CNS Orphans and Disease Subsegments: The Road Less Traveled

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The contents of this presentation are not meant to be comprehensive, but to encourage a spirited dialogue. Feedback, comments and corrections are welcome.
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25th Annual Cancer Progress Conference
March 4 – 5, 2014
New York City
www.cancerprogressbyDH.com

**THERAPEUTIC INSIGHT**
BioEurope Spring
March 10 – 12, 2014
Turin, Italy
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:


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CNS Orphan/Subsetting Insight Briefing
In CNS Broadly, The Balance has Tipped Toward Too Much Risk

- In the context of an increasingly generic standard of care, the commercial risk now associated with many of the major CNS diseases (e.g., depression, epilepsy, migraine, schizophrenia, ADHD) has become too big for many big and specialty pharma companies.
The Pharma Brain Drain

- Big and specialty pharma companies, who were once willing to take on the clinical risk inherent in CNS drug development to realize the commercial reward, are now exiting the space en masse.

AstraZeneca cutting 2,200 R&D jobs, slashing neuroscience in restructuring
_FierceBiotech_ Feb. 2012

GSK cuts neuroscience R&D staff in RTP
_FierceBiotech_ Feb. 2011

Novartis to shut brain research facility
_Nature_ Dec. 2011
Opportunities to Balance the Risk in CNS

- Those companies who are not ready to give us up on CNS see an opportunity to balance the risk by targeting orphan diseases - and high unmet need market subsegments.
Opportunities to Balance the Risk in CNS
The Orphan Promise

The Orphan Promise: low cost/short timeline development program, friendly regulatory process, pricing flexibility, minimal commercialization costs and market exclusivity.

- **Development Pros**
  - Potential Fast Track, Priority Review
  - Tax credits and fee waivers
  - Grants
  - Advocacy support
  - Enthusiastic clinical investigators
  - Higher than average clinical success rates

- **Commercialization Pros**
  - 7-year market exclusivity
  - Motivated patients
  - Advocacy support
  - Pricing flexibility
  - Minimal competition
  - Targeted sales force
Pharma is Embracing the Orphan Strategy

GSK Rare Diseases was set up in February 2010 to discover, develop and deliver new and innovative medicines to treat rare diseases. Our ambition is to create a sustainable portfolio of affordable medicines that can make a real difference patients living with often devastating and life-threatening conditions. At the beginning of 2012 we had three potential new medicines in late-stage development.

Our research priorities are not determined by potential market size. Our research organization, the Novartis Institutes for BioMedical Research (NIBR), is to actively target rare diseases where we have clear understanding of the disease's underlying cause and where there is real unmet medical need.

Pfizer's Orphan and Genetic Disease Research Unit (OGD) is adopting an innovative and collaborative approach to the development of new medicines whereby it looks to develop strategic partnerships with academic and commercial enterprises to create novel therapeutics across the spectrum of rare diseases. A key mission is to create next generation medicines by exploring pathogenic mechanisms that apply to clusters of monogenic diseases. Many orphan diseases are caused by protein misfolding, mistrafficking, and/or accumulation, and OGD is focusing on building capabilities to explore and address these aspects of proteinopathy.
Orphan Disease: A Multibillion Dollar Category, and Growing

- EvaluatePharma finds that the market for orphan drugs, based on the consensus forecast for the leading 500 pharmaceutical and biotechnology companies, will grow by 7.4% per year (CAGR) between 2012 and 2018 to $127bn.
But, Payers are Pushing Back on Orphan Prices

PROCYSBI™ (cysteamine bitartrate, Raptor Pharmaceutical Corp.) delayed-release capsules, is FDA approved (via a 505(b)(2)) pathway for the management of nephropathic cystinosis in adults and children 6 years and older.

- PROCYSBI is a delayed-release version of cysteamine (Cystagon), a drug approved in the 1990s to extend the lives of the few than 1,000 patients worldwide with the potentially fatal orphan disease cystinosis. Many of those patients are infants who, if they don’t take the drug, lose kidney function, require a kidney transplant and often die by the time they are teenagers.

- The immediate-release formulation requires strict adherence to a 6-hour dosing schedule (including a middle-of-the-night dose) to maintain adequate therapeutic drug levels. Patients and caregivers struggle to comply with the frequency of dosing and the drug side effects, which include severe GI distress (nausea, vomiting) and an exhaled rotten egg smell and body odor. The requirement for middle-of-the-night dosing is the most significant compliance burden noted by patients, with approximately 70% to 80% of patients failing to comply with prescribed dosing.

- PROCYSBI has an improved dosing and side effect profile that is expected to increase treatment compliance, which may reduce the potential need for kidney transplant later in life.
Who is Paying for PROCYSBI?

Raptor Pharmaceutical Corp. will launch an ultra-Orphan drug this quarter that it has shown to be non-inferior to a cheaper alternative. The company has yet to get any payers on board, but believes it can win them over based on the drug’s ability to improve compliance and quality of life for patients with nephropathic cystinosis.

Raptor has set the U.S. list price of Procysbi (RP103) at $250,000 annually. The immediate-release formulation of the drug, Cystagon cysteamine, is marketed by Mylan Inc. for about $10,000 per year.

... a payer told BioCentury it is not inclined to cover the drug without proof of long-term clinical benefit and cost savings. Getting those data could take at least five years...
CNS is Underrepresented in the Orphan Market

- Oncology therapeutics dominate orphan drug approvals, accounting for 33% of the marketing authorizations from 2006 to 2011.
- Of the ~60 orphan drug approvals (2006-2011), 17% are for CNS disorders.

Orphan Drug Approvals by Therapeutic Area (2006-2011)
The CNS Gap is Widening

- Of the 460 drugs in clinical trials for orphan diseases, only 37 are for CNS indications. And those cluster around a few disease types.

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**Orphan Drug Clinical Pipeline**

- Autoimmune disorders: 18
- Blood disorders: 12
- Cancer: 107
- Cancer, blood: 79
- Cancer, skin: 31
- Cancer-related conditions: 10
- Cardiovascular diseases: 6
- Eye disorders: 11
- Gastrointestinal disorders: 10
- Genetic disorders: 67
- Growth disorders: 5
- Infectious diseases: 31
- Neurological disorders: 37
- Respiratory disorders: 14
- Transplantation: 20
- Other: 37

**Categories:**
- Neurodegenerative Disease (e.g., ALS, HD)
- Developmental/Learning Disabilities (e.g., Fragile X)
- Spinal Cord Injury
- Intractable/Refractory Epilepsy
Traditional CNS Challenges Still Hold for Orphan Diseases

- Disease biology?
- Validated targets?
- Validated biomarkers?
- Definitive diagnosis?
- Time of intervention?
- Trial design?
- Subjective clinical endpoints?
- Placebo response?
- Outcome measures?
- Well defined disease burden?
Orphan CNS Today: Range of Price (and Value)

- Fabrazyme
- MS Drugs
- Sabril
- Acthar
- Banzel
- Xyrem
- Xenazine
- Ampyra
- Rilutek
- Cuvposa
- MS Drugs
- Sabril
- Xenazine

Average Annual Cost of Therapy (WAC)

- $5,000 - $20,000
- $25,000 - $40,000
- $50,000 - $130,000
- $150,000 - $400,000+

Value Proposition

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Orphan CNS Today: Range of Price (and Value)

- MS disease-modifying drugs set the bar.

Redbook: DH Analysis
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CNS Orphan/Subsetting Insight Briefing
MS Disease Modifying Drugs: Set the Bar and Price

- Disease-modifying MS drugs target a medically relevant subsegment of the overall patient population (relapsing-remitting disease), qualifying them as orphan drugs.
- The value proposition is clear: delay of disease progression.
- The $14+ billion dollar MS market (worldwide), dominated by big pharma and specialty companies, continues to grow at a significant pace, driven by new market entrants and aggressive US price hikes.

Multiple Sclerosis Category Market Share By $ Sales

Source: Company data; Cowen and Company
Orphan CNS Today: Range of Price (and Value)

- Symptomatic MS therapy struggles to establish market access.
AMPYRA / FAMPYRA: The Challenge of Establishing Value to All Stakeholders

- Ampyra (Acorda/Biogen Idec), an extended-release oral agent that blocks axonal potassium channels, was approved in Jan. 2010 with an indication to improve walking in patients with MS.

- In 2009, Acorda partnered ex-U.S. rights to dalfampridine with Biogen Idec in return for a $110MM upfront payment, up to $400MM in regulatory, sales and clinical milestones, and tiered double-digit royalties on ex-U.S. sales.

- After an initial rejection in the EU, the CHMP of the EMA recommended conditional marketing authorization of Ampyra (Fampyra in Europe) in mid 2011.

- The drug was off to a solid launch with ex-U.S. sales of $35MM in H1:12 (mostly from Germany). However, in May 2012 Germany’s IQWiG ruled that Fampyra was associated with no incremental benefit, throwing the still ongoing pricing negotiations with the GBA into doubt.

Ron Cohen, CEO of Acorda Therapeutics, regrets not consulting insurers early about its AMPYRA, the first drug to help multiple sclerosis patients walk better.

CHEManger Europe Dec. 2011
Orphan CNS Today: Range of Price (and Value)

- Modest benefit limits pricing flexibility.
Cuvposa: Value to the Patient

- Cuvposa (glycopyrrolate) Oral Solution (Shionogi Pharma Inc.) was approved by the FDA in July, 2010 to treat chronic severe drooling caused by neurologic disorders in children ages 3 years to 16 years, a condition that affects QoL and can impact the ability to swallow.

- Glycopyrrolate was approved decades ago to treat peptic ulcers and reduce salivation in patients under anesthesia.

- When used off label, oral tablets had to be crushed to treat drooling in children with neurological disorders. **Cuvposa is a cherry flavored oral solution that is easier to administer and provides the optimal dose for each patient.**

- In clinical trials, 78% of children on the drug reached clinical improvement in drooling (vs. 19% with placebo).

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**Merz, Inc. Announces the Acquisition of CUVPOSA® (glycopyrrolate) Oral Solution, First and Only FDA-Approved Treatment for Pediatric Chronic Severe Drooling Associated With Neurologic Conditions**

Aug. 27, 2012

*The addition of CUVPOSA® reflects Merz’s commitment to neurology*

"The FDA has classified CUVPOSA® as an orphan drug since sialorrhea is a rare disorder in pediatric patients with neurologic conditions," said Kapil D. Sethi, MD, FRCP, Professor of Neurology and Director of the Movement Disorders Program at Georgia Health Sciences University and Senior Medical Expert of Neurology at Merz Pharmaceuticals, LLC. "Due to the limited treatment options available, sialorrhea is an all-too-often poorly managed condition in pediatric patients suffering from neurologic disorders such as cerebral palsy. CUVPOSA®, the only FDA-approved treatment on the market, is an important advancement in the treatment of chronic severe drooling in children with neurologic disorders."
Cuvposa: But Payers Aren’t Buying It

Conclusion (Product Value): **Cuvposa brings uncertain clinical value to the treatment of chronic severe drooling, however it may offer some convenience** over other options because of dosing flexibility for individual patients, and would preclude the need for tablets to be crushed before administration.

Decision: Maintain Cuvposa as **non-preferred/non-formulary** because there is uncertain evidence for efficacy and there are other less costly formulary options. (Cuvposa is $227-$373 per 30 day Rx; oral glycopyrrolate tables are $79 per Rx).
Rilutek: Moderate Value for a Desperate Disease

- Rilutek (riluzole, Sanofi) is the only drug indicated for the treatment of amyotrophic lateral sclerosis (ALS), a persistent and progressive disease that causes muscle weakness, disability, and eventual death (typically within 3-4 years of diagnosis). While its exact mechanism of action is unknown, Rilutek is believed to modulate glutamate signaling.
- Rilutek was approved in 1995 based on the results of two Phase III studies which showed an average 3 month increase in survival (or time to tracheostomy). Current sales of ~$200M.
- KOLs consider Rilutek an important component in the treatment of ALS, with solid evidence to support a modest survival benefit.
- However, as the disease progresses, the benefit does not outweigh the cost to the patient – even if minimal (an estimated 75% of patients pay less than $50 co-pay per prescription).

Living for Today, Locked in a Paralyzed Body

ALS patients and their families are forced, on a daily basis, to take stock of the meaning and quality of their lives and to make repeated decisions about how much is too much. Patients with the illness, Dr. Ganzini said, are 25 times as likely to die by doctor-assisted suicide as people with other diseases. Dr. McCluskey, a neurologist in Philadelphia, said that at least 90 percent of patients with ALS decided to die when they could no longer breathe on their own, although medical science can extend their lives much longer (i.e., tracheostomy).

The New York Times (2004); Rilutek product label

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The Next Generation Therapies for ALS

- After nearly two decades since the launch of the first drug indicated for ALS (Rilutek), we are now poised to have two new therapies for this devastating disease – one a neuroprotective agent (dexpramipexole), the other addressing muscle strength and function (tirasemtiv).

Biogen Announces It Will Discontinue Development of Dexpramipexole
January 3, 2013
Dexpramipexole: Neuroprotection

- Dexpramipexole (KNS-760704) exhibits neuroprotective capabilities comparable to pramipexole (Mirapex), potentially mediated through the modulation of aberrant mitochondrial ion channel conductance, but with significantly reduced affinity toward dopamine receptors and less associated side effects (e.g., somnolence, vivid dreams, loss of impulse control).

Background On Dexpramipexole

(R)-(+) enantiomer of pramipexole, which is approved as a treatment for Parkinson’s disease and restless legs syndrome in the US (Mirapex®) and EU (Mirapexin®/Sifrol®)
- Pramipexole is not a racemic mixture of both enantiomers, but exclusively the (S)-(−) enantiomer
- Clearly defined clinical endpoints based on Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS-R), a surrogate marker for survival
  - Gross motor activity
  - Fine motor activity
  - Respiratory function
  - Bulbar function (speech, swallowing)

Source: Biogen Idec

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Dexpramipexole: Neuroprotection

- Knopp completed a two-part, double-blind Phase II trial and published the results in Nature Medicine in December 2011. Part 1 analyzed multiple BID doses versus placebo over 12 weeks. In part 2, following a 4-week placebo washout, patients were re-randomized to either 50 mg/day or 300 mg/day dexpramipexole and treated for 24 weeks.

- Phase II data are considered “better than any other ALS Phase II trial”.

**Dexpramipexole: Phase II Findings**

**Part 1 (12 weeks)**
- KNS-760704 achieved its primary endpoint evaluating safety and tolerability
- Also showed a dose-dependent trend in slowing the rate of disease progression as measured by the ALSFRS-R
- Greatest benefit observed in the 300 mg dose group

**Part 2 (24 weeks active Tx)**
- Following re-randomization after a placebo washout, results again suggested a dose-dependent trend in slowing the rate of disease progression as measured by the ALSFRS-R
- Trend toward a survival benefit in the 300 mg group compared with the 50 mg group
- In an exploratory test combining mortality and functional outcomes, subjects in the 300 mg group had a significantly improved outcome compared with the 50 mg group

Source: Biogen Idec
Dexpramipexole Fails in Phase III and Lessons Learned

Biogen Idec Reports Top-Line Results from Phase 3 Trial Investigating Dexpramipexole in People with Amyotrophic Lateral Sclerosis (ALS)

Jan. 3, 2013-- Today Biogen Idec (NASDAQ: BIIB) reported top-line results of EMPOWER, a Phase 3 trial investigating dexpramipexole in people with amyotrophic lateral sclerosis (ALS). The trial did not meet its primary endpoint, a joint rank analysis of function and survival, and no efficacy was seen in the individual components of function or survival. The trial also failed to show efficacy in its key secondary endpoints. Additional analyses of multiple subpopulations failed to demonstrate any efficacy among these groups. Based on these results, Biogen Idec will discontinue development of dexpramipexole in ALS.

According to the ALS Association, despite the disappointment there were some important lessons learned from dexpramipexole.

• A new measure of drug benefit was tested and found to be robust enough for use in future trials.
  — Primary endpoint: Combined Assessment of Function and Survival (CAFS), a joint rank score that combines ALSFRS-R and survival designed to take into account the impact of mortality on changes in functional performance.

• A new system for identifying ALS at its earliest stages should make much earlier diagnosis possible in the future.

• Differences between patients on and off riluzole supported the survival benefit of this drug in a trial that was more sophisticated than the one that led to its initial approval.

• The importance of developing biomarkers was emphasized “to track drug response and disease progression, in order to better evaluate the results of smaller trials and avoid the time and expense of larger ones with drugs of unknown promise.”
Tirasemtiv: Increasing Muscle Strength

- Tirasemtiv is a Phase IIb-ready compound in development for symptoms of ALS by Cytokinetics, a biotech company with focused expertise in the cytoskeleton and biology of muscle function.
- Tirasemtiv is a novel small molecule that aims to impact skeletal muscle contraction by selectively activating the fast skeletal muscle troponin complex and increasing its sensitivity to calcium. This effect has the potential to result in increased skeletal muscle force and delaying the time to muscle fatigue.

Additionally, Cytokinetics has reported that Tirasemtiv has also shown significant improvements in muscle strength and function in preclinical studies.

Cowen and Company report (2012); Cytokinetics website
Tirasemtiv: Increasing Muscle Strength

- PoC was established in three Phase IIa trials (CY 4021, n=67, CY 4024, n=49 and CY 4025, n=27); total of approximately 140 ALS patients. These trials were primarily designed to test the compound’s safety and tolerability, in addition to looking for signs of its efficacy.
- Data were reported at the 63rd (2011) and 64th (2012) American Academy of Neurology Annual Meeting.
- Tirasemtiv was well-tolerated (some transient dizziness), with no serious AEs observed.
- While not powered to show significance in efficacy endpoints, tirasemtiv showed a positive trend in efficacy measures in all three studies.

Cowen and Company report (2012); Cytokinetics website
Tirasemtiv: Increasing Muscle Strength

- Phase IIa Study CY 4024 (2-Weeks):
  - Double-blind, randomized (3:1), placebo-controlled trial designed to evaluate the safety and tolerability of multiple doses in 49 patients with ALS.
  - Part A: 24 patients were enrolled and randomized to receive a daily dose of 125 mg, 250 mg, or 375 mg of tirasemtiv or placebo, for two weeks. Patients in Part A did not receive Rilutek.
  - Part B: 25 patients were enrolled and randomized to receive a daily dose of 125 mg, 250 mg, or 375 mg of tirasemtiv or placebo, for two weeks. All patients in Part B received 50 mg qd Rilutek for two weeks.
  - The primary endpoint of the trial was safety and tolerability, with evaluation of ALSFRS-R score, measurement of muscle fatigue, measurement of pulmonary function (MVV), physician and patient global assessment as secondary endpoints.

Source: Cytokinetics presentation

Cowen and Company report (2012); Cytokinetics website
Tirasemtiv: Ongoing Phase IIb Trial

- Results from the ongoing Phase IIb trials (expected end of 2013) will inform global registration programs for tirasemtiv in ALS

**BENEFIT-ALS Phase IIb Clinical Trial**

Blinded Evaluation of Neuromuscular Effects and Functional Improvement with *Tirasemtiv* in ALS

- ~500 patients with ALS
- Multi-national, double-blind, placebo-controlled trial
- 1 week open-label treatment with *tirasemtiv* at 125 mg twice daily
- 12 weeks double-blind, twice daily oral ascending doses of *tirasemtiv* vs. placebo
- 1:1 Randomization
- ALSFRS-R, MVV, etc.
- Screening, Visit 0, Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, Visit 8, FU
- Screening, Open-label *Tirasemtiv* lead-in, Dose-Titration, MTD Phase, *Tirasemtiv* washout

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Tirasemtiv: Multiple Orphan (and Non-Oprhan) Opportunities

Skeletal muscle activators have potential use across multiple orphan (and non-orphan) indications where muscle weakness and fatigue are symptoms of the disease.

Cytokinetics Announces Presentation of Phase IIA Clinical Trial Data of Tirasemtiv in Patients with Myasthenia Gravis
South San Francisco, CA - March 21, 2013
Cytokinetics, Incorporated (Nasdaq: CYTK) announced the presentation yesterday of positive data from a completed Phase IIA “Evidence of Effect” clinical trial of tirasemtiv in patients with generalized myasthenia gravis (MG) during the Emerging Science Program at the 65th Annual Meeting of the American Academy of Neurology.

Cytokinetics Announces Grant From Families with Spinal Muscular Atrophy for Preclinical Development of Tirasemtiv
South San Francisco, CA - April 4, 2013
Cytokinetics, Incorporated (Nasdaq: CYTK) and Families of Spinal Muscular Atrophy (FSMA) announced the award of a grant from FSMA to Cytokinetics to support preclinical research on muscle function in a mouse model of spinal muscular atrophy (SMA) to be conducted with the company’s fast skeletal muscle troponin activator, tirasemtiv.
Orphan CNS Today: Range of Price (and Value)

- Clearly establishing and building value.

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<thead>
<tr>
<th>MS Drugs</th>
<th>Sabril</th>
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<td>Banzel</td>
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<td>Xyrem</td>
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<td>Ampyra</td>
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<td>Cuvposa</td>
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Average Annual Cost of Therapy (WAC)

- CNS
  - $5,000 - $20,000
  - $25,000 - $40,000
  - $50,000 - $130,000
  - $150,000 - $400,000+

- Non-CNS
Xyrem: Building Value, Protection and Price

- Xyrem (sodium oxybate) is the only FDA-approved medication for narcolepsy with cataplexy and excessive daytime sleepiness (EDS). It was approved on July 17, 2002, based on Phase III studies which showed a decrease in the number of weekly cataplexy attacks vs placebo by ~50-70% within a month of starting therapy and >90% by one year.
  - Sodium oxybate is derived from gamma-hydoroxybutyrate (GHB), a DEA Schedule I controlled substance with a high risk of abuse and diversion.
- Current sales of $415 M in 2012; industry analysts project US revenues of over $1B by 2016.

**FIGURE 8. Xyrem projected price increases**

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<td>10,401</td>
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<td>10,303</td>
<td>10,328</td>
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<td>22%</td>
<td>20%</td>
<td>18%</td>
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<td>13%</td>
<td>11%</td>
<td>5%</td>
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Source: JMP Securities LLC, Company reports
Xyrem: Building Value, Protection and Price

• **Value**
  - Specified as “treatment standard” (i.e., first-line) in the American Academy of Sleep Medicine practice parameters in 2007.
  - Restricted access program (Xyrem Success Program); assistance to physicians (e.g., patient education) and patients (e.g., nursing guidance).
  - Post-marketing surveillance data showing very low incidence of abuse, misuse, dependence, drug-facilitated sexual assault, overdose, fatalities, and diversion.
  - Patient assistance program defrays out-of-pocket costs.

• **Protection**
  - Orphan status
  - Jazz's IP covers Xyrem’s restricted access program (Xyrem Success Program), formulation and method of use

• **Price**
  - With growing value and protection, Jazz has been able to increase the price of Xyrem ~8-fold over the past six yrs; continuing in the double digits.

Jazz Pharmaceuticals website; Brean Murray Carret & Co. Sept. 27, 2012 analyst report; SG Cowen Therapeutic Categories Outlook
Orphan CNS Today: Range of Price (and Value)

- The top of the value chain.

Average Annual Cost of Therapy (WAC)

- $5,000 - $20,000
- $25,000 - $40,000
- $50,000 - $130,000
- $150,000 - $400,000+

CNS

Non-CNS
For Some Disorders, the Value is Apparent in the Consequences of Inadequate Treatment

Infantile Spasms: Little Seizures, BIG Consequences

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Sabril (vigabatrin) – addressing highly unmet needs

Infantile spasms (IS):
- ~2,500 patients/year in the US with IS
- Serious disease with substantial unmet medical need
- 70-90% suffers from mental retardation, mortality of around 5%

Refractory complex partial seizures (rCPS):
- ~ 1 million patients in the US suffer from rCPS
- 30-36% of patients are refractory
- Poorly controlled by current therapies
- Uncontrolled seizures has ~40x higher risk of inflicting mortality

Questcor Overview

Flagship Product: Acthar Gel

Key Therapeutic Areas:
- Nephrotic Syndrome, Multiple Sclerosis Relapse, Infantile Spasms, Rheumatology Indications
- Significant areas of unmet need; large growth potential

Strategy:
- Expand awareness, appropriate use of Acthar in key specialties
- Develop Rheumatology and other on-label indications

Financials:
- Profitable, positive cash flow, strong balance sheet

Company websites; Epilepsy Curr. 2006 May; 6(3): 63–69.
Acthar Gel: The Challenges of Pricing for Expansion

The New York Times

Questcor Finds Profits, at $28,000 a Vial
December, 29, 2012

In September, 2012 Questcor share price plummeted after Aetna said it would no longer pay for Acthar, except to treat infantile spasms, because of lack of evidence the drug worked for other diseases.
Mr. Bailey, Questcor’s C.E.O., defends his company’s practices. He says that when Questcor raised Acthar’s price, it did not initially intend to market the drug for other uses.
He also says that Questcor isn’t competing with low-price alternatives, but that it is marketing the drug as a treatment when those alternatives fail.
Still, given that Questcor is now pursuing billion-dollar opportunities far beyond the treatment of infantile spasms, is the high, orphan-drug price still justified?
“We could lower the price and make less money,” Mr. Bailey says, “and then we would be sued by our shareholders.”
Orphans as Potential Entry Into a Broader Patient Population

- Companies like Novartis, Roche and Seaside Therapeutics are targeting Fragile X, an orphan monogenetic disorder, with clinical stage programs focused on the modulation of glutamate or GABA neurotransmitters with hopes that this research will provide insight that may extend into other developmental disorders such as autism.
Fragile X/Autism: A Setback for Seaside (and Roche)

An Experimental Drug's Bitter End

June 6, 2013

- On May 1, Seaside announced that arbaclofen, which is also known as STX209, had not met the main goal of reducing social withdrawal in a 150-patient midstage study of children and young adults with autism. But the drug did succeed on a different measure — the clinicians' assessment of the patients.

- Arbaclofen had previously failed in a Phase 2 trial for Fragile X with a primary endpoint of reducing irritability and later in two Phase 3 trials assessing social withdrawal.

- But given the failures in the clinical trials, Seaside’s development and commercialization partner, Roche says it has decided not to license arbaclofen, apparently ending financial support for studies of the drug.

- “We concluded that arbaclofen wasn't going to provide a real difference for patients,” Luca Santarelli, head of neuroscience research at Roche, said in an interview.
Xenazine: Creating Value Where There Was None

- Xenazine is the only FDA-approved treatment for chorea associated with Huntington's disease.
- Chorea is the hallmark symptom of HD and affects about 90% of people who have HD, and is characterized by involuntary repetitive, jerky, dance-like movements.
- Peak (2014) sales estimate of just over $280M.
Xenazine: Creating Value Where There Was None

- Efficacy was established in a 13-week study and open label extension up to 80 weeks.

- Primary endpoint: Chorea was assessed using the Total Maximal Chorea (TMC) score from the UHDRS.

- Secondary endpoints: Clinical Global Impression scale and individual sections of the UHDRS.

- At 80 weeks, reduction in mean TMC score by 4.6 (SD 5.5) UHDRS units (p<0.001).

- Did not impact cognition or global improvement after 2 years of therapy.

The Unified Huntington’s Disease Rating Scale (UHDRS) was developed by the Huntington Study Group as a clinical rating scale to assess four domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity.

Xenazine: Leaves Plenty of Opportunity to Address Unmet Need

• Troubling side effects: somnolence, dysphagia and increase in Parkinsonian symptoms.

• Black-box warning for increased risk of depression and suicidal thoughts and behavior (in an already highly vulnerable patient population)

• Only addresses one domain of the disease: motor symptoms, and only the chorea type movements.

Roos. R. 2010. Orphanet J of Rare Diseases 5:40; www.xenazineusa.com
Lundbeck Continues to Take on the Big Market Risk

- With the Celexa/Lexapro franchise losing exclusivity in 2012 and sales for Lundbeck’s portfolio of orphan products not what the company has been accustomed to, Lundbeck continues to take on the big market risk.
  - Xenzaine (Huntington’s disease) peak (2014) sales estimate of just over $280M.
  - Sabril (infantile spasms) peak sales at ~100M
  - Onfi (Lennox-Gastaut syndrome) peak sales at ~90M

Brintellix (vortioxetine, Lundbeck/Takeda) is a multimodal anti-depressant (5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the serotonin transporter). With expected approval in 2013, Brintellix promises to offer efficacy similar to existing anti-depressants, but with a better profile on sexual dysfunction, nausea and cognition. Analysts estimate peak sales of well over $1B. Brintellix has been filed based on 10 Phase III studies, 70% of which met the primary endpoint, across more than 7,500 patients.

<table>
<thead>
<tr>
<th>Without sexual dysfunction at baseline</th>
<th>placebo</th>
<th>Brintellix 15mg</th>
<th>Brintellix 20mg</th>
<th>Cymbalta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without sexual dysfunction during study</td>
<td>63.6%</td>
<td>64.4%</td>
<td>64.4%</td>
<td>46.8%</td>
</tr>
<tr>
<td>With sexual dysfunction during study</td>
<td>36.2%</td>
<td>35.6%</td>
<td>35.6%</td>
<td>53.2%</td>
</tr>
<tr>
<td>Difference in incidence from placebo</td>
<td>-1.4%</td>
<td>-4.4%</td>
<td>-41.6%</td>
<td>+17.4%</td>
</tr>
</tbody>
</table>

EvaluatePharma; American Psychiatric Society
Opportunities to Balance the Risk in CNS

Subsegments
Subsegmenting to Balance Risk

- After fighting it for years, Pharma is warming up to the de-risking benefits of sub-segmenting as a way to tackle the big markets
  - Medically relevant subsegments (may or may not be orphan)
  - Specialty markets
  - Genetic subsegments
  - Biomarkers
  - Companion diagnostics
Medically Relevant Subsets

- Medically relevant subsets are discrete areas of unmet need and/or opportunity within the context of larger patient populations, such as:

Disease subsets include:

- Intractable disease (e.g., refractory epilepsy, treatment-resistant depression)
- Patient segments with debilitating symptoms (e.g., migraine with severe nausea & vomiting)
- Early-onset, aggressive disease (e.g., pediatric multiple sclerosis)
- Symptoms associated with late-stage, advanced disease (e.g., motor complications associated with late-stage Parkinson’s disease)
- Disabling comorbid symptoms (e.g., extreme fatigue in MS patients, cognitive impairment in PD) – i.e., supportive neurology
Neurology Supportive Care: The Size & Magnitude of the Need

- “Neurologists are frustrated, along with their patients and caregivers, and would love to have something to effectively treat depression, cognitive impairments, aggression and fatigue.”

- “The most common cause of disability for the multiple sclerosis (MS) patient is cognition, not motor symptoms.”

- “We can have the best immunomodulator in the world (for the treatment of MS), but patient quality of life will still suffer.”

- “Even at the early-stages, PD patients have significant issues with memory and problem solving.”

- “Psychosis is the major reason why patients with Parkinson’s disease (PD) and Alzheimer’s disease are admitted to nursing homes.”

Poor Quality of Life
Pimavanserin: A Supportive Neurology Product on the Horizon

- Parkinson’s disease psychosis, or PDP, is a debilitating disorder that develops in up to 60% of patients with PD.
- PDP is associated with increased caregiver stress and burden, nursing home placement, and increased morbidity and mortality.
- The level of unmet need is evident in the fact that today PDP is largely treated off-label with antipsychotics despite the black-box warning related to increased risk of death and potential to exacerbate motor symptoms.
- Pimavanserin (Acadia Pharmaceuticals) is a non-dopaminergic Phase III selective serotonin 5-HT2A antagonist/inverse agonist in development for the treatment of PDP.
- Peak year revenue estimates for pimavanserin are over $1B.
Pimavanserin: Meaningful Differentiation from SOC

- Data from pimavanserin’s pivotal Phase III study were announced at the 2013 AAN Annual Meeting and showed robust and consistent efficacy across a wide array of study measures.
- Pimavanserin met the primary endpoint demonstrating highly significant antipsychotic efficacy on the 9-item SAPS-PD (scale to assess psychosis in PD) scale (p=0.001). Pimavanserin also met the key secondary endpoint for motoric tolerability as measured using Parts II and III of the Unified Parkinson’s Disease Rating Scale, or UPDRS and significant improvements in the Clinical Global Impression Severity, or CGI-S, scale (p<0.001), the Clinical Global Impression Improvement, or CGI-I, scale (p=0.001), and a CGI-I responder analyses (p=0.002).

![FIGURE 1. Pimavanserin Study 020 Summary of Efficacy Across Measures](image-url)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Rater</th>
<th>Analysis</th>
<th>Day 43 Outcome</th>
<th>Effect Size</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Antipsychotic efficacy</strong></td>
<td></td>
<td></td>
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<tr>
<td>Primary</td>
<td></td>
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<td></td>
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<tr>
<td>SAPS-PD</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>Placebo (n=90) -2.73 (0.67) PIM 40mg (n=95) -5.79 (0.66) Treatment A -3.06 (0.94) 95% CL (-4.91, -1.20)</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>SAPS-H % Change</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>-14 (4.71%) -3 (4.8)% 23 (8.8%) 95% CL (-36%, -11%)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAPS-HD</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>-3.14 (0.73) -6.51 (0.72) -3.37 (1.03) 95% CL (-5.40, -1.35)</td>
<td>0.50</td>
<td>0.001</td>
</tr>
<tr>
<td>SAPS-H % Change</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>-15 (4.71%) -30 (4.7%) 24 (8.7%) 95% CL (-37%, -10%)</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAPS-D</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>-2.10 (0.49) -4.18 (0.49) -2.06 (0.70) 95% CL (-3.46, -0.71)</td>
<td>0.45</td>
<td>0.003</td>
</tr>
<tr>
<td>SAPS-PD ≥ 20% Reduction (Post-Hoc)</td>
<td>Independent (Central)</td>
<td>MMFM</td>
<td>-1.12 (0.38) -2.28 (0.38) -1.16 (0.54) 95% CL (-2.22, -0.10)</td>
<td>0.33</td>
<td>0.033</td>
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<tr>
<td><strong>Supportive</strong></td>
<td></td>
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<tr>
<td>CGI-I</td>
<td>Site Investigator</td>
<td>MMFM</td>
<td>3.45 (0.14) 2.78 (0.14) -0.67 (0.20) 95% CL (-1.06, -0.27)</td>
<td>0.51</td>
<td>0.001</td>
</tr>
<tr>
<td>CGI-I Responder</td>
<td>Site Investigator</td>
<td>g2 test</td>
<td>26% 49% 23% 95% CL (9%, 37%)</td>
<td>--</td>
<td>0.002</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Site Investigator</td>
<td>MMFM</td>
<td>-0.44 (0.12) -1.02 (0.12) -0.58 (0.17) 95% CL (-0.92, -0.25)</td>
<td>0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
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<tr>
<td>SCOPA-night</td>
<td>Site Investigator</td>
<td>MMFM</td>
<td>-0.49 (0.33) -1.42 (0.32) -0.93 (0.46) 95% CL (-1.04, -0.02)</td>
<td>0.31</td>
<td>0.045</td>
</tr>
<tr>
<td>SCOPA-Day</td>
<td>Site Investigator</td>
<td>MMFM</td>
<td>-0.99 (0.34) -2.21 (0.34) -1.22 (0.48) 95% CL (-2.17, -0.27)</td>
<td>0.39</td>
<td>0.012</td>
</tr>
<tr>
<td>Caregiver Burden (CB)</td>
<td>Caregiver</td>
<td>MMFM</td>
<td>0.40 (0.96) 3.94 (0.95) 3.54 (1.35) 95% CL (7.00, 1.67)</td>
<td>0.50</td>
<td>0.002</td>
</tr>
<tr>
<td>CB - Categorical (little or no burden cat.)</td>
<td>Caregiver</td>
<td>CMH</td>
<td>35% 43% 35% 95% CL -- 95% CL --</td>
<td>--</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Source: Company reports
ACADIA Pharmaceuticals Announces Expedited Path to NDA Filing for Pimavanserin Following Meeting with FDA. Single Pivotal Phase III -020 Study and Other Supportive Data Sufficient for Future NDA Filing for the Treatment of Parkinson’s Disease Psychosis

SAN DIEGO--(BUSINESS WIRE)--Apr. 11, 2013-- ACADIA Pharmaceuticals Inc. (NASDAQ: ACAD), a biopharmaceutical company focused on innovative treatments that address unmet medical needs in neurological and related central nervous system disorders, today announced that the U.S. Food and Drug Administration (FDA) has agreed that the data from the pivotal Phase III -020 study, together with supportive data from other studies with pimavanserin, are sufficient to support the filing of a New Drug Application (NDA) for the treatment of Parkinson’s disease psychosis (PDP). As a result, ACADIA will no longer conduct the Phase III -021 study that was planned as a confirmatory trial and was scheduled to be initiated later this month.
Conclusions

• Orphan disorders and subsegments of larger patient populations where high unmet need remains offer potential opportunities to balance the risk/reward profile in CNS.

• While disease modification (and better, a cure) is the Holy Grail, many CNS disorders are in desperate need of symptom improvement to improve function and QoL. This holds true for CNS orphans and subsegments.

• The absolute scientific risk remains high for these programs, but the risk-adjusted benefit looks a whole lot better than it does for the traditional, big CNS diseases (smaller, shorter clinical studies; potentially less safety risk in high unmet need patient groups).

• In addition, the cost of failure is significantly lower than for the bigger indications - and the reward can be significant.

• To realize value, companies must define, measure and quantify clear and meaningful value to all stakeholders: physicians, patients, caregivers and payers.
Defined Health is pleased to present:

**CANCER PROGRESS**
25th Annual Cancer Progress Conference
March 4 – 5, 2014
New York City
www.cancerprogressbyDH.com

**THERAPEUTIC INSIGHT**
BioEurope Spring
March 10 – 12, 2014
Turin, Italy
www.therapeuticinsight.com

Defined Health will also be participating in the following industry events:

- BioPharm America 2013 | September 17 - 19, 2013 | Boston, MA |
- LES Annual Meeting | September 22 – 25 | Philadelphia, PA |
  [http://www.lesusacanada.org/meetings/annual-meeting/2013-annual-meeting](http://www.lesusacanada.org/meetings/annual-meeting/2013-annual-meeting)
- Life Sciences Summit | November 20 - 21, 2013 | New York City |
- BIO-Europe Spring® | March 10 - 12, 2014 | Turin, Italy |