatment for the vast majority of patients. There are patients that are treated with epilepsy surgery, but that's quite rare. There are patients that are treated with special diets, usually high-fat diets but that's also rare, and brain stimulation devices for epilepsy are just beginning and there are also not that commonly used, so medication is the hallmark of treatment and we have 25 plus antiseizure medications. How do we do? Well, this is all commerce. This is not a child with West syndrome, this is all commerce. If you have newly diagnosed epilepsy and an inappropriate medication is prescribed, about 50% of patients will be seizure-free. It doesn't mean they're side-effect free, but about half of patients are seizure-free on their first medicine. Try a second drug. If you're not in seizure-free on the first, we'll get about 13% more patients who are seizure-free. Again, it does not mean you are side-effect free, you are seizure-free, which then leaves about 40% of patients in the category called treatment-resistant after two antiepilepsy drug trials. And if you are not seizure-free after your first 2 drug trials, we will continue to try additional medications in monotherapy or combination therapy and we will try, we will look into surgery and dietary treatments, et cetera, but the reality is, if you have persistent seizures after 2 appropriately chosen drug trials, you probably have a rough, rough time ahead, to gain complete control of your seizures. It's in the -- maybe the 10% range, if the first 2 medication trials were not affective.

And now side effects. Side effects fall into 2 categories: Tolerability and safety. So how common are tolerability side effects? So you feel drowsy, you feel dizzy, you have headaches, you're not thinking clearly. Well, if you ask patients in an office visit, have any side effects? Maybe 10% to 40% will admit to having side effects. If you give them a checklist, a standardized checklist, 60% to 90% will report side effects. So side effects are the norm, not the exception, with our current selection of medications. And quality-of-life studies have shown, perhaps surprisingly to some, that medication side effects has a greater impact on quality of life than seizures. Now seizures -- unpredictable seizures, are not good for your overall quality of life, I don't want to downplay that in any way, but everyday, 365 days a year, taking a medicine that makes you tired, headachy, clouds your thinking, adversely affects your quality of life even more than breakthrough seizures. And then there are safety problems, which certainly get a lot of attention in the antiepileptic drug world, although they are, in clinical practice, relatively rare, ration about 5% usually reversible, occasionally it can progress to a life-threatening allergic reaction, that's true of any medicine, but that's uncommon, thankfully. There are reversible liver and blood count abnormalities in maybe about 5%, and thankfully, there are rare, but not 0, irreversible liver or bone marrow failure, or life-threatening allergy. But the key to side effects or the tolerability side effects are patients, even those who achieve seizure freedom are not free of side effects. They're affected by them in some way. So how do we treat our specific pediatric syndromes that we're talking about in a little more detail today. So infantile spasms. Well, I told you the patients have clusters of seizures daily, 10, 100, there are 2 FDA-approved treatments for infantile spasms, the ACTH, Acthar gel and vigabatrin or Sabril, and after about a month of treatment on either one, sometimes combined, about 50% of children respond. That's not great. So that means 50% have not responded and are still having daily clusters of spasms and still have that horrifically abnormal EEG, and then even the 50% that do respond, there are frequent relapses over the next 3 to 6 months. And this data is going to be presented this weekend at the American Epilepsy Society meeting in Philadelphia. The disappointing response rate and relapse rates of our current approved treatments for infantile spasm. What about Dravet syndrome? Well, they have not necessarily daily seizures, they have perhaps 10 to 20 seizures a month, but they are -- they come in clusters, and they're often prolonged, 30 minutes, an hour. So it's a different seizure profile, but it's certainly disabling.

With our best available treatments, which are terrible, they might have 3 to 6 seizures per month, but still unpredictable prolonged clusters. So there's no approved treatment for Dravet Syndrome. And then, Lennox-Gastaut syndrome, the trials that have been done in general, the patients have had 90 seizures a month, many with crashing to the ground, and a typical approved drug will give a 50% seizure reduction in 50% of patients, which is -- will get you an FDA approval, and it does help patients, but the patients are still having 45 seizures a month, even with our best available treatments. So the unmet needs are obvious. So what's the potential role for cannabidiol? Well, there's obviously a huge treatment gap with infantile spasms, Dravet syndrome and Lennox-Gastaut syndrome. It is not known whether cannabidiol is effective for those epilepsy syndromes, but there are certainly anecdotal evidence that suggest they might be, and the studies are critically important to complete, but maybe what's really -- what's driving all of the hype about cannabidiol? It's the belief that it is probably, I think, better worked out than the efficacy. It's the belief that the side effect profile will be favorable. Cannabidiol is different enough compound from our typical seizure medicines, and there is enough experience with it, that certainly, the widespread belief is that it will not have the same rates of sedation, dizziness, headache, clouding your thinking and the other lists of our traditional antiepilepsy drug side effects. So if the side effect profile turns out to be true, the favorable side effect profile, that in and of itself will be a blockbuster advance for epilepsy treatment.

So in summary, epilepsy: Very common, surprisingly common, 1 in 26 people will develop epilepsy at some point, that's about 2 people in this room. The goal of those seizures and those side effects is rarely achieved, may be seizure freedom, overall, in about 60% of patients, about 40% continue to have seizures and some side effects, some tolerability issues in essentially everyone. And the agents in development, including cannabidiol, have the potential to fill the many treatment gaps that we have right now with pediatric epilepsy. Thank you very much.

#### **Unknown Executive**

So with that, we're going to commence the panel discussions, and Alain and Alan, my colleague and I will be walking around the audience with microphones, so if you have a question, we'll come to you, and please feel free to address any of the speakers.

## Question and Answer

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### Jason N. Butler

*JMP Securities LLC, Research Division*

Butler from JMP Securities. A question for Dr. Gudín. You gave an overview of the 3 sublingual spray candidates that Insys has in development, Buprenorphine and naloxone. Could you talk about maybe, how you see the specific delivery formulation being applicable, relative to the currently available products, and how you might use it in certain patients?

### Unknown Executive

Yes, sure. I find that patients appreciate sublingual spray technologies that have with Subsys. I'm not sure if there's any patient satisfaction studies out there, but when you ask patients and you give them the spray, I've always found there's something about actively administering a drug for patients, even there is some psychological placebo benefit to it, they feel like they're doing something. So they welcome sublingual sprays, you've seen PK data, I mean it's -- the mode of delivery doesn't matter as much for getting it in. Although with Buprenorphine sublingual happens to be the way. So I think for the patients or the clinicians who know about Buprenorphine already as a molecule, will be familiar with sublingual delivery, this will just be another route of administration. And similar for, in the lock zone, I think going from an intranasal to a sublingual spray, it's almost like a spray technology's not going to be a big change, or a big paradigm shift for them. So I think it'll be welcome by the community, sublingual administration is effective, easy, it doesn't [indiscernible] the amount of education that goes into it, it's just a -- less than a minute of showing patients how to do it, how the uptake will be by the market, I couldn't comment.

### David A. Amsellem

*Piper Jaffray Companies, Research Division*

David Amsellem from Piper Jaffray. So a couple of buprenorphine-related questions. First, just -- this is a commercial -- commercialization question, but how you think about coexisting with BELBUCA in the chronic pain setting, bearing in mind that BELBUCA will have quite a bit of a head start, so that's #1. Number 2 is, in terms of the actual device, can you talk about the potential to be able to make a multidose device that stands right now, it's a single applicator, so is that something that you think you'll be able to do? Do you have -- and is the absence of that potentially problematic? Thanks.

### John N. Kapoor

*Executive Chairman, Chief Executive Officer and President*

I'll answer that question. I think, in terms of multidose, we are working on a device with Aptar, with our partner, in a multidose device among others. Right now, our device can only deliver 100 microliters, so if we want to deliver more than 100 microliters, as you know, some of our higher strength Subsys has 2 devices in 1 delivery, but we've made a lot of progress in getting 200 microliters developed and we're supposed to get the delivery of those by end of 2016. And that will also give us flexibility in the multidose, and some of these, we need a counter, so that's been developed as we speak, and we should have that also available by end of the year. So that's on the multidose question. The other question about commercial, we've been behind the BELBUCA product. I think -- we feel that the acceptance of Subsys -- of the sublingual, as we saw in Subsys, we were #5 or 6 in our launch time, but because of the ease of delivery and better absorption, helped us get #1 in market share. So I'm not saying the same will happen with BELBUCA, but we believe that we should be able to get our share of the market, it will be significant. Dan, you may want to comment...

### Daniel Brennan

*Chief Operating Officer and Executive Vice President*

I don't have much to add. I think that the patient value and the speed of onset and the ease of administration should play out favorably. It will be a little bit of a downside that they have beat us to market, but sometimes it's okay to be second and better.

**Randall S. Stanicky***RBC Capital Markets, LLC, Research Division*

Randall Stanicky, RBC Capital Markets. Dr. Brust, can you just talk about the economic sensitivity of your patients, moving from a generic Marinol to possible Syndros?

**Douglas Glenn Brust**

I guess I really couldn't comment on that, as far as -- one of the things I'd like to say is that, in a clinical setting now, as all my colleagues we were just discussing earlier, as a clinician, we use medications for off-label indications all the time, and Marinol has label for AIDS wasting, but in my practice, as an off-label use, we use it frequently for nausea, and in that setting, almost everyone has nausea, especially when they start new meds and when they have -- their regimens have like, working meds in them, and they take them all at once, so they get gastritis. So the way we, I use Marinol, is they take it beforehand, before they're going to take their meds, but it's not predictable. So in my setting, in patients that are commercially insured, yes, they would use it, but I couldn't expand that to say what the commercial interest is.

**Randall S. Stanicky***RBC Capital Markets, LLC, Research Division*

And follow-up for Dan. A lot of details today. Can you just confirm for us, that in 2017, we should keep thinking about Insys selling 5 different products?

**Daniel Brennan***Chief Operating Officer and Executive Vice President*

I hope that's correct, that's one of the reasons why I joined on board. It could very well be the case of I'm trying to think I'm on my feed here, the number of products, but hopefully, new indications and new studies done with Subsys, and then with naloxone, [indiscernible] and [indiscernible], I mean, that could very well be the case, and then on top of the syndrome [indiscernible] we're launching next year.

**Unknown Analyst**

This is [indiscernible] from Leerink Partners. So the question that I had related to dronabinol. Just thinking about -- so physicians that we've spoken to, showing excitement about the PK profile of the molecule, but we just -- one of the things that they typically show concerns about is just clinical validation, and just wanted to kind of get a sense of what trials or what clinical data, if any, that Insys is trying to collect to trying to give support to in as Dr. Gudim mentioned, so to just show more clinical validation of dronabinol as -- in terms of its efficacy, and what patients could benefit most from it.

**John N. Kapoor***Executive Chairman, Chief Executive Officer and President*

Yes, so just to be very clear, we are getting Syndros approved for the 505(b)(2) pathway, so our label is going to mirror what's currently the labeling for Marinol. I know Dr. Brust alluded to other uses, but they're his clinical prerogative to do so. Our label will be that of Marinol. We will have the PK data and the PK data certainly, as I mentioned, shows the lower variability and also shows the faster onset of levels. The clinical target for that, we are not conducting clinical trials to correlate that, but we assume that lower variability is a highly desirable attribute for physicians and for patients, and also a faster onset of levels. So the use in the clinical setting will be dictated by those clinicians who value those attributes such as the lower variability and the faster onset of levels.

**Unknown Executive**

I'll just add. I mean, we'll try to make efforts to get data in there, about the lower variability, as well as the speed of onset and we'll just have to see how that goes in our discussions with the FDA on the labeling.

**Unknown Analyst**

You did mention, over time, you are considering clinical trials for agitation and Alzheimer's and are so, initially will be only the indication that Marinol has, but in the future, perhaps other indications.

**John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

Absolutely. Those indications that they discussed, or both of those are -- we're actively pursuing those. And that will provide data in different settings beyond what is currently in the label.

**David Michael Steinberg**

*Jefferies LLC, Research Division*

Dave Steinberg from Jefferies. Dr. Gudin, when a patient presents for breakthrough cancer pain, and you decide to prescribe a transmucosal fentanyl product, what are the key metrics in your decision? Whether to use Subsys, [indiscernible], et cetera, et cetera?

**Jeff Gudin**

It's a good question, and basically make it patient preference. I have sample units, or a little poster of each of them. You probably recognize that with Managed Care barriers OTFC or [indiscernible], is the one that they most commonly get, either first line or what the insurance companies recommend that they get. But I explained to them and some patients say, who would spray anything in their nose, and I give them a little explanation of what that delivery system is like. Some patients say, you may put my finger in my mouth, like all the way up in my mouth, I'm not going to do that, so I leave it up to the patients, I try to be fair, or fair balanced in offering them the available products. But as I mentioned before, Subsys is -- seems to be a very well accepted delivery system, no hands in the mouth, quick, simple spray. Patients actually feel something, whether it's part of the drug or part of the incipient's, but I do offer patients, based on their preference, different types of delivery systems.

**David Michael Steinberg**

*Jefferies LLC, Research Division*

And just a follow up. Dr. Brust, that was a very vivid example you give us of the hunter and the helicopter and how off label use for Subsys means a lot. How difficult is it to navigate the turf [indiscernible] program when you pick one who prescribes something off-label, how heavily is it scrutinized by the payers? How difficult and cumbersome is the process?

**Douglas Glenn Brust**

Yes, it is quite cumbersome, as it is for all medications, and for some unknown reason in the last year, we've even been forced to prior off generic MF content. I mean they almost prior off everything, it's getting to be an incredible battle for clinicians on the frontline, in an era of dwindling reimbursements. I gave an example on the break, I tell my patients now, when it comes to lidocaine patches they all want, I'm going to write you the prescription, but I'm not doing -- it's not going to get paid for, and I am not doing your prior off. So if you want them, you're going to pay for them. Otherwise, I could spend an entire day on prior authorizations for just 1 simple topical patch-type medication. So it has become a barrier, I'm hoping that government intervenes here. I saw a quick, not sure if it was made public, but an email from, I think it was the New York State Pain Society that's going to petition New York State to force managed-care companies to pay for abuse to tar and opioids. They want doctors to be part of the solution, they have to give us tools, they have to give us some rights. I mean, if you think about it, I've mentioned before, my Suboxone clinic, the most common drug they ask for? Oxycodone immediate release. No abuse deterrent property. If it's not part of any REMS program, it's generic, it's cheap, that's what they go for, so there isn't a lot of focus on abuse [indiscernible] these emerging technologies, but until the regulatory bodies in our government intervenes, it's going to be a challenging landscape.

**Unknown Executive**

I just want to underscore that also. I take care of almost 1,300 outpatients, and admittedly they are very complicated patients, but we employ 3 full-time nurses that only do prior authorizations 40 hours a week. That is 1 job you don't want.

**Rohit Vanjani***Oppenheimer & Co. Inc., Research Division*

Rohit Vanjani, Oppenheimer. I have questions for John and Dan. On Subsys, are you still anticipating a revenue growth for 2016, and if you are, so I think you said the indications may take some time, is it going to be volume growth [indiscernible], or is it mostly pricing and rebating, and then separately for Syndros [ph] on BELBUCA, you mentioned the [indiscernible] study. I just wanted to confirm that, that was the only study that there will be before admission. I just want to make sure there was no soft tissue study that will be required as well?

**John N. Kapoor***Executive Chairman, Chief Executive Officer and President*

Yes, so the buprenorphine spray, I think we showed two pathways, where one was for the acute pain and the other was for the chronic pain. For the chronic pain, it's the indication that BELBUCA has, and our studies will be in [indiscernible] and chronic, and in the opioid-experienced population. Separately, the indication that we are seeking is for the acute pain, and there we have a single study using the bunionectomy model, and we believe that should adequate for the purpose of pursuing that indication.

**Daniel Brennan***Chief Operating Officer and Executive Vice President*

And for your first question, the way that I've seen it and talked with my new boss and my CFO is that, I do think that there will be revenue growth next year. It won't necessarily -- it'll be my job to make it on units, but my guess would be, estimates on flat units, but price increase plus some good things that are being done with the rebidding and the gross to net, could have topline growth in the 10% to 20% range. Again, with some additional strategies and with some, certainly, that when the clinical studies come out, that is going to help. That's further down the road.

**Lisa Wilson**

And we have some questions from the webcast attendees. Why Liposomal Paclitaxel, the lack of fit with the commercial focus? And the second question, can you please discuss your R&D spending plans, given the breadth and depth of the pipeline.

**John N. Kapoor***Executive Chairman, Chief Executive Officer and President*

I'll take that. Liposomal Paclitaxel was a product that we acquired when we acquired NeoPharm back 3, 4 years ago. A company that I was personally very familiar with, and I believe the Liposomal delivery system for paclitaxel, it's for cancer patients, and many of our efforts in sublingual and other products address supported care of cancer patients, so it's not like, with not in the oncology market, we are, we deal with oncologists all the time, we have an advisory panel that works with us on many of our oncology products. So we seek significant fit, and we can bring a lot of benefit to the patient population, if we can get approval in some of the indications that Dr. Santosh talked about. We believe that -- we had looked at Abraxane and some of the data that we have generated in the past, at NeoPharm, the 2 products are very comparable, even though they are different in terms of -- one is a, Abraxane is a complex of albumin with the [indiscernible] molecule, ours is a liposomal, encapsulated [indiscernible], but we believe the behavior could be very similar. So you have a product, last, I estimate was \$1 billion or whatever it was, Abraxane. If we get approval, we -- our cost of producing that product would be much less, and we can market this product and create substantial value. And the second question was?

R&D says, we have said that, we think we can, we might spend up to \$100 billion in 2016, and as you can see, our pipeline, many projects in Phase III already, and a lot of the projects that you saw in terms of our effort in something, or molecules up to 15 or 20 molecules, we have, although this program's moving forward, it's sometime's difficult to talk about everything, like in a platform today, but we have very exciting stuff going on in the company, and that was one of the purpose we had, just wanting to have this session with you all, to show you what we are, what we are doing and a lot of people in our R&D formulation, in our plants, getting ready to develop many new products in the coming years.

**David A. Amsellem***Piper Jaffray Companies, Research Division*

This is David Amsellem from Piper Jaffray again with a couple of follow-ups. Number one is, on the sales infrastructure, so you've talked about the hospital setting, you talked about the chronic pain setting, and you do have significant infrastructure already in place, but help us understand how are you thinking about the salesforce expansion, and then, what is realistic over the next few years as these opportunities bear fruit. And then, secondly, on cannabidiol, can you walk us through, to the extent you can, what you think is tangible, and maybe shed some light on your IP strategy on that product?

**Unknown Executive**

I can take the first question. I really haven't been able to look beyond Subsys plus Syndros, as far as the sales force is concerned. Not yet considering any expansions into those other areas. But looking at Subsys, I think that we have, between 230, 250 sales reps right now, there is considerable overlap with Syndros prescribing. There is still some broadening with Syndros that we're still stuck in the prescriber data, but I wouldn't expect any significant expansion of the Salesforce, probably a reorganization. My assumption and guess is that all of the sales reps will probably carry more products, perhaps to different degrees, as far as they're willing. But that's as far as I've looked and into the other products, we'll take that as they move closer.

**John N. Kapoor***Executive Chairman, Chief Executive Officer and President*

Your question regarding IP for cannabidiol, we always, when we develop formulations, we file patents on our formulation, and in the case of cannabidiol, we believe that, that will hold true. These formulations are tied in with our blood level studies, [indiscernible] studies and the precedence that you can obtain patents definitely in the United States, with that kind of an effort. We also believe that the molecule itself -- our plant has done tremendous amount of work in terms of our ability to produce the [indiscernible] at a very low cost, and these are processes that we think we have proprietary technology that we have, looking at whether we should file patents on it or just keep it proprietary, and take advantage of our ability to make these molecules at a very low cost. So we think that, if we succeed in -- as was pointed out -- if CBD is as good as we think it might be, your cost advantage, we believe this going to go a long way. So we're very optimistic about that.

**Unknown Analyst**

Two questions please, Mitchell Blood [ph] from [indiscernible] Capital. For Dr. Dlugos, you mentioned of course, the now-famous child from Colorado, who responded, or seemed to respond to cannabidiol. But you didn't give your comments on your own sense of probable or possible efficacy, other than this fairly well publicized case report. Can you comment on that, please?

**Dennis J. Dlugos**

Yes. It's unknown. Yes, I mean, the trials are to be done about whether it is effective for seizure reduction in Dravet or LGS or any of the syndromes. And because of the DEA scheduling issues, it's not as if anybody had some extensive experience in their pocket, where they can talk about their experience. So the honest answer is, no.

**Unknown Analyst**

No, meaning it's unknown?

**Dennis J. Dlugos**

It's unknown. It's unknown.

**Unknown Analyst**

For Dr. Gudín, what that -- in clinical practice, what is your definition of failure of a receiving turf, prior to giving Subsys, or what is the REMS definition, as you interpret it? In other words, if a patient says yes, I

really want Subsys, and you say, well, your plan requires that you get [indiscernible] first. Can describe that? Can you have the patient say no, no, that won't work for me, and is that a failure? Does a patient actually have to take it, and conclude that it's not effective?

### Jeff Gudin

Yes, it doesn't just have to be a therapeutic failure, it could be a tolerability or adverse effect potential involved for those patients who develop a [indiscernible] trouble, irritation from rubbing the powdered lozenge on the side of their cheeks. Patients who come back and say, hey I've been to the dentist 6 times this year, where I haven't had to go at all. I mean it is a sugarcoated lozenge that they leave sitting against the side of their teeth. So there are some reasons other than efficacy that we might change patients from 1 formulation to the other. Taste is sometimes unpleasant, even though, coming from me as a sweet guy, who think who wouldn't like sweet, but it has a weird kind of taste. So there are reasons, again, other than lack of efficacy, and for some patients it is efficacy, even though we tell them it should be rapid in onset, they tell us hey, listen it takes me, 10 to 20 minutes for this thing to dissolve in my mouth, and I got to keep twirling it, they -- I'd appreciate rapid onset, but that delivery system is not for me. And that's when we really make the managed care fight. Some conditions go right to some of the [indiscernible] one of the other brand [indiscernible] products, because they have their preference. Managed care has beaten me because to submission to trying to improve the product first and then, they are approved [indiscernible] first, and then offering as a second-line, the newer, branded products.

### Unknown Executive

Just one nuance to my question. Does trying wouldn't be considered trying if you sat with the patient and I really think you should take this [indiscernible], and the patient says, no, no, no, I really -- that won't work for me, I've never tried it, but I really want Subsys?

### Jeff Gudin

That's an opinion that's -- I don't know. I haven't thought about it. I don't think I have an answer for that.

### Unknown Analyst

Couple of quick questions. Dr. Dlugos, I know you said that you weren't certain that there was evidence of efficacy or it's unknown. I in live in Colorado, and we have people who have moved to this state specifically to seek treatment, but I've also seen the data that suggests that there's bias in [indiscernible] reporting. Those who were residents prior to legalization saw less effect than those who moved to the state, that see an effect. So I'm kind of curious, from your personal experience, 2 questions: One, have you ever seen or treated a patient who's been treated with cannabidiol; and then the other, is there a mechanistic reason why you think it might work?

### Dennis J. Dlugos

So the Colorado experience is not pharmaceutical grade cannabidiol, and maybe I didn't make it clear enough, the difference, the anecdotes out there, including Charlotte, is not pharmaceutical grade cannabidiol, and it's not sort of regulated in any typical way. So you are correct that the broader -- again, open label case report data from Colorado, not everyone is like Charlotte, for sure, but that's not the product that Insys is developing. Perhaps some of the tolerability side effect experience from those patients might be relevant, but we don't even know that. So anything about a state-based to order more shadowy medical cannabis is not clearly directly relevant. As far as patient experience, so the [indiscernible] we're participating [indiscernible] in the [indiscernible] study, that's not an efficacy study. So it was well tolerated, you get it wasn't designed to comment on efficacy, as I'm sure you know, there is a plant based formulation of pharmaceutical grade cannabidiol that has open label studies, some through academic institutions, some through states, that are proceeding. We at Children's Hospital have patients who had enrolled in some of those trials. No placebo, no control, so you can't really comment on efficacy. It is generally well-tolerated, that's not Insys' formulation, so again it's a long answer to say, it's unknown. The potential is huge, but the facts we actually know, especially with control groups is not just extremely limited, but at this point, is absent.

**Unknown Analyst**

Mechanistically, the reason why you think it might?

**Unknown Executive**

Yes, there -- I mean, I'm not a [indiscernible] scientist, but I -- there are, it -- there's a long history of marijuana THC derivatives in treatment for epilepsy, and there are actually studies from the '70s that were done, not -- certainly not on pharmaceutical grade cannabidiol, but mechanistically, yes, there are reasons to believe that cannabidiol can be effective for treatment of seizures.

**Unknown Analyst**

And 1 question for Insys. I know we've talked a lot about the pipeline and the fact that you expect to have new products. It's still not exactly clear what that timeline is or the path, specifically, for [indiscernible] for opioid addiction, could you be a little more specific about the timeline? I've heard different things -- I've heard things, and [indiscernible] if trials were underway, now we're hearing that trials are going to begin, and yes, there's still a plan to file by the end of next year. I just want to better understand exactly what that path is.

**John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

So let clarify that. I cover a few things, in the [indiscernible] for example, we have currently an ongoing trial, right. now, we'll share the results of that in January. Those results, if you show that we have levels that are comparable or exceed those of the intramuscular [indiscernible], then certainly we proceed and have discussions with the FDA, and could potentially be the basis for approval. So that [indiscernible] be determined once we have those results and have those discussions. So that could be a potential filing in next year, depending on the results. Buprenorphine/naloxone, and I presented one study that we're currently doing, that's looking at the lower dose. Subsequent to that, we will be conducting the studies for the higher dose in some of the other studies that I mentioned, like the dose proportionality study, all of those you now, signing for success, lead to a filing at the end of next year. So that's buprenorphine/naloxone. I think there was -- was there another one that you wanted to put a clarity on, or...

On [indiscernible]. Yes. The [indiscernible] study is certainly, we, start those in the first half of 2016. We today have a fairly content. We can get those studies done in 2016, leading to finding for that particular indication in 2016. So those are the 3 I would highlight for the purposes today. The others that we currently have ongoing development in, will play out as we get those trials and the data readout.

**Rohit Vanjani**

*Oppenheimer & Co. Inc., Research Division*

Rohit Vanjani again from Oppenheimer, for Dr.Dlugos. I think, that cannabidiol once injected orally converts to THC anyway. Is that or will that be a concern for [indiscernible] and would they want to see other formulations that maybe avoid, [indiscernible] liver metabolism? Then secondly, for Santosh, on [indiscernible] it was briefly mentioned in the kind of 20 or so, product we have under development under sublingual spray, is there any more detail on the timeline of that program, or where that program is doing?

**John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

So for the -- on the [indiscernible], as we highlighted that as a formulation in development, this follows our typical model, where we conduct an initial study, which is proof of concept to assess the formulation, currently where it's going is in the fine tuning part of the formulation, so that fine tune formulation, we hope will be sometime next year and we'll conduct a subsequent study.

**Dennis J. Dlugos**

And as far as your question about multiple formulations, I mean, clinicians, we always welcome multiple formulations, for chronic daily dosing, oral formulations are the mainstay, they're for seizure rescue

treatment, nasal, oral, sublingual or IV formulations would be welcome, I think that's down the path, but I think if the -- if an oral form of cannabidiol, pharmaceutical grade, is found to be safe and effective, then that would be a fine advance, and if other formulations come, great.

Well, I mean, I'll defer to other, more medicinal chemists about the -- what the conversion to THC means chemically for the body. As far as the side effect profile that we think we know, CBD formulation, to my knowledge, do not appear to have clinically THC-related side effects. Yet if anyone else in the panel or in the room wants to comment more about that, that's fine. But that not, frankly not been an issue I've heard discussed, so -- and it's certainly not [indiscernible] THC-related side effects in our limited CBD epilepsy experience.

**John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

You're saying that CBD converts into THC in the body, in the gut, I mean, you have any data on that?

**Unknown Executive**

Well, we don't have that indication in our formulation. We do see very minor, minor formation of THC, but not to the any significant extent. So and we haven't seen that data, I mean, we try to in vitro, just taking in the lab, to see if we can convert CBD into THC, and in our experiments, there's only a very small amount of conversion that occurs from CBD to THC.

**Andrew Rosenblum**

Andrew Rosenblum on for Matrix Capital. Two quick questions on Syndros. For the management team first, you guys talked about a \$200 million opportunity there in the near term, at about like a \$500 million market opportunity, weighted average cost. How do you guys think about that coming from CIMB versus AIDS-related wasting, if you could kind of break out how you're thinking about that market evolving, and then maybe a follow-up for Dr. Brust, what percent of you [indiscernible] scrips are to commercial insured payers?

**Daniel Brennan**

*Chief Operating Officer and Executive Vice President*

Your first question, I think there is up to a \$200 million a year, I wouldn't call that in the near term. I would think that, that would be more towards the peak, as we're looking at it. And we really haven't -- I haven't anyways, I don't think that the group has yet looked at the breakdown between the 2 indications and where that's coming from. We're more instead looking at the entire Marinol use currently, taking and understanding what the current pricing is, some thoughts in our head of where the pricing would go to, with the Syndros, and an estimation of the conversion percentage that we could be able to get with the improved patient characteristics of our version. So there's a thought that we would be able to get up to a peak of \$200 million, and of course, we're going to have to see how it launches, and ultimately, if we get to that potential.

**Douglas Glenn Brust**

So most of the Marinol we prescribe is generic. And that, even in the generic form as we talk about prior authorizations before, many of the managed care plans require prior authorization for Marinol. And only -- actually I just found out the other week, we had one, because these nurses, I should have brought along with me, we have one plan that will only pay for, actually brand Marinol, but inasfar as being able to obtain, and I've been able to obtain Marinol for any patient that want it, or because they do not have to -- as we were talking about before, they don't have to fail another drug before you start it. And I could not give you the breakdown of the commercial payers, whether they pay for brand or only generic, but I would say the vast majority just pay for generic at this point.

**Lisa Wilson**

I don't think we have any further questions. Dr. Kapoor, I'll turn the stage back over to you for any concluding remarks.

**John N. Kapoor**

*Executive Chairman, Chief Executive Officer and President*

Well I, again, want to thank you, all, for taking time from your busy schedule and coming to listen to our story, and again, as I said at the onset, we believe that our company is not as well understood, and this is the day we, starting to tell you our story. And we plan to do that as we move forward, and we've got a great team, I believe in place, that can take this company forward to the next level. So thank you, again, for coming.

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