Trends-in-Medicine

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by Nigel Staite and Lynne Peterson

SUMMARY

The sleep market is strong, prices are stable, and the outlook for near-term growth appears to be good. ♦ Competitive bidding is currently on hold, but it is likely to be implemented in some form in 2011, and device manufacturers are concerned it could lead to a significant decrease in pricing, stifle innovation, and lead to a monopoly dominated by a few large companies. ♦ At-home diagnosis of OSA will not emerge as a significant market segment until reimbursement improves, but CMS is very interested in this, and DMEs are positioning it as a way for sleep labs to capture additional revenue. ♦ CPAP manufacturers are taking different approaches to compliance monitoring. More sophisticated flow generators are being developed, and wireless monitoring is emerging, but at significant added cost. ♦ Restless legs syndrome and fibromyalgia received some, but not very much, exposure at the meeting.

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SLEEP 2009

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Sleep 2009, a joint meeting of the American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS), was attended by ~5,000 people from both societies. As expected, a large number of exhibits featured continuous positive airway pressure (CPAP) equipment and diagnostic devices for obstructive sleep apnea (OSA). Only three pharmaceutical companies had prominent exhibits for sleep-related therapies – Cephalon for Nuvigil (armodafinil), Sanofi-Aventis for Ambien (zolpidem), and Jazz Pharmaceuticals for Xyrem (sodium oxybate).

Sleep-disordered breathing (SDB) broadly refers to a group of disorders characterized by abnormalities of breathing pattern (such as stopping breathing) or abnormal reduction in the volume of breaths while sleeping. An estimated 50 million people in the U.S. suffer from OSA, the most common type of sleep-disordered breathing. OSA occurs when the upper airway (near the back of the mouth) collapses during sleep, obstructing the airway and preventing air from entering the lungs. OSA is caused by multiple factors, including sleep-induced relaxation of the throat muscles and tongue, enlarged tonsils and adenoids, an abnormally small airway diameter in the back of the mouth and throat, and extra soft tissue in and around the throat due to obesity.

COMPETITIVE BIDDING

Competitive bidding was supposed to start earlier this year (January/February), but it has been delayed and is being re-evaluated as part of the Obama Administration's current healthcare reform initiative. It was due to be re-visited this spring or summer. Industry comments about the outlook and impact of competitive bidding included:

- "Competitive bidding is currently on hold. The government has said it will re-bid towards the end of the year and decrease costs by 25%. Short-term, I expect CPAP sales to drop. Over the long-term, I think innovations will drive costs and better value."
- "Basically it's driving people out of business. Competitive bidding was up for about seven days, then they took it down. On the basis of a bid, one guy I know rented a warehouse, bought equipment, hired employees, etc., and then got stuck with it all. Also, people were bidding outside their territory and poaching business. Now, the government is taking a fresh look. The fur is really flying. There are lobbying groups in Washington DC trying to block it and others trying to limit its impact. The danger is the market will evolve to preferred suppliers. Pricing pressure will make it uneconomic to innovate. Apria and the other big companies will simply carve up the business among them."

- "We don't know yet to what degree it will impact the CPAP market. That depends how it's implemented."
- "Competitive bidding will be re-visited this fall for a concrete decision. It's supposed to be implemented in 2011. It could set up a monopoly situation. I saw something similar up in Canada when one of the provinces put home oxygen supply up for bidding, and one company got all the business. But if it's done right, say -9.75%, so that everyone can play, then it will be manageable."
- "The impact of competitive bidding is still unknown. It could decrease prices and stifle innovation. That's the question we ask ourselves at all our business meetings. We continually strive to add technological advances that improve compliance and reduce a patient's other medical costs."

THE CPAP MARKET

Currently, the CPAP market appears to be doing well, despite the recession, though competitive bidding is on the horizon and casting a shadow over the outlook. Industry sources were not worried that new devices or technology will disrupt the market in the near future. Interestingly, there was disagreement on who drives patient device choice – sleep labs or durable medical equipment (DME) providers. Pricing is holding steady and industry sources are optimistic about the future, especially due to new referral sources.

Referrals

Most referrals for CPAP currently come from sleep medicine specialists, ENT (ear, nose, and throat) physicians, and pulmonologists, but some primary care doctors are starting to focus on OSA. And there are several other factors that sources believe will help drive the CPAP market, such as:

- **Trucking.** The trucking industry is pushing for government regulation to require long-distance drivers to undergo screening for SDB and OSA.
- **Diabetes.** Diabetes educators (CDEs and/or BC-ADMs) are also becoming very active in referring patients.
- **Neurologists.** Referrals are also increasing from these specialists.
- **Spouses/domestic partners.** This is becoming an increasingly important driver for a person with snoring and apnea to seek medical attention. PCPs then refer to a sleep specialist. One source said, "Bed partners are definitely becoming more of a factor, driving patients to see their PCP and then a sleep medicine specialist. PCPs are becoming more aware of sleep disorders."
- **Consumer awareness.** Consumers are becoming more health conscious and want better general health. A source said, "They are becoming more aware of snoring and restless legs syndrome, not just OSA. Sleep *quality* is becoming more of a health concern."
- **Primary care physicians (PCPs).** This was described by one source as being key for future referrals (to sleep specialists) and growth.
- **Obesity.** A Virginia sleep specialist indicated that he is seeing more women referred to his practice for OSA, "Most of them weigh 300 pounds. Obesity is a significant problem."

Market Growth

Industry sources were very optimistic about the future of the CPAP market. Comments about the CPAP market outlook included:

- "(It's) very strong, even in this economy. Reports indicate home medical equipment (HME) and DME dealers are seeing 10% annual growth in masks and flow generators. Some reports cite 12%-14% and others 8%-10%. I think 10% is a fairly representative figure. Eighty percent of patients with OSA are still undiagnosed, so there's still a huge opportunity in this market. This is a $2 billion industry. There's always talk of drugs or implants coming that will treat or cure OSA, but they've never emerged."
- "There's nothing on the horizon to displace CPAP as the gold standard therapy. There's always talk of pharmacologic therapy, but one has never emerged."
- "CPAP is still a growth market. Only 10%-20% of OSA patients are being treated, and 80% are undiagnosed. I don't see anything that will replace CPAP for now; it's the gold standard of therapy.Other approaches are untested or unproven."
- "The real variable is the patient, not the device. This is a very subjective industry – driven by comfort. Everybody's breathing pattern is a little bit different and changes from night to night. People's faces are different shapes. People respond differently to different devices."
- "The DMEs really drive the patient's choice of product, not the manufacturer. DMEs recognize they can't just push low-quality machines into the market and not follow up. So the CPAP market supports *quality* products."
- "The sleep labs are really the driver for the choice of CPAP device. They have to have a level of comfort with the machine, so companies like us work with sleep labs to educate them on the features and performance of the device. Then, they have to go to the DMEs with an attractive business model. You won't find a sleep lab recommending only one device, but they'll probably have a small range of devices they have confidence in."
- CPAP is still a strong and growing market, but it's now in a bit of a holding pattern. There's always the threat that someone will find a drug treatment for OSA, so CPAP companies are expanding into the diabetes and cardiology markets."

- "Only 5%-8% of patients with OSA are currently diagnosed, so the prospects for growth in the business are good."
- "The current growth rate is still very strong. I'd say in the mid-teens. Eighty percent of patients are undiagnosed, so there's still a lot of room for growth. We're now getting big companies like GE and Phillips-Respironics moving into the market, so it's still growing."

Pricing

Pricing appears to be holding steady. Comments included:

- "Prices for flow generators and masks are fairly stable right now."
- "Prices of machines and masks are very stable – maybe more stable now than they have been in the past. There's always pricing pressure, but it's not a real issue at the moment."
- "Prices will have to decrease (in the future) because of competitive bidding, and there's probably going to be a decrease in supply."

Home Diagnostic Testing

At-home diagnosis of OSA has yet to emerge as a significant market segment because of low reimbursement. The Centers for Medicare and Medicaid (CMS) appears to be somewhat conflicted at the moment. It is interested in the potential of home diagnostic testing to save money by filtering patients before they are assessed by a sleep lab. But at the same time, CMS doesn't want to create a situation where patients can obtain CPAP or related equipment without being diagnosed and educated by a sleep specialist. DMEs are positioning at-home diagnosis as a way for sleep labs to capture additional revenue. For the time being, this segment is unlikely to evolve further until reimbursement improves.

Different approaches have been taken to diagnostic devices. For example, ResMed has a diagnostic device that's about half the price of its competitors, and Braebon offers both a 6- and a 12-channel recorder, with the 12-channel device costing ~$4,500.

Comments included:

- "In Europe, diagnosis has been driven from the bottom-up. So, at-home diagnosis is well established because it existed before all these sophisticated CPAP solutions. In the U.S., it's coming *after* the solution, plus it has the potential for creating technical challenges for the patient to do the right things."
- "This is still a very small, emerging market. DMEs are not allowed to get involved in at-home diagnosis. The reason it hasn't evolved is it's still a new concept, and there are reimbursement issues."
- "At-home diagnostic testing been around for many years in Europe, especially France. It's still in its infancy here in the U.S., but it is starting to grow…Home diagnosis hasn't evolved yet because reimbursement isn't as attractive as it could be."
- "At-home diagnosis is still percolating below the surface because CMS is trying to restrict its (CPAP) use. CMS doesn't want patients to go on CPAP based on home diagnosis alone. They still want professional evaluation and patient-education."
- "The at-home diagnostic market is starting to open-up because $200-$400 in reimbursement is available depending upon what you are doing. Device companies are getting interested in it as a screening tool before a patient gets sent to a sleep lab…Dentists are buying these units in order to screen and diagnose OSA patients and to adjust the elevation of an oral appliance to prevent snoring. They can look at the data and crank up the elevation, if necessary."
- "I think at-home diagnosis will take off eventually. The issue at the moment is reimbursement. Yes, between $200-$400 can be available, but I've heard of cases where it's as low as $160. DME companies are starting to get involved, buying a bunch of ambulatory monitors. I've heard one group of sleep lab physicians in California is setting up a separate company to go after the nursing home segment. Medicare is looking at it from the perspective of whether it can save them money by filtering out patients before they are sent to a sleep lab. But if you are going to do an at-home diagnostic on a patient, you are probably pretty sure they have a problem and will need a visit to a sleep lab. Reimbursement will be the driver for this market."
- "I'd say we are poised and ready for the portable home diagnostic market. People are waiting to see what the reimbursement rates will be. The early estimate is $150 for testing. We are not looking to *replace* the sleep lab. Instead, we want to help them reduce overcrowding and decrease lost business due to cancellations."

Compliance Monitoring

CMS requires compliance monitoring for DMEs to get reimbursement for flow generators and scheduled replacement of masks and hoses. Will this help the market? Industry sources weren't sure. One said, "It's probably too early to tell if compliance monitoring will shift the market to higher-end machines. Some financial models suggest easier data access may drive sales of these products, but it could just be a spike that will return to baseline." Another said, "The compliance requirement is definitely driving the market to higher-end machines. Only one company currently has wireless monitoring, and that adds to the cost. Some patients are apparently being billed as much as $60 per month for wireless monitoring." A third said, "You don't need to throw a whole load of technology at the problem."

Different companies have come up with different monitoring solutions. For example, every ResMed flow generator has both a data card and an internal hard drive that backs up all the data in the event the data card is lost. ResMed also offers wireless connectivity through AT&T using its ResTraxx system. The data are collected by a ResMed server and then made available to DMEs so that they can look up their patient and submit the data for reimbursement.

DeVilbiss' SmartCode remote therapy monitoring offers remote tracking of adherence data. SmartCode is included in every IntelliPAP machine and contains all the information required for compliance monitoring over a 30-day period without any extra cost or fees. The DME provider can call the patient, and the patient can read the code over the telephone at their convenience. The code can then be entered into a website which automatically generates a report that can be submitted for compliance and reimbursement.

New Devices

A variety of new products have become or are becoming available. However, none appear to be game-changers.

General Electric

GE will be launching new CPAP-related products, possibly at the American College of Chest Physicians meeting in San Diego, October 31-November 5, 2009. No specific details about these new products were available.

ResMed's Swift LT and Swift LT for Her facemasks for OSA patients

The SWIFT LT incorporates several new features, including:

- Full 360 degree rotation on the air hose at the front of the mask, replacing the side connection.
- Venting holes in the front of the mask, making it quieter.
- Double-wall nasal pillows which make a better seal. A ResMed sales rep said patients report that it feels as though they are getting less air forced up their nose, "Some patients come back saying, 'My setting must be wrong.' We know immediately what they are talking about and explain the difference is the new pillows."

Differences in the SWIFT LT for Her facemask include:

- A light blue headband (vs. dark blue in the regular SWIFT LT).
- A range of smaller-sized nasal pillows.
- A booklet containing facts about OSA in women.

SWIFT LT for Her is currently outselling the regular SWIFT LT facemask by approximately 2:1 at ResMed's largest distributors. A ResMed sales rep commented, "Women love it, because it's made specifically for them." And the number of women being diagnosed and referred with OSA is increasing.

Respironics

Respironics is trying to position itself as the *Total Solution Company* for OSA. New products at Sleep 2009 included:

- A **total facemask** that covers the entire eyes, nose, and mouth. A Respironics sales rep said, "It forms a better seal and has premium headgear."
- **Auto SV Advanced BiPAP**, which is awaiting FDA 510(k) approval. An official said, "We hope to launch it in July (2009)." The machine performs both diagnostics and monitoring:
  - Auto EPAP (expiratory positive airway pressure) based on our proven REMstar Auto algorithm.
  - Obstructive vs. clear airway apnea detection.
  - Enhanced auto back-up rate.
  - Bi-Flex pressure relief technology.

SomnoMed's SomnoDent

This custom mouthpiece is designed to reduce snoring. The company has focused on recruiting and training dentists, who take an impression and then send it to the company to make a custom device, which takes 7-12 days. Snorers wear it when they sleep. It works by moving the lower jaw slightly forward, tightening the soft tissue and muscles of the upper airway. SomnoDent came to the US about three years ago, via Australia and Germany.

Ventus Medical's Provent

This privately-held company has a new, alternative, prescription-only device therapy for OSA that the company claims is "discreet, easy to use, disposable, and comfortable to use throughout the night, regardless of a patient's sleep position." The device uses nasal EPAP, incorporating a novel Micro-Valve design that is placed over the nostrils and secured with hypoallergenic adhesive. During inhalation, the valve opens allowing nearly unobstructed airflow. During exhalation, the valve closes, limiting airflow through two small openings, which increases expiratory pressure. Currently, Provent is only available in limited locations in the U.S. through sleep physicians.

Three posters were presented on Provent:

1. **Mechanism of action study.** Dr. Dennis Hwang of New York and colleagues reported that Provent therapy produced marked improvement in sleep-disordered breathing in 8 of 11 treated patients, with some residual sleep-disordered breathing during REM sleep. Of the 8 patients, 5 had a complete response and 3 a partial response. An investigator said, "We believe it is…(intranasal) pressure, known as autoPEEP (positive end-expiratory pressure), that keeps the airway open until the patient inhales and may increase the end-expiratory lung volume; thus creating a pull on the trachea and upper airway. This is how Provent therapy prevents apneic episodes and helps patients with sleep-disordered breathing."

2. **Effectiveness vs. CPAP.** Using modeling scenarios, a company official looked at apneas and hypopneas prevented during hours of use and those not prevented due to lack of use, finding that Provent therapy may prevent more abnormal breathing events than CPAP. She said, "This model demonstrates the importance of factoring in compliance rates when choosing a therapy for treating obstructive sleep apnea."

3. **Pooled data analysis.** A pooled analysis by company and academic researchers found a significant change in the Apnea-Hypopnea Index (AHI) in 58 patients, which they said demonstrated the viability of Provent in the treatment of OSA. Dr. Philip Westbrook of UCLA said, "Given Provent therapy is much easier to try than other therapies (mandibular advancement devices and surgical approaches), it could be an early consideration for the treatment of OSA."

PHARMACOLOGIC THERAPY OF SLEEP DISORDERS

ACTELION/GLAXOSMITHKLINE's almorexant (ACT-078573)

Actelion and GlaxoSmithKline (GSK) did not present any data on almorexant at the meeting, and neither company had a booth on the exhibit floor. Actelion and GSK entered into an exclusive worldwide collaboration (excluding Japan) in July 2008 to jointly develop and commercialize almorexant. Results of the Phase III RESTORA-1 trial in primary insomnia are expected in 2H09. GSK is currently pursuing two orexin antagonists, Actelion's compound and its own molecule, SB-649868, which is about to enter Phase III trials. Interestingly, three abstracts mentioned almorexant: a Johnson & Johnson study that compared JNJ-10397049, a specific Ox2R antagonist, to almorexant; a University of Pennsylvania rat study using almorexant; and a University of Texas, Austin, study in sparrows using almorexant.

GLAXOSMITHKLINE's SB-649868, an orexin antagonist

Dr. Paulo Bettica of GSK presented data on SB-649868, which drew a lot of interest. PK/PD modeling was shown in a poster, and proof-of-concept data were presented in lecture. The effective dose of SB-649868 appears to be ~20 mg, and it has been tested and shown effective in normal subjects, in patients with insomnia, and in a noise sleep disturbance model. Early studies were performed with a sub-optimal formulation, and the tablets had to be taken 1.5-2 hours before bed and with food. GSK now has a new formulation that doesn't require dosing with food. There is no next-day effect (hangover, etc.) at doses less than 80-100 mg. Dr. Bettica said, "It works on both subjective and objective sleep measures, which is important."

CEPHALON's Nuvigil (armodafinil, R-modafinil)

Nuvigil is the single isomer formulation of Cephalon's Provigil (modafinil). Nuvigil was launched right before Sleep 2009 – on June 1 – and is scheduled C-IV by the Drug Enforcement Administration (DEA). Cephalon has been providing samples via its sales reps but only to physicians actually prescribing Nuvigil. Several doctors indicated they were either not aware of samples or had not received any yet. A Michigan neurologist said he was not currently getting Nuvigil samples but was expecting them soon. A Virginia sleep specialist said Cephalon has not been providing many Nuvigil samples, "They are mainly handing out a copay coupon which knocks the cost to the patient way down." A Cephalon sales rep explained that the company was not restricting sampling to any one physician group, "They just have to be prescribing. The copay program at participating pharmacies gives up to $50 off the copay provided the third-party copay is at least $10. So, it brings the patient's cost down from $60 to $10. For other insurance plans there's a $600 copay card which is good for 12 prescriptions. It's simply 12 x $50."

A Cephalon sales rep explained the half-life of the S-isomer is only 3 hours vs. 15 hours for the R-isomer (armodafinil). Another employee described the difference between Provigil and Nuvigil as "all in the PK curve data," which was presented in several posters at the meeting. Both isomers of modafinil are biologically active, but Dr. Mona Darwish of Cephalon said, "S-modafinil is rapidly cleared by the liver leaving Provigil patients with only half the dose for the rest of the day. If you try to match the peak of the Nuvigil plasma concentration curve with Provigil, then you lose on the tail, and if you match the tail, you lose on the peak. So, armodafinil provides more effective drug concentrations throughout the day."

Cephalon conceded there is nothing to prevent doctors from prescribing Provigil BID, and Provigil has been studied at doses up to 400 mg/day. However, Dr. Darwish said, "You would have to decide whether to split the daily dose – say 2 x 100 mg or double it (2 x 200 mg). I think there would be side effect problems at 400 mg dosed twice per day." A physician expressed a contrary perspective, "Have you heard anything that hasn't come from the company? Has the shorter half-life of Provigil been a problem? Is there a reason why patients couldn't take a second dose? So, is it really worth an extra $10?" A Cephalon sales rep confirmed that giving a patient a second dose of Provigil is up to the prescribing physician. A second dose of Nuvigil is not an option in the current prescribing information.

One notable Nuvigil poster presented the results of a jet lag study in otherwise normal individuals. The study was a randomized, double-blind, placebo-controlled, parallel-group comparison of Nuvigil 50 mg or 150 mg/day vs. placebo in 427 patients with a history of jet lag disorder. Dr. Richard Bogan of SleepMed, who was presenting the poster, said, "I think it's really neat to pull off approval by two IRBs

(institutional review boards) on different sides of the Atlantic. 50 mg of armodafinil is a piddly dose. We'd never use it in narcolepsy patients, but then they're not normal. The Nuvigil label allows for dosing up to 250 mg, and there's a clear dose-response relationship. The potential jet lag market is two-thirds of international travelers. But how many east-bound time zones the FDA will require to approve a drug for jet lag is a confounding issue. The effect size in this study was comparable to what we've seen in shift workers and narcolepsy patients. It's a big signal on the first day, bigger than we've seen in other settings. I think Cephalon will file for this indication. Given the data in the other indications, it should really be a no-brainer for the FDA. I hope they won't require a second study."

Another poster reported on a comparison of the PK profile of Provigil and Nuvigil, concluding, "The terminal half-life does not fully define the duration of action of a medication. While armodafinil and modafinil have comparable half-lifes after a single dose, they exhibit different PK profiles. Modafinil has a biphasic elimination profile, while armodafinil has a monophasic elimination, resulting in higher plasma drug concentration later in the day. This difference suggests that armodafinil may have the potential to maintain its wakefulness-promoting effects later in the day. As a result, treatment with armodafinil may be less likely to require higher doses and/or multiple doses."

Nuvigil in Patients with Jet Lag

Measurement	Nuvigil 50 mg n=142	Nuvigil 150 mg n=143	Placebo n=142
Primary endpoint #1: Wakefulness by MSLT sleep latency score on Day 1-2	7.7 (p<0.0001)	11.7 (p<0.0001)	4.8
Primary endpoint #2: PGI-S on Days 1 and 2	Nss	1.6 (p=0.0441)	1.9
MSLT (Multiple sleep latency test)			
Day 1	5.6	9.7	3.4
Day 2	9.9	13.8	6.2
Day 3	12.1	14.8	8.2
PGI-S (Patient global impression of severity)			
Day 1	2.2	1.7	2.1
Day 2	1.6	1.5	1.6
Day 3	1.2	1.4	1.4
Karolinska Sleepiness Scale			
Day 1	5.7	4.8	6.3
Day 2	4.0	3.7	4.7
Day 3	3.6	3.6	4.0
Safety			
Headache	16%	25%	11%
Nausea	2%	13%	4%
Diarrhea	4%	5%	3%
Palpitations	<1%	5%	0
Circadian rhythm disorder	<1%	4%	0
Fatigue	2%	3%	0

A small (5-patient), randomized, double-blind, placebo-controlled, crossover study presented at Sleep 2009 looked at patients with shift work disorder and found they were more alert and less prone to napping at night after taking Nuvigil vs. placebo. Previous studies had shown only a 1.7-3.0 minute improvement on SWSD (shift work sleep disorder) with Nuvigil, but this study got better results by using a more select group of patients – those with a symptom-based diagnosis rather than a sleep lab value diagnosis. In these patients, nocturnal sleepiness dropped 12.65 minutes with 150 mg Nuvigil vs. 5.68 minutes with placebo ($p<0.05$).

Cephalon sponsored a dinner symposium titled, *Sleep Wake Disorders: Long-term Neurocognitive, Executive, and Behavioral Consequences and Clinical Controversies*. The key messages appeared to be:

- Neurocognitive deficits can occur without the feeling of sleepiness.
- Structural changes in the brain that occur as a result of untreated OSA may not be reversible.
- OSA may lead to showers of emboli in the vasculature, and snoring may increase carotid intimal thickness by acoustic vibration.
- CPAP may not be a complete treatment for OSA and may still leave some impairment of executive function.

Only two slides during the symposium contained any information about modafinil or armodafinil. No information was provided to the audience about how armodafinil is different from modafinil or about any advantages.

Dr. Michael Thorpy of Albert Einstein College of Medicine simply noted that:

- Both drugs are FDA-approved for obstructive sleep apnea/hypopnea syndrome (OSAHS) and SWSD.
- Armodafinil improves episodic memory quality in treated OSA patients with residual sleepiness.
- Should we be doing more to assess cognitive function in sleep-impaired patients?

A doctor in the audience asked if there was any tolerance to modafinil. Dr. Thorpy answered, "None has been reported so far with either modafinil or armodafinil." Privately, however, a Midwest neurologist said he uses Provigil for his MS patients and only prescribes one dose per day. In his experience some patients become tolerant to modafinil after 2-3 weeks. If treatment is stopped for 5-7 days, response returns, "It's not a metabolism issue. It seems to be desensitization in the brain."

INTRA-CELLULAR THERAPIES' ITI-007 (formerly ITI-722), a low-dose 5HT-2_A antagonist

ITI-007 acts on novel intracellular phosphorylation pathways. This compound is primarily a 5HT-2_A antagonist, but it is also a dose-dependent pre-synaptic partial D2 agonist and a post-synaptic D2 antagonist. At higher doses it also inhibits 5HT reuptake.

Intra-Cellular Therapies is currently performing a PET study in normal volunteers to assess the dopaminergic effect of the drug. So far, it appears the effect is linear with respect to dose. ITI-007 improves sleep maintenance by increasing slow-wave sleep and decreasing time awake after sleep onset (WASO).

Intra-Cellular Therapies does not plan to develop ITI-007 for sleep *per se* and believes it may be a useful therapy for schizophrenia and/or depression, as well as conditions in which insomnia is a comorbid condition. The company has a second development candidate that increases wakefulness.

SANOFI-AVENTIS' Ciltyri (eplivanserin), an HT-2_A antagonist

This drug is a first-in-class agent being developed for chronic insomnia with nocturnal awakenings. Eplivanserin was submitted to European regulators as well as the FDA in November 2008. It is intended to help patients who have difficulty falling asleep and is expected to have no significant next-day effects (drowsiness, hangover) vs. the benzodiazepines and GABAergic drugs. Eplivanserin will be dosed once in the evening. Middle-of-the-night (MOTN) dosing will not be an option for patients who awaken early.

A Sanofi-Aventis presenter said, "There are no food effects, so patients can take it with their evening meal, before they go to bed. Tolerability issues are a few headaches, some dizziness, and GI side effects, but nothing significant…I envision eplivanserin being used on a continuous basis in appropriate patients with periodic assessment by their physician. It would not be a *prn* (as needed) medication."

Data presented at Sleep 2009 showed total sleep time, sleep quality, refreshing sleep, and concentration all improved with eplivanserin, while awakenings during the night and morning sleepiness decreased. No rebound insomnia was reported. In a Phase III trial, 1,145 patients with chronic insomnia and sleep maintenance difficulties were randomized 3:1 to eplivanserin 5 mg/day or placebo for 12 weeks, followed by a 40-week extension phase, during which all patients received eplivanserin.

Eplivanserin showed significant improvement vs. placebo on the primary endpoint of patient-reported wake-time after sleep onset at Week 12 (a difference of 13 minutes, $p<0.0001$) as well as significant improvement in the principal secondary endpoint of the daytime functioning items of the Functional Outcomes of Sleep Questionnaire (FOSQ) at Week 12. In addition, the eplivanserin patients had meaningful improvement in measures of work- and leisure-related activities vs. placebo. Sleep-onset latency did not differ significantly between treatment groups. Eplivanserin was generally well tolerated. Treatment-related adverse events included were dizziness, diarrhea, somnolence, dry mouth, constipation, diverticulitis, and upper abdominal pain.

Six eplivanserin posters were scheduled to be presented at Sleep 2009, but two were withdrawn, and one wasn't presented. The three posters that were presented did not appear to attract much attention. Here are the results from two of the three posters:

1. **Driving.** A study reported that eplivanserin 5 mg given for 21 days did not alter driving or cognitive/psychomotor performance in patients with sleep maintenance insomnia while Valeant Pharmaceuticals' Dalmane (flurazepam) markedly impaired driving and cognitive psychomotor performance. The findings came from a 28-patient, single-center, randomized, double-blind, placebo-controlled, double-dummy, repeated dose, 3-way crossover study.

On Day 20 of each treatment period, patients completed a driving test, and they were evaluated with respect to standard deviation of lane positioning and number of lane crossings. The test was repeated at 2, 12, 16, 20, and 23 hours after taking the assigned therapy (eplivanserin or flurazepam). The deviation in lane positioning and the number of lane crossings increased significantly with flurazepam ($p<0.0001$) but not eplivanserin. Flurazepam also was associated with significant impairment vs. placebo in composite scores for power of attention ($p<0.05$) and quality of episodic secondary memory ($p<0.0001$), but those parameters did not differ significantly from placebo with eplivanserin.

Eplivanserin Effect on Driving and Cognitive/Psychomotor Performance

Measurement	Flurazepam vs. placebo n=28	Eplivanserin vs. placebo n=26
Standard deviation of lane positioning	<0.05 from 2-14 hours	Nss at any time point
Number of lane crossings	<0.05 from 2-16 hours	Nss at any time point
Brake reaction time	Nss	Nss
Power of attention (maximum difference)	At 2 hours, p=0.0187	At 20 hours, p=Nss
Quality of episodic secondary memory (maximum difference)	20 hours, p=0.0018	23 hours, p=Nss, 0.0754
Quality of episodic secondary memory over 24-hour period	<0.0001 the whole time	Nss the whole time
Safety		
Somnolence	17 patients	3 patients
Nervous system disorders	0	30.8% (headache, somnolence, and balance)
GI disorders	7.1%	11.5% (nausea, dry mouth, vomiting)

2. PK/PD study of cognitive and psychomotor performance. A study in healthy volunteers found that repeated dosing with eplivanserin 5 mg did not produce a significant global effect on next-day morning psychomotor and cognitive performance vs. placebo. The results came from a two-part, double-blind, randomized, placebo- and active-controlled, 4-way crossover study in 24 adults.

PK/PD Study of Eplivanserin and Cognitive/Psychomotor Performance

Measurement	Flurazepam vs. placebo	Eplivanserin vs. placebo	Eplivanserin + Ambien IR vs. placebo
Primary endpoints			
Overall treatment effect	p=0.00 01	Nss, p=0.0603	Nss, p=0.1337
Choice reaction time	p<0.0003	Nss	Nss
Compensatory tracking task	p=0.005	Nss	Nss
Immediate word recall	p=0.0001	Nss	Nss
Delayed word recall	p=0.0001	Nss	Nss
Bond-Laser VAS – alertness	p=0.0031	Nss	Nss
CFF threshold	Nss, p=0.2005	p=0.0002	p=0.002
Safety with study drug (not placebo)			
	Placebo	**Eplivanserin**	**Eplivanserin + Ambien IR**
Headache	25%	25%	4.2%
Dizziness, somnolence, and asthenia	4.2%	29.2%	4.2%
Somnolence	0	29.2%	4.2%

SOMAXON PHARMACEUTICALS' Silenor (doxepin), an H_1 antagonist

The company believes Silenor will improve sleep maintenance. An NDA was submitted in June 2008, and the FDA issued an approvable letter in March 2009. A Somaxon official said, "We just re-submitted last week (early June 2009)." The issue is apparently QTc interval data and FDA questions about subjective sleep measures. The QTc data have now been reviewed by the FDA's Cardio-Renal Division, and a Somaxon official said, "They've told us it's okay, so we are hoping for a Class I re-submission review, but we suspect the FDA may well assign it a Class II review." Somaxon expects approval for insomnia but not for sleep induction and maintenance because there were no data collected on those endpoints in the clinical trials. The official said, "We might develop an orally disintegrating tablet, do an onset trial, and get three more years of exclusivity." The speaker for a talk on the doxepin Phase III results was a no-show.

SOMNUS THERAPEUTICS' zaleplon controlled-release

There were five posters supporting this controlled-release formulation of zaleplon, using SkyPharma's Geoclock chronotherapy delivery system. Proof-of-concept PK and pharmacodynamics (PD) data were shown for a 15 mg tablet in three different novel formulations – 2 hour delayed but immediate release (IR); 2 hour delayed and 2 hour controlled release (CR); or 1 hour delayed and 4 hour CR.

All of these posters were based on results of a Phase I, double-blind, randomized, placebo-controlled, crossover study in 19 healthy volunteers.

1. **PK.** This study found that all three 15 mg formulations tested had consistent active drug concentrations at different time points, with rapid decline after T_{max}. Most adverse events were mild/moderate. One person reported moderate/severe anxiety and a moderate increase in blood pressure after formulation "C" and was discontinued from the study.
2. **PD.** This suggested morning dosing, with the PD profile related to the PK profile.
3. **Subjective alertness after 1 dose.** The study found significant increases in subjective sedation and feeling of sleepiness with all three formulations, and the increases occurred at a later time post-dose than with zaleplon IR.
4. **Sleep latency.** All three CR formulations significantly increased sleep tendency vs. placebo and vs. zaleplon IR during 1-4 hour post-dose time period. The different formulations had dif-ferent time courses of sleep-promoting activity, corresponding to the plasma drug level.
5. **Sedation.** All three CR formulations showed maximum sedation from 3-5 hours post-administration by changes in EEG and Karolinska Drowsiness Test.

TRANSCEPT PHARMACEUTICALS' Intermezzo (3.5 mg zolpidem sublingual tablet)

This is being positioned for MOTN *prn* dosing. The tablet melts, but the patient also chews the remaining pieces, so there is both sublingual and gastrointestinal (GI) absorption. Dr. Russell Rosenberg of NeuroTrials Research in Atlanta explained, "There was a trend over 4 weeks for patients to use fewer, rather than more, tablets per week, which supports *prn* use." MOTN dosing did not appear to be a hot topic in the poster sessions.

An NDA for a zolpidem sublingual tablet (ZST) is currently under review by the FDA. A decision had been expected in July or August 2009, but shortly after the meeting the FDA announced it was extending its review cycle by three months to consider dosing instructions it had requested from Transcept but had only recently received. Transcept now anticipates a decision on the NDA on or before October 31, 2009.

Two posters on Intermezzo were presented at Sleep 2009.

1. **PRN use.** A study by Thomas Roth, PhD, chief of sleep medicine at the Henry Ford Hospital Sleep Disorders and Research Center, *et al* evaluated the efficacy of Intermezzo taken on an as-needed (*prn*) basis during a one-month period for the treatment of MOTN awakenings followed by difficulty returning to sleep. The randomized, 4-week, double-blind,

placebo-controlled study was conducted in 295 outpatient adults with insomnia. Intermezzo was to be taken only when needed at the time of awakening with difficulty returning to sleep.

An interactive voice response system (IVRS) was used for patient data collection. Results indicated that, compared to placebo, Intermezzo significantly reduced latency to sleep onset after MOTN awakenings and improved sleep quality and next-day alertness ratings throughout the treatment period. Furthermore, Intermezzo improved the post-MOTN sleep maintenance parameters of wake after sleep onset and the number of awakenings vs. placebo. The drug was well tolerated, and no safety issues were identified.

PRN Efficacy of Intermezzo

Measurement at Week 4 post-MOTN dosing	Placebo	Intermezzo	p-value
Latency to sleep onset (change from baseline)	~ -10 min.	~ -28 min.	<0.0001
Total sleep time (change from baseline)	~ 22.5 min.	~ 28 min.	Nss
Total time in bed post MOTN-awakening	286 min.	301 min.	---
Overall reduction in patients awake 60 minutes after awakening	~ 25%	~ 17%	0.006
Number of awakenings			
0 awakenings	~ 16%	~ 30%	<0.001
>0 but ≤1 awakening	~ 42%	~ 46%	
>1 but ≤2 awakenings	~ 26%	~ 18%	
>2 awakenings	~ 15%	~ 7%	
Findings on dosing nights *			
Sleep quality	5.2	5.8	<0.001
Morning alertness	5.2	5.7	<0.004

* on scale of 1-9, with 9 best

2. Post hoc rebound analysis. A preliminary post hoc analysis of a 4-week outpatient study in adult primary insomnia patients with a documented history of MOTN awakening found that Intermezzo does not cause rebound. That is, there was no adverse effect on sleep on non-dosing nights. Rebound is typically defined as the effect after a medication is discontinued, when the symptoms being treated by that medication return with severity greater than before the medication was first taken.

The analysis evaluated the sleep characteristics on non-dosing nights and average weekly tablet use. On nights when medication was not taken, no rebound effects were seen, as determined by total sleep time, sleep latency at the beginning of the night, and sleep quality. In the study, 65% of patients did not take medication nightly, and there was no evidence of increased utilization of the drug over the 4-week treatment period.

Intermezzo Effect on Non-Dosing Nights

Measurement on non-dosing nights	Placebo	Intermezzo	p-value
Time to sleep onset	51.0 min.	47.3 min	Nss
Total sleep time from bedtime	369.5 min.	320.3 min.	Nss
Next morning sleepiness/alertness scores	5.0	5.3	Nss
Sleep quality scores	5.1	5.3	Nss

Restless Legs and Periodic Limb Movement Syndromes (RLS & PLMS)

Approximately 10% of adults suffer from RLS at any given time, of which ~2.5% have symptoms >2-5 times per week. In addition to the discomfort of RLS, epidemiology studies suggest these patients are at increased risk of developing hypertension and cardiovascular problems. RLS is accompanied by elevations in heart rate and blood pressure during nocturnal periodic limb movements (PLMs). This appears to be a consequence of autonomic dysregulation associated with microarousal and PLM rather than generalized increased sympathetic tone. An expert said, "The key missing data at the moment is whether treatment of RLS, in addition to treating PLMs, results in a corresponding improvement in blood pressure and heart rate control and other autonomic functions."

Dr. Arthur Walters of New Jersey described treating nocturnal PLMS to obviate the risks for heart disease, stroke, anxiety, and depression as "the new frontier." He posed the question, "Does treating PLMS decrease heart rate during attacks of PLMs?" Dr. David Rye of Emory University commented, "This begs for a drug study, since this is a fairly new concept." Prof. John Winkelman of Harvard urged the audience to use their contacts and badger pharmaceutical companies to do such a study, "It needs to come from the pharmaceutical industry...Pharma and the (sleep) field would have a lot to gain."

Dr. Raffaele Ferri of Sicily stated that PLMS involves periodic and non-periodic leg movements and that dopamine agonists only treat the periodic movements, "We need to start thinking about the whole syndrome." Dr. Walters agreed, "We may need to revisit the old idea of treatment with vasodilators." Prof. Winkelman added, "It would be interesting to see the effect of combining a dopamine agonist and a benzodiazepine for PLMS." Dr. Ferri indicated he is already doing a study to look at this combination.

RLS patients with low serum ferritin can be treated with intravenous (IV) iron. Those with normal iron levels are generally treated with a non-ergot dopamine agonist – e.g., ropinirole or Boehringer Ingelheim's Mirapex (pramipexole) – an anticonvulsant (e.g., gabapentin), or opioids. Opioids are another good treatment option for the discomfort of RLS. Short-acting opioids such as oxycodone or hydrocodone are used, as well as methadone for a longer duration of action. Prof. Winkelman said, "Dopamine agonists are extraordinary drugs that have had a profound effect on patients' lives."

Ropinirole, now generic, has a half-life of 6-8 hours, is metabolized primarily in the liver, and has a fast onset of action. Mirapex, which will be generic in 2010, has a longer half-life (10-12 hours), is metabolized primarily by renal excretion, and has a slower onset of action, all of which make it less effective as a *prn* treatment. Both drugs have similar side effects, and approximately one-third of patients develop augmentation (paradoxical worsening of symptoms). Boehringer Ingelheim did not have an exhibit promoting Mirapex at the Sleep 2009, but there were two posters that appeared to be unmanned during the author presentation period. In an agreement with Boehringer Ingelheim, Barr is expected to launch generic pramipexole in January 2010, 10 months ahead of patent expiration. In return, Barr will pay Boehringer Ingelheim a royalty on sales.

NEUROGEN's aplindore (DAB-452) for RLS

Aplindore is in Phase II development for RLS. It was described as "a very potent partial dopamine agonist (DA), with more activity on D2 than D3 receptors," unlike other DAs that have more activity on D3 than D2. Aplindore reaches C_{max} in 2 hours, has a half-life of 7 hours, and is metabolized by multiple liver cytochrome P450 enzymes. If approved, it would be a once-daily therapy for RLS.

One Phase II study has completed within-subject dose escalation/ titration, with periodic limb movement (PLM) the primary endpoint. Neurogen is conducting a second Phase II trial, using parallel dose groups and IRLS (International Restless Legs Scale) scoring. Phase III development is rumored to be on hold until Neurogen can secure additional financing. Potential advantages of aplindore are better tolerability (less nausea and dizziness) and possibly a lower incidence of augmentation, but there are no data yet to support the latter.

PFIZER's Lyrica (pregabalin) for RLS

Neurontin has been used successfully to treat RLS and is particularly good for helping patients sleep. Lyrica is in clinical development for RLS, and data from the first controlled trial were presented at Sleep 2009 by Dr. Diego Garcia-Borreguero of Spain. The trial design attempted to minimize a placebo response by incorporating a 2-week placebo run-in and eliminating patients who had >40% response during that period.

At Week 12, after dose-titration, the change in the IRLS score was significantly different for pregabalin vs. placebo ($p<0.05$), and the mean dose was 337.5 mg. Approximately 73% of patients in the pregabalin group were responders (>50% response) vs. only 38% in the placebo group. The effect size was described as "comparable to pramipexole studies and stronger than ropinirole. Rotigotine has produced slightly higher responses, but that maybe due to the fact those studies had a slightly different patient type."

Side effects were unsteadiness (50% vs. 10.7%) and daytime sleepiness (43.3% vs. 14.3%). One physician expressed surprise that the dose of pregabalin was so high, "We typically use 50 mg, or maybe 100-150 mg, and it works." Dr. Garcia-Borreguero explained that the dosing in this trial was based on old gabapentin data, and they didn't want to miss an effect on polysomnography. Prof. Winkelman commented that increasing frequency and types of adverse events seen with higher doses of an active drug in a randomized double-blind clinical trial could un-blind an investigator. "How do we handle this in our studies? It may not be long before the FDA gets concerned about this and requires us to do active comparator trials."

UCB's Neupro (rotigotine transdermal patch) for RLS and Parkinson's Disease

This has been off the market in the U.S. and has had a "no new patients" and a "one-month supply" restriction in Europe because of crystallization issues in the patch. European regulators (the EMEA) indicated May 29, 2009, that it is satisfied that cold-chain distribution and storage is preventing crystallization problems and has recommended the current restriction be lifted. Endorsement by the European Commission is pending.

UCB is expecting Neupro to return to the U.S. market early next year. It is not clear yet what the FDA will require, but cold-chain distribution and storage is very likely. In the long-term, however, UCB will need to develop a new manufacturing process that eliminates or minimizes the synthesis of the rotigotine polymorph that crystallizes at temperatures above 80°C. Like Mirapex, rotigotine has a long half-life and so will be continuous therapy. Most U.S. physicians that used Neupro before it was withdrawn from the market liked the product.

A retrospective analysis was presented at Sleep 2009 of long-term data in 620 patients who entered open-label extension studies of two double-blind clinical trials with Neupro. Researchers reported good symptom relief and no spike in augmentation. There was no dose relationship with augmentation.

Augmentation at 1 Year with Neupro in RLS

Measurement	Neupro
Augmentation	9.4%
Clinically-relevant augmentation	2.9%

However, an expert cautioned it is probably too early to tell whether or not rotigotine patients will develop augmentation. "When you start manipulating the dopaminergic system in the brain, it's pretty good at finding a way to fight back," he said.

XENOPORT/GSK's gabapentin enacarbil (XP-13512) for RLS

This is an improved formulation of gabapentin with better absorption characteristics. An NDA was submitted September 16, 2008, but withdrawn November 10, 2008, to reformat data. The application was resubmitted January 9, 2009, and so a decision is expected by mid-November. Recently, the FDA has disallowed XenoPort's proposed brand name (Solzira). A XenoPort official said, "So, it's back to the drawing board. It's a pity. We all liked the name." There was no indication at the meeting what the new brand name might be.

XenoPort presented eight posters, all but one of which had been presented at the American Academy of Neurology meeting in April 2009. The one new poster showed pharmacokinetic (PK) and tolerability data from study XP-081. Gabapentin enacarbil displayed better absorption, more dose-proportionality, and less inter-patient variability vs. generic gabapentin. A XenoPort official said, "Plus it's an extended-release formulation, so it is once-daily dosing. That may be important for indications other than RLS, such as neuropathic pain where patients need full coverage throughout the day."

Subjective measures of sleep quality were included in both Phase III RLS trials (PIVOT-1 and -2). A polysomnographic study is underway, and no data are available yet. GSK has apparently not filed an MAA (Marketing Authorization Application) with European regulators for RLS, but XenoPort believes GSK will file the neuropathic pain indications, assuming the data are positive. Gabapentin enacarbil is currently in Phase II development for post-herpetic neuralgia (PHN), diabetic peripheral neuropathy (DPNP), and migraine. Anti-convulsant therapies are unlikely to be associated with augmentation in RLS.

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