Hyperion Therapeutics, Inc. (HPTX)

Initiating Coverage of Hyperion Therapeutics with a Market Outperform rating; Orphan and Beyond

MARKET OUTPERFORM | Price: $24.68 | Target Price: $30.00

MARKET DATA

Price	$24.68
52-Week Range:	$9.95 - $26.50
Shares Out. (M):	20.3
Market Cap ($M):	$501.0
Average Daily Vol. (000):	47.0
Cash (M):	$50
LT Debt (M):	$8

Source: Thomson Reuters and JMP Securities LLC

FY DEC		2012A	2013E	2014E
Revenue ($M)	1Q	$0.0	$0.3	--
	2Q	$0.0	$1.9	--
	3Q	$0.0	$8.1	--
	4Q	$0.0	$11.8	--
	FY	**$0.0**	**$22.1**	**$78.0**
EPS	1Q	($25.16)	($0.44)	--
	2Q	($15.26)	$0.07	--
	3Q	($0.44)	($0.05)	--
	4Q	($0.50)	$0.11	--
	FY	**($4.45)**	**($0.31)**	**$0.96**

Source: Company reports and JMP Securities LLC

STOCK PRICE PERFORMANCE

INVESTMENT HIGHLIGHTS

Orphan and beyond; initiating coverage of Hyperion Therapeutics with a Market Outperform rating and $30 price target. Hyperion recently launched Ravicti for the treatment of urea cycle disorders (UCDs), a group of ultra-orphan diseases affecting at least 2,000 people in the U.S. which are characterized by toxic levels of ammonia. As a delayed release formulation, Ravicti was designed to be significantly more tolerable than its predecessor, Buphenyl - a life-saving chronic therapy for patients with UCD - leading to improved compliance and hinting at longer term neurological outcomes. Given the concentrated market and high level of anticipation for Ravicti, we believe that Hyperion can quickly create a profitable business in the UCD market, which we value at $120 million at peak. However, the larger opportunity lies in a subsequent indication, hepatic encephalopathy (HE), a market that dwarfs UCD. On the heels of a compelling proof of concept study in HE, the company is working with the FDA on the design of a pivotal study, slated to begin mid-2014. Thus, we like both the near-term and long-term prospects for Hyperion and we believe the second indication could serve as the basis for an ultimate acquisition of this company. Our $30 price target is based on a risk-adjusted, discounted cash flow analysis assuming peak sales of Ravicti in UCD of $122M in 2017 and peak sales of Ravicti in HE of $525M in 2024, assuming a 60% chance of approval.

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INVESTMENT THESIS

On February 1, 2013, the FDA approved Ravicti for the treatment of urea cycle disorders (UCD), an ultra-orphan disease affecting about 2,000 people in the U.S., roughly half of whom are diagnosed. As a delayed release formulation, Ravicti was designed to be significantly more tolerable than its predecessor Buphenyl, leading to improved compliance and hints at long term neurological benefits. Ravicti has also shown early promise as a treatment for hepatic encephalopathy (HE) and given the sizable market opportunity, Hyperion is preparing to initiate a pivotal program in mid-2014. Though the stock has had a nice run, driven largely by the recent approval and early launch, we believe shares of Hyperion will continue to outperform given that UCD is relatively de-risked, in our view, the commercial launch should be relatively smooth and over the next several years, shareholder value should grow as Ravicti makes its way to the larger HE market.

Commercial risk mitigated by readiness of the community

Patients with urea cycle disorders (UCD) lack an intact urea cycle, resulting in excess ammonia. When plasma ammonia reaches a tipping point, an acute crisis ensues causing cognitive damage and potentially coma or death. The only chronic therapeutic option for patients has been Buphenyl, which scavenges ammonia from the blood and removes it through the urine. However, with 40 noxious tasting pills required per day with meals, Buphenyl is poorly tolerated and contains greater than the World Health Organization (WHO) daily recommended salt intake. Our due diligence suggests that patients are willing to risk death rather than bear the burden of Buphenyl, which in our view, speaks to the degree of unmet medical need in the market.

Our due diligence with the UCD Foundation suggests many patients and caregivers are anxiously awaiting approval of Ravicti

Ravicti is a reformulation of Buphenyl designed to deliver the same amount of drug found in 40 pills of Buphenyl in 17.4mL of clear, tasteless liquid taken three times daily with meals. Moreover, Ravicti is not a salt. Our due diligence with the UCD Foundation suggests that many patients and caregivers have been anxiously awaiting the approval of Ravicti and therefore, we anticipate rapid adoption of Ravicti from patients currently on Buphenyl, about 50% of the diagnosed UCD population in the U.S., or 500 patients, as well as newly diagnosed patients. In our opinion, patients not currently on therapy could be more difficult to reach; however, we think Ravicti could bring some of these patients back into treatment or get them started on treatment for the first time.

Rapid path to profitability

We project that Hyperion could reach profitability next year

Hyperion is focused on the U.S. launch of Ravicti while also exploring ex-U.S. options. In the U.S., about 60 physicians write 80% of the scripts for Buphenyl at about 22 sites, allowing for efficient marketing with a small footprint of about a dozen sales and reimbursement specialists. Given the readiness of the UCD market and the limited commercial infrastructure, we project that Hyperion could reach profitability next year with about $67M in Ravicti revenue; we do not believe the company will need additional financing ahead of this benchmark.

Option to own the market

Owning both Ravicti and Buphenyl could allow Hyperion to bring two drugs into a narrower price range

Hyperion has an option to purchase Buphenyl form Valeant. In our view, owning both Ravicti and Buphenyl could afford Hyperion the ability to bring the price of the two drugs into a more narrow range, making the pharmacoeconomic argument even more compelling. Hyperion will owe Valeant mid- to high-single digit royalties on net sales of Ravicti, as well as sales milestones and developmental milestones up to $16 million related to Ravicti approval in HE and up to $7 million in all other indications.

Newly allowed patents lower IP risk

Hyperion recently received notice of the allowance of claims related to use of fasting ammonia levels as a baseline to fine tune dosage of Ravicti. Hyperion counsel believes that these patents will protect Ravicti through 2032. The composition of matter patent for Ravicti expires in 2015, so without the new patents, exclusivity would extend only through 2018 with Hatch Waxman and until 2020, should Ravicti be granted orphan status. Feedback from the FDA leads management to believe that orphan designation will soon be granted on the grounds that the absence of sodium in Ravicti is a significant improvement in the treatment of UCD.

Hepatic encephalopathy opens up strategic options and $1.5B market opportunity

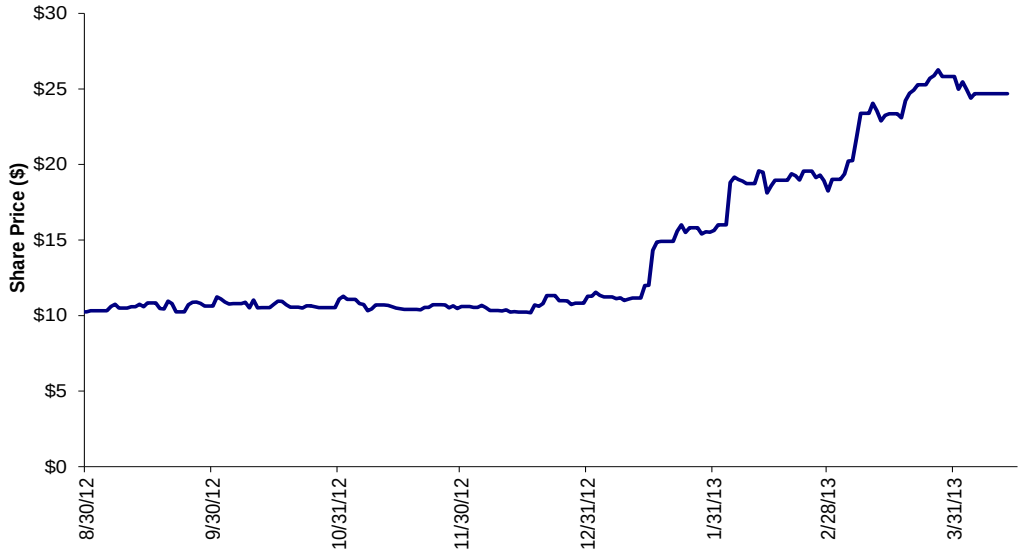
HE data presented at the AASLD meeting last November were compelling

HE occurs in about 70% of patients with liver cirrhosis, or an estimated 150,000 Americans. Excess ammonia is thought to play a central role in the pathophysiology of the disease, which can lead to lethargy, confusion, and other neurological symptoms, up to and including coma. The central role of ammonia in HE and the similarity of cognitive symptoms to those seen in patients with UCD inspired Hyperion to explore Ravicti in a Phase 2 study in HE. HE data presented at the AASLD meeting last November were compelling and after some strategic deliberation the company has committed to a registration study with an eye towards commercialization.

HE market opportunity dwarfs that of UCD

We believe launch of Ravicti for HE in the U.S. will force a significant price reduction for Ravicti in UCD unless the company develops a formulation unique to the HE market; however, our analysis shows that we believe the HE market opportunity dwarfs that of UCD, which justifies the decision to decimate the UCD market. Based on our analysis of the competitive landscape, we currently believe an approval in HE could lead to 35% penetration at peak which translates into about $525 million in the U.S. alone. Development of the HE indication could attract an acquirer, given the size of the opportunity. While we believe the changes of reformulating Ravicti uniquely for HE is unlikely, we see significant upside for Hyperion if they can find a way to uniquely address both markets.

FIGURE 1. Price Chart for HPTX



Source: Thompson Reuters and JMP Securities LLC

FIGURE 2. Upcoming Catalysts

1H13	Decision to purchase Buphenyl/Ammonul	UCD	Launched
2013	Submit a SPA for Phase 3 HE study	Ravicti	Phase 2
mid-2014	Begin Phase 3 study in HE	Ravicti	Phase 2

Source: Company reports and JMP Securities LLC

VALUATION

Hyperion is mostly valued on the prospects for Ravicti in two indications: UCD and HE. Our $30 price target is based on a risk-adjusted, discounted cash flow analysis.

Urea cycle disorders (UCD) is an ultra-orphan indication with roughly 2,200 patients in the U.S., half of which are diagnosed. Today, about half of patients are treated with Buphenyl and we see these patients as a source of early adoption of Ravicti with ~70% switching in the first year after launch. We estimate 20% penetration into those currently disengaged from Buphenyl therapy and assume the vast majority of newly diagnosed patients would receive Ravicti. Ravicti is currently priced at an average price of $250,000-$290,000 (dosed by weight) with 14% gross to net adjustment for payor discounts and considering the serious nature of the disease, we anticipate a higher level of compliance of 85%.

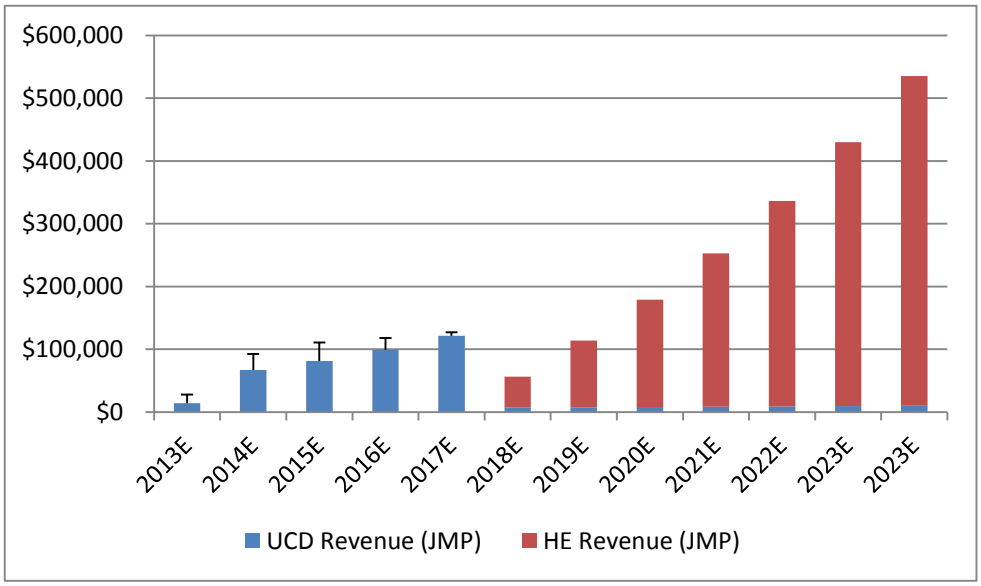
We reach $122M in peak U.S. sales in 2017 and $30M at peak ex-U.S. With minimal infrastructure required to sell Ravicti, we believe Hyperion can turn profitable next year with the Ravicti indication alone. If Ravicti is approved in HE, we would anticipate a rapid decline in revenue derived from UCD given a much lower price for the product. In our base case assumption, we assume launch of Ravicti for HE in 2018 and a decrease in price for all indications resulting in a drop-off in UCD revenue of $7.0M, partially offset by HE revenue of $50M in 2018.

Hyperion is also preparing to initiate a Phase 3 program for Ravicti in HE. Based on promising Phase 2 data, we assign a 60% probability of success to the HE program. There are about 150,000 patients in the U.S. with overt HE. The most common treatment options include Salix's Xifaxan, priced at $11,000 per year with 30% market share (our estimate), and lactulose, priced at about $45 per prescription (approx. $600/year). We assume Ravicti is priced at 10% premium or $15,400 to Xifaxan at launch in 2018. Assuming 35% penetration into Xifaxan naïve patients in 2024, we estimate peak revenue to be $525M. There is upside to our estimates if Hyperion can demonstrate a benefit on top of Xifaxan – something not obvious in the Phase 2 data.

Hyperion has an option to acquire Buphenyl from Valeant. While we expect minimal revenue from Buphenyl, there is strategic value to this asset as Hyperion can help the pharmacoeconomic argument for Ravicti by raising the price of Buphenyl. We assign a 90% probability of the transaction being completed this year.

Our $30 price target for shares of Hyperion is based on a risk-adjusted, discounted cash flow analysis, a discount rate of 11% based on a CAPM analysis and a terminal growth rate of 5%.

FIGURE 3. JMP Ravicti Revenue Estimates (000's) (consensus shown by error bars)



Source: Thompson Reuters and JMP Securities LLC

FIGURE 4. Risk-adjusted, Discounted Cash Flow Analysis

Discounted Cash Flow Valuation														
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Terminal	
Revenues	22,096	77,999	106,901	126,418	151,467	87,112	120,868	191,752	272,009	362,697	464,893	579,773		
Buphenyl/Ammonul	7,594	8,469	8,625	6,779	4,871	0	0	0	0	0	0	0		
Ractivi	14,502	67,301	81,451	99,276	121,777	6,966	7,694	8,151	8,635	9,147	9,690	10,265		
HPN-100 in HE	-	-	-	-	-	49,702	106,462	171,032	244,233	326,967	420,219	525,063		
License fees and milestones	-	2,230	16,825	20,363	24,819	30,444	6,712	12,570	19,141	26,582	34,984	44,444		
COGS	1,741	9,802	11,796	14,173	17,210	9,067	18,265	28,669	40,459	53,778	68,785	85,653		
R&D	10,500	25,000	35,000	25,000	20,000	30,000	15,000	10,000	8,000	8,000	8,000	8,000		
SG&A	21,500	23,520	24,696	25,931	37,641	48,273	50,687	53,221	55,882	58,677	61,610	64,691		
Operating Income (EBIT)	**(11,645)**	**19,677**	**35,409**	**61,314**	**76,616**	**(228)**	**36,916**	**99,862**	**167,668**	**242,242**	**326,497**	**421,430**		
Weighted Risk	97%	96%	83%	83%	83%	42%	59%	58%	57%	57%	56%	56%		
Tax	0%	0%	0%	5%	5%	5%	5%	10%	15%	20%	30%	30%		
Risk adjusted Net Income	(11,245)	18,901	29,551	48,554	60,625	(91)	20,766	51,918	81,303	109,709	129,635	166,703	916,327	
Year for discounting	0	1	2	3	4	5	6	7	8	9	10	11	12	
	$ (11,245)	$ 17,036	$ 24,006	$ 35,551	$ 40,009	$ (54)	$ 11,133	$ 25,087	$ 35,409	$ 43,065	$ 45,865	$ 53,159	$ 263,365	
NPV	**$ 582,385**													
+ Current Cash & Equivalents	$ 106,673.2													
Value of the Company	**$ 689,058.0**													
- L-T Debt	$ 2,500													
Value of Equity	**$ 686,558.0**													
Value per Share	**$ 29.51**													

Source: JMP Securities LLC, Company reports

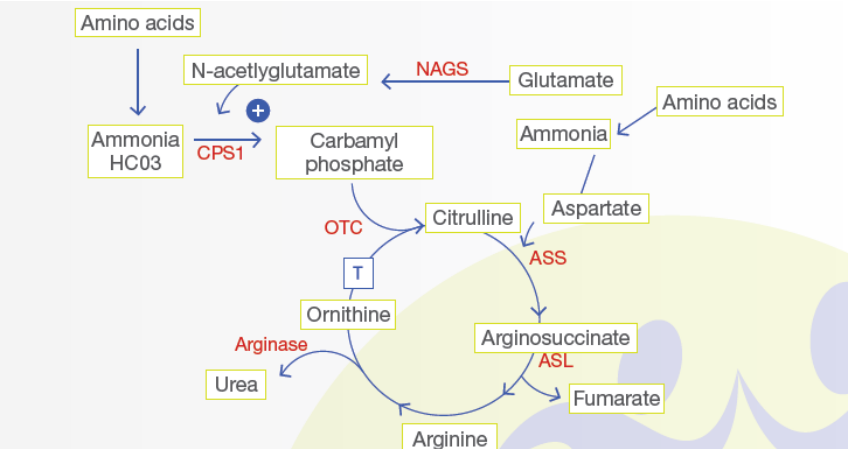
UREA CYCLE DISORDERS

The majority of the UCDs are autosomal recessive disorders

The urea cycle removes excess nitrogen, mostly acquired through protein intake, (which accumulates as ammonia) from the body in the form of urea. The cycle involves six enzymes and two transporters (Figure 5) and a deficiency in any one of the enzymes can lead to an increase of ammonia (hyperammonemia) to levels that are toxic. Onset and severity of UCD are determined by the missing enzyme and the type of mutation, although there is a spectrum of severity for each deficit. Generally, a deficiency in OTC, CPS1, NAGS, ASS, or ASL can lead to an accumulation of ammonia in newborns, whereas patients with arginase deficiency tend to present later in life (Figure 6).

Deficiencies affecting the upstream enzymes in the urea cycle, those above citrolone, are concentrated in the liver and are usually the most severe. The majority of the UCDs are autosomal recessive disorders, meaning that two copies of the defective gene are necessary to manifest the disease. However, the most common enzyme deficiency, OTC, is an X-linked disorder found mostly in males where a single copy of the gene is sufficient for clinical manifestation. In contrast, females with an OTC deficiency have a more mild disease leading to problems with executive function despite a normal IQ and may not be diagnosed until they are in their 40s or 50s.

FIGURE 5. The Urea Cycle (Enzymes in Red)



Source: Nat Rev

FIGURE 6. Types of UCD Deficiencies

Enzyme Deficiency	Onset	Severity	Prevalence
N-Acetylglutamate Synthase (NAG)	newborn &late onset	generally severe	0.013 in 100,000
Carbamyl Phosphaste Synthetase 1 (CPS-1)	neonatal & late onset	lethal, some heterogeneity	1 in 800,000 to 1,000,000
Ornithine Transcarbamylase (OTC)	newborn (males)	severe in males, variable in females	1 in 14,000
Argininosuccinate Synthetase (AS)	neonatal & late onset	depends on mutation	1in 100,000
Argininosuccinate Lysase (AL)	early in life	moderate	1 in 70,000
Arginase (ARG)	later in life	moderate	1 in 2,000,000

Source: NIH UCD Overview

UCDs are very rare, occurring in 1 in 30,000 live births each year, or about 130 babies

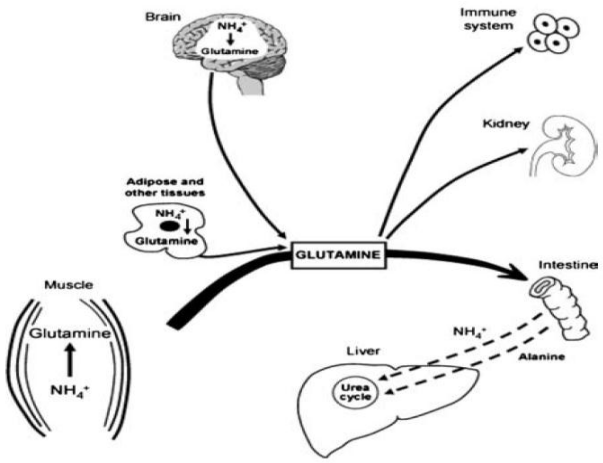
UCDs are very rare, occurring in 1 in 30,000 live births each year, or about 130 babies and many cases go undiagnosed. For instance, the most severe may lead to death without diagnosis and experts suggest that these disorders may account for 20% of sudden infant death syndrome (SIDS). On the other end of the spectrum, mild cases, often rectified by diet, may also go undiagnosed. In the U.S., newborn screening has been implemented for ARG and ASS and the UCD foundation is lobbying to add OTC, CPS1, and NAGS to the health and human services (HHS) recommended newborn screening panel which could increase diagnosis of the disease in the coming years. This process has been slow due to macro-government factors (sequestration), but will likely be implemented in the next five years.

A study of 260 patients found that 60% of patients presented for the first time outside of the first 21 days of life. 100% of patients first present with neurological symptoms, such as loss of consciousness, though many present with vomiting or infections. Often it is hard to distinguish a UCD from sepsis when a patient first presents to the hospital with a crisis and afterwards, brain damage resembles that seen from stroke. Once a hyperammonemic crisis is identified, it is fairly straightforward to determine which enzyme the patient is deficient in through amino acid analysis.

More about ammonia

In healthy individuals, plasma concentrations of ammonia are maintained under 40umol/L by conversion into glutamine or extraction by the kidneys (Figure 7). The brain has 1.5 to 3 times the concentration of ammonium than the blood because of brain metabolism and passive diffusion through the blood brain barrier. The brain does not have an effective urea cycle, so ammonia either passively diffuses out of the brain or is used by astrocytes for glutamine synthesis. Excess ammonia is toxic to the brain and features of ammonia toxicity include lethargy, seizures, cerebral edema and ataxia with more mild forms resulting in confusion and slowed or delayed growth. This ammonia toxicity is likely compounded by increased glutamine, which can also become neurotoxic. In neonates, rapid response to hyperammonemic events is crucial to prevent brain damage or death. A French outcomes study following 217 UCD patients, found 84% mortality in neonatal onset cases, which represented just of half of the 217 cases during the course of the study.

FIGURE 7. How Ammonium is Used in the Body



Source: Diabetes, Obesity and Metabolism, 2009

TREATMENT OF UCD

Generally, treatment of UCD requires a team of specialists including a metabolic specialist, pharmacist, nephrologist, intensive care physician, and a nutritionist, as well as laboratory staff with the ability to quickly turn around blood levels.

Acute treatment

If a patient is in acute crisis, the first goal of the ER is to lower intracranial pressure, adjust nutrients to reverse catabolism (breakdown of nutrients), and transfer the patient to a medical center equipped to handle ammonia detoxification by administering Ammonul (a combination of PAA and benzoate) in the hospital setting via a central venous catheter at a 250mg/kg loading dose over two hours followed by the same dose over 24 hours. In extreme crises, with ammonia above 500umol/L, hemodialysis is recommended to remove ammonia from the blood.

Chronic treatment

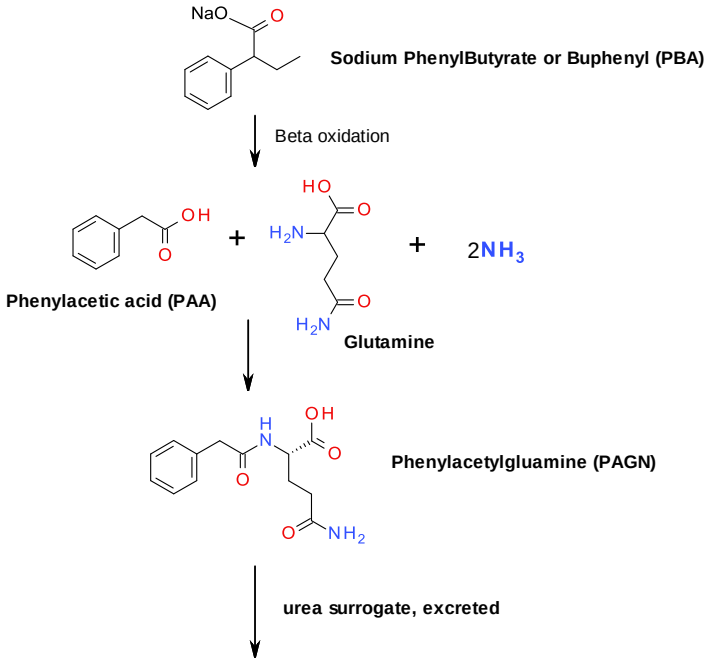
The first line of treatment for UCDs is a restriction of dietary protein. Depending on the deficiency, different specific amino acids or cofactors are added to the diet, for example, those with OTC or CPS deficiencies need L-citrulline or L-arginine, respectively, to fuel the rest of the urea cycle.

Prior to Ravicti, there were only two approved medicines for UCD: Buphenyl for chronic treatment and Ammonul for management of acute crises

Prior to the approval of Ravicti last month, there were two approved chronic medicines for all UCD patients: Buphenyl to maintain low ammonia levels when dietary restrictions are not sufficient and Ammonul to lower levels during an acute crisis.

Buphenyl works by creating a urea surrogate that rids the body of excess ammonia (Figure 8). Buphenyl is a sodium salt of phenyl butyric acid (PBA) that is oxidized to phenyl acetate (PAA) in the body. PAA, in turn, is combined with glutamine and two ammonium ions to form pheynlacetylglutamine (PAGN) and is excreted in the urine. Thus, for each PAGN molecule excreted, two ammonia moieties are excreted, the same amount of waste nitrogen excreted via urea. Patients who cannot tolerate Buphenyl may take sodium benzoate which combines with glycine and one ammonium ion. However, it is less effective than Buphenyl, potentially due to Buphenyl also lowering the level of glutamine, which can be neurotoxic if present at high levels. Originally, PAA itself was given as a therapy; however, the smell of the compound both outside the body and excreted in sweat was unbearable.

FIGURE 8. Buphenyl as a Urea Surrogate to Remove Excess Ammonia



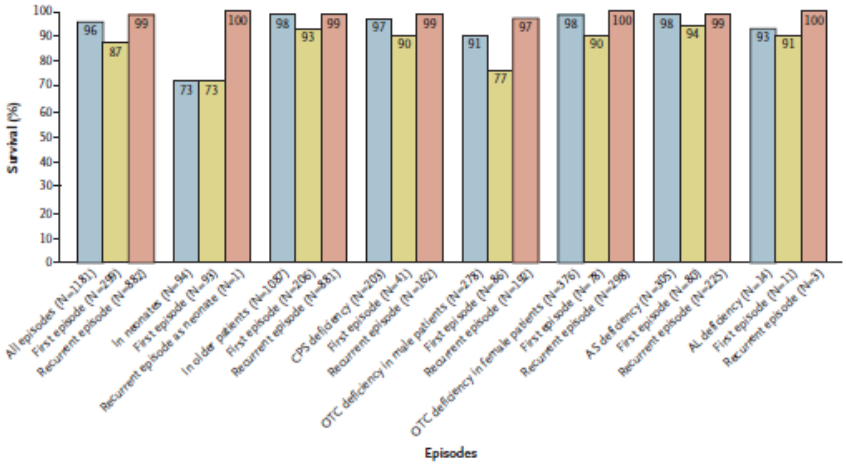
Source: Company reports and JMP Securities LLC

For ASL, a UCD subtype, arginine can be used as replacement therapy. However, it has been shown that low levels of arginine combined with Buphenyl may be more effective in controlling ammonia levels than the use of high levels of arginine alone. In 2010, carglumic acid was approved for patients with NAG deficiency in conjunction with Buphenyl therapy. Another therapeutic option is liver transplant, especially for those patients missing one of the upstream enzymes that are concentrated in the liver.

Benefits of therapy

The benefits to using Ammonul to control an acute crisis are well documented. In a 25-year outcomes study of patients receiving Ammonul during a crisis, the overall survival rate was 84%. Most deaths occur within the first two months of life with neonatal hyperammonemia being associated with the worst outcomes of those that survive, with survival correlated to lower peak ammonium levels during crisis. Neonates in first crisis and males with an OTC deficiency had the lowest survival rates (Figure 9). Normal development is possible after a neonatal crisis with treatment; however, various studies have shown that between 40-80% of children with a crisis have developmental disabilities.

FIGURE 9. Survival by Age and Enzyme Deficiency



Source: NEJM, 2007

In contrast, the benefits of chronic Buphenyl therapy have not been well documented and only recently has the UCD consortium compiled data to look at the natural history of the disease. The consortium has also worked to standardize protocols for treatment of UCD patients, leading to better outcomes; however, it is believed that poor compliance to medication has limited the potential benefits of therapy. Although only anecdotal, our due diligence suggests that patients who are monitored and have their ammonia levels tightly controlled have better outcomes. At a recent medical education event, KOLs in UCD stressed that unlike many rare genetic disorders, UCD patients can grow up to live lives similar to the rest of the population. However, this requires patients to be compliant with medication with ammonia levels that are tightly controlled.

Buphenyl is effective, but difficult to tolerate

About half of patients in the U.S. diagnosed with a UCD take Buphenyl

Only about half of patients in the U.S. diagnosed with a UCD take Buphenyl. The untreated patient population reflects a spectrum of disease severity, with about 40% of these patients suffering from hyperammonemic crises and learning disabilities. The issue with Buphenyl is its poor tolerability. Often, as patients enter adulthood they choose to stop taking the Buphenyl and risk death due to the burden of therapy. Below, we examine the issues with Buphenyl therapy:

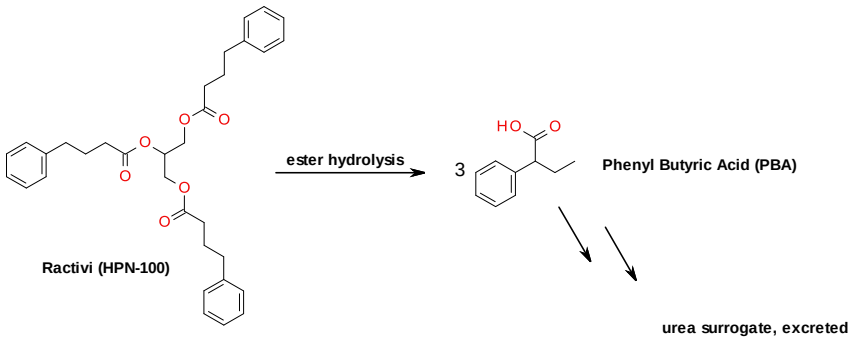
Often, as patients enter adulthood they choose to stop taking the Buphenyl and risk death due to the burden of therapy

- High pill burden - up to 40 pills daily based on weight, administered three to six times per day with meals.
- Noxious taste and smell - Buphenyl is noxious tasting and smelling, making compliance a challenge. The taste plus the large number of pills necessitate a G-tube for administration in 45% of pediatric patients.
- Quality of life - our due diligence suggests that Buphenyl also disrupts the social life of children. During school hours, they must sit with a nurse for about an hour to make sure they do not vomit. In addition, the smell is difficult for others to tolerate, which can lead to a host of social issues.
- High sodium content - Buphenyl is a salt, where each tablet contains 62 mg of sodium, so the full dose of 40 pills exceeds the maximum amount of sodium recommended per day.

THE SOLUTION: RAVICTI

Ravicti (glycerol phenylbutyrate) is a pro-drug of phenylbutyric acid, the neutral form of Buphenyl (PBA) (Figure 10). The molecule incorporates three molecules of PBA on a tri-glycerol backbone that are released when cleaved by pancreatic lipases in the GI tract.

FIGURE 10. Ravicti



Source: Company reports and JMP Securities LLC

In our view, Ravicti has four clear benefits over Buphenyl:

1. It is not a salt
2. It is formulated as a clear liquid with little to no smell or taste
   - The liquid has the viscosity of corn syrup and has little to no taste.
   - Some associate a slightly metallic taste to the liquid that is short lived (10 seconds)
3. It delivers three times the PBA in one molecule, lowering amount of medication required
   - The compound is a liquid with 17.4mL equivalent to 40 pills of Buphenyl
4. It allows for more consistent ammonia control with slower release as PBA moieties are cleaved from the glycerol backbone by enzymes

Our due diligence suggests that patients who have been involved in Ravicti clinical trials consider the drug life-altering

Our due diligence suggests that patients who have been involved in Ravicti clinical trials consider the drug life altering. Children and young adults can self-administer with minimal impact on quality of life. We believe these factors should lead to better compliance and improved patient outcomes. Moreover, patients with hypertension will be able to receive the full dose of drug and we anticipate that some patients who have discontinued Buphenyl may re-engage in therapy.

Data reaches non-inferiority - just missing superiority

Three clinical trials were the basis for approval of Ravicti: the pivotal 006 study in adult patients and two open-label Phase 2 studies (003 and 005) in adults and pediatric patients, respectively (Figure 11).

The pivotal study was a double-blind, randomized cross-over trial comparing blood ammonia levels between Ravicti and Buphenyl in 44 UCD patients who were well controlled on Buphenyl at baseline. In terms of enzyme deficiency, OTC was the largest contributor, consistent with the prevalence of OTC within the UCD population. The dose of Ravicti was equivalent to the baseline Buphenyl dose. Ravicti plus placebo pills or Buphenyl pills plus placebo liquid were administered three times daily with meals for 14 days after which subjects crossed over to the alternate therapy.

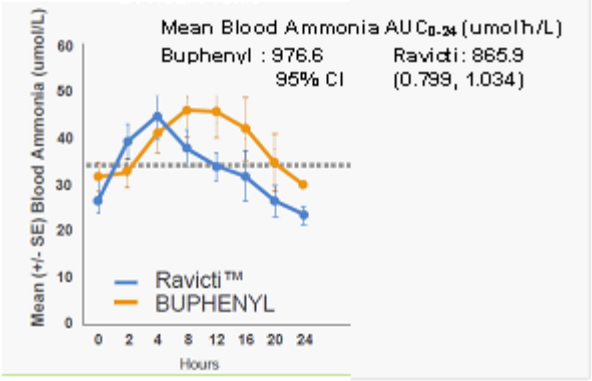
On the last day of each 14-day treatment period, ammonia levels were monitored for 24 hours via blood sample. The study showed that Ravicti met the criteria for non-inferiority to Buphenyl for the primary endpoint of 24 hour area under the curve (AUC) ammonia exposure (Figure 12). The upper limit of the confidence interval needed for superiority was 1.0 with Ravicti just missing the cut off at 1.04.

FIGURE 11. Clinical Trial Overview

	UP 1204-003	HPN-100-005	HPN-100-006	HPN-100-005SE/HPN-100-007
Phase	2	2	3	2/3
n	14	11	45	77
	open label	open label	blinded	open label
time of therapy	7d each	7d each	14d each	12 mnth (Ravitci only)
mean age	35.71	10.18	32.73	24.68
UCD subtype (%)				
OTC	85.7%	81.8%	88.9%	8.2%
CPS			4.4%	1.3%
ARG				1.3%
ASS	7.1%	9.1%	6.7%	7.8%
ASL		9.1%		3.9%
HHH	7.1%			3.9%
Primary endpoint	non-inferior	non-inferior	non-inferior	

Source: Company Reports and JMP Securities LLC

FIGURE 12. Ammonia Control Day 14 (Pivotal Study)



Source: Company reports

Safety profile similar to Buphenyl

Our analysis of the pivotal data suggest there are more treatment emergent adverse events (AEs) associated with Ravicti than Buphenyl (45.5% versus 33.3%) (Figure 13); however, most were mild and gastrointestinal (GI) related – side effects consistent with the disorder itself. In addition, headache was more frequent in the Ravicti treatment period and this may reflect expected neurotoxicity. We believe

some of the increase in AEs while on Ravicti may be related to study design – because patients were on Buphenyl at baseline, Buphenyl related AE's became part of background noise. The only SAE in the Ravicti phase was gastroenteritis. There was one hyperammonemic crisis during the Buphenyl portion of the study and one patient discontinued on Buphenyl citing headache and high ammonia levels. Importantly, there were no clinically significant changes in laboratory or ECG values. Despite these differences in AE's in the pivotal study, feedback from the UCD Foundation suggest that Ravicti is much more tolerable then Buphenyl and we believe the high retention rate of >90% in the study reflects this point. Net-net, we believe Ravicti represents an improvement in tolerability, despite some increased in mild GI toxicity.

FIGURE 13. AEs in Ravicti Pivotal Study

System Organ Class Preferred Term	Number of Patients, n (%) NaPBA (N = 45)	 GPB (N = 44)
Patients Reporting at Least One Related TEAE	15 (33.3)	20 (45.5)
Gastrointestinal Disorders	10 (22.2)	15 (34.1)
Abdominal discomfort	2 (4.4)	0
Abdominal pain	1 (2.2)	3 (6.8)
Diarrhea	2 (4.4)	7 (15.9)
Dyspepsia	2 (4.4)	2 (4.5)
Flatulence	1 (2.2)	6 (13.6)
Nausea	3 (6.7)	1 (2.3)
Oral discomfort	2 (4.4)	0
Nervous System Disorders	3 (6.7)	6 (13.6)
Headache	2 (4.4)	6 (13.6)
General Disorders and Administration Site Conditions	2 (4.4)	4 (9.1)
Fatigue	1 (2.2)	3 (6.8)
Metabolism and Nutrition Disorders	3 (6.7)	1 (2.3)
Decreased appetite	2 (4.4)	1 (2.3)
Increased appetite	2 (4.4)	0
Psychiatric Disorders	2 (4.4)	0
Food aversion	2 (4.4)	0

Source: Company Reports

Warning about PAA toxicity

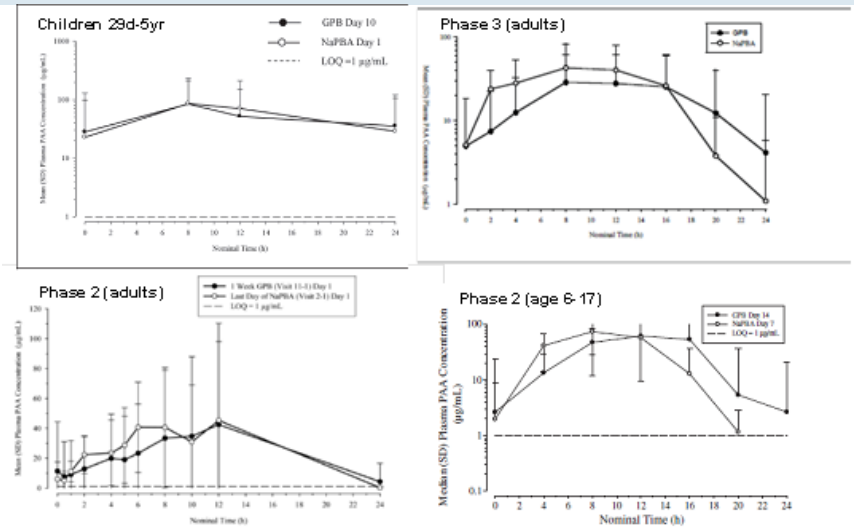
The Ravicti label warns of the metabolite PAA which can lead to signs of neurotoxicity (confusion, headache, or sleepiness) at high exposure levels and recommends reduction in dose. We do note an elevated rate of headache in the pivotal study (Figure 13) of 13.6% versus 4.4% however; PAA levels were comparable and in fact numerically lower in Ravicti versus Buphenyl arm (Figure 14). In our view, this is not a deterrent to physicians prescribing Ravicti, as most are already used to the profile of Buphenyl.

Highlights of metabolite analysis

Hyperion analyzed pharmacokinetic data from over 3,000 plasma and urine samples. Levels of PBA, PAA, and PAGN were variable with PAGN levels in the urine correlating best with dose of therapy. We note that when Buphenyl was approved, only PBA levels in adults were evaluated. Since that time, however, there have been data correlating high levels of PAA exposure (peak levels of 544ug h/mL) to neuro-cortical toxicity. Peak PAA levels from Buphenyl therapy tend to be at least seven times lower

than toxic levels and we believe the extensive PK data generated by Hyperion support that metabolite levels from Ravicti therapy are similar and do not exceed those observed for Buphenyl. Our analysis of the data suggests that use of Ravicti will not lead to PAA exposure at levels higher than Buphenyl and that neither drug exposes patients to toxic PAA levels. Nonetheless, because of its chronic administration, the FDA felt compelled to include it as a warning in the label; however, we think the small physician community is well aware of the dynamic and this should not impact utilization.

FIGURE 14. PAA levels



Source: Company Reports

40% decrease in hyperammonemic crises

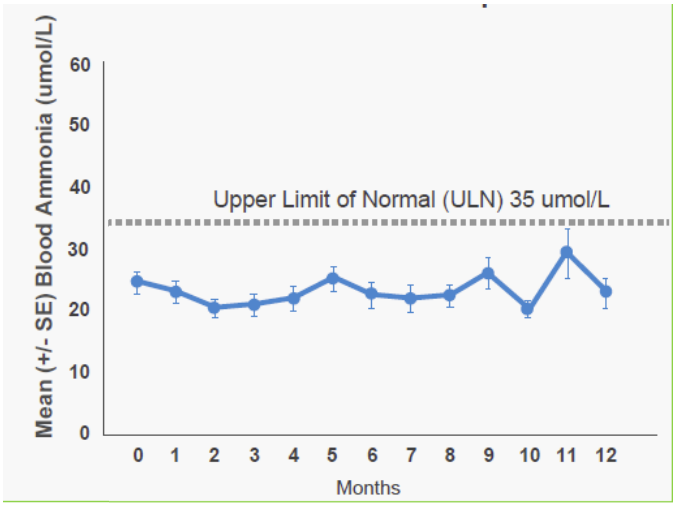
Improved control of crisis and neurological function with Ravicti

Long-term neurological outcomes were assessed through twelve-month open label extension (OLE) phases of the two Phase 2 studies where all patients received Ravicti. Enrollment was also opened to new patients including pediatric patients and those with UCD subtypes not represented in the other studies. Enrollment in the OLE was high with all 26/26 of the pediatrics and 40/44 of the adults, which speaks to the excitement about Ravicti amongst patients. Mean ammonia levels were consistent with fasting levels observed during the pivotal study (Figure 15).

Adult neurological scores remained steady over one year and pediatric scores improved

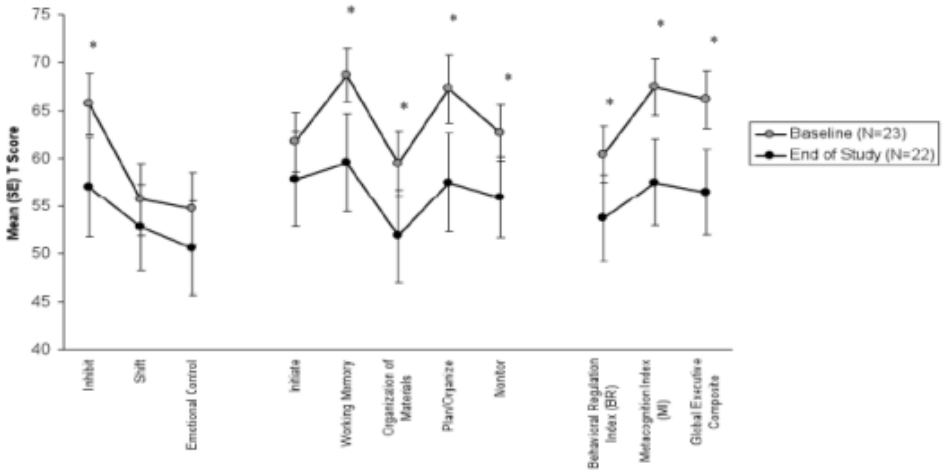
We are particularly impressed with the 40% decrease in hyperammonemic crises compared to the prior 12 months. In addition, ammonia levels during the crises trended to be lower, which theoretically could result in less damage. Importantly, adult neurological scores remained steady over one year and pediatric scores improved (Figure 16), suggesting that Ravicti treatment can protect, and in some cases improve, long term neurological function for UCD patients. While these data are not included in the label and were scored by caregivers and not physicians, they have been published and are well known in the community and physician base and are potentially indicative of the benefits of therapy.

FIGURE 15. Ammonia Control over 12 Months



Source: Company Reports

FIGURE 16. Domain T scores in Pediatric Patients (lower number=higher function)



Source: Hepatology, 2012

Post marketing commitments should not be a large burden

Post marketing commitments include evaluations in younger populations, metabolite distribution in break milk, metabolite-drug interaction study, initiation of therapy in Buphenyl naïve patients and a UCD registry.

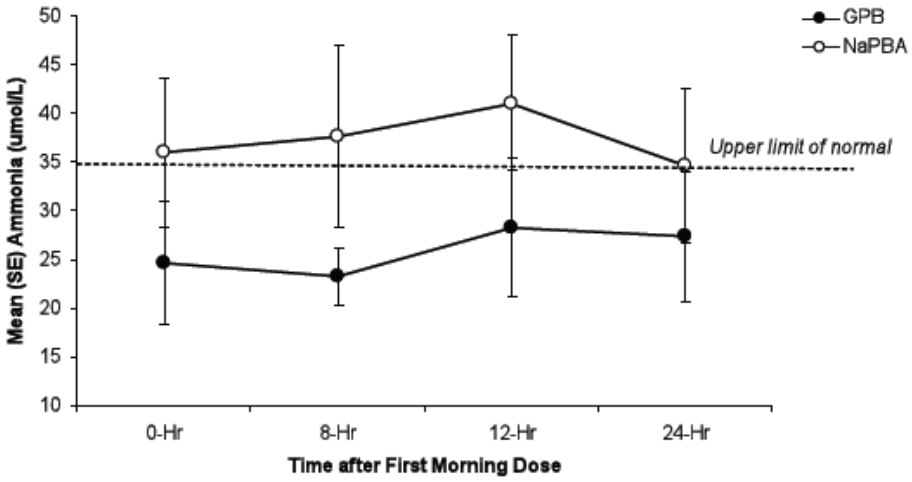
Ravicti is not yet indicated for children <2 years of age

Studies in neonates

Ravicti is not yet indicated for children <2 years of age given the limited data the company had at the time of submission. Hyperion conducted a crossover study in children aged 29 days to five years and showed similar efficacy and other age groups (Figure 17). However, only four patients between the ages of two months and two years completed the study and many were sick, making it difficult to consistently draw blood and obtain pharmacokinetic data. Therefore, Ravicti is currently only indicated in children two years and older. Ravicti is specifically contraindicated in children younger than two months due to theoretical immature pancreatic enzyme function which could interfere with the metabolism of PBA from the Ravicti backbone.

Towards expanding the label to include this younger population, the FDA has requested Hyperion conduct a study in patients from 2-24 months of age and <2 months to generate pharmacokinetic and efficacy data to expand approval into these important subgroups. We are optimistic that Hyperion can achieve this goal in the next three years. Commercially, this demographic expansion is relatively small with 14% of patients <2 years old and given weight base dosing scheme we estimate <10% of the commercial opportunity. However, the unmet medical need is great and better ammonia control and tolerability from birth should translate to better long-term outcomes for these patients.

FIGURE 17. Ammonia Levels in Young Children



Source: Company reports

Manufacturing ready to meet demand

Drug product for Ravicti is manufactured by Helsin in Switzerland and DSM in the Netherlands and fill/finish takes place in Massachusetts. We believe manufacturing for launch in on track as management indicated that they have sufficient drug to supply patients through 2013 and another manufacturing campaign is scheduled for Q4, which should provide sufficient drug supply into 2014. Ravicti is stable for at least 36 months at room temperature and is not light sensitive. The gross margin for Ravicti should be greater than 90% excluding a royalty to Dr. Brusilow and to Valeant (Ucyclyd) Pharmaceuticals in the mid-to-high single digit range.

Decision on Orphan Exclusivity expected soon

The composition of matter patent for Ravicti expires in 2015 but market exclusivity is extended through 2018 via Hatch-Waxman. If Ravicti were to gain orphan drug exclusivity upon approval, this would extent market exclusivity until 2021. We believe it is challenging for compounds in the 5052b pathway to receive orphan exclusivity; however, management believes they are well positioned based on FDA feedback the absence of sodium in Ravicti represents a major contribution to care of UCD patients. We expect that a decision could be communicated within a few months.

Intellectual Property tied to the Ravicti label should block generics

Hyperion recently announced that the USPTO will grant claims regarding target levels of plasma ammonia levels for patients on ammonia scavenging drugs. Through is research, Hyperion discovered that because UCD patients have large swings in plasma ammonia, the target should be based on fasting levels and should be no more than half the upper limit of normal. This patented claim is included in the Ravicti label and as such, a generic would be unable to include this instruction in their label, effectively blocking generic competition.

CLEARLY DEFINED U.S. MARKET OPPORTUNITY

Hyperion recently made Ravicti available via two specialty pharmacies. Given the high cost of Ravicti, in our opinion, facilitating patient access through Hyperion's patient hub and reimbursement system is integral to a successful launch. Hyperion has outsourced this capability to a firm seasoned in this area. The UCD market is concentrated in about 22 tertiary referral centers where approximately 60 metabolic geneticists write 80% of the Buphenyl scripts. To address these physicians, the company has hired seven sales reps to educate the marketplace about Ravicti and help transition patients from clinical drug to commercial supply.

Our due diligence with the UCD foundation suggests that awareness of Ravicti is high amongst those patients on Buphenyl and physicians and patients have been anticipating the arrival of Ravicti and we expect many early adopters in this group. On the other end of the spectrum, because the disease causes serious neurological damage, there is a significant impoverished contingent and some of these patients may be harder to reach. Not unlike other rare diseases, the key concern of patients is cost. Pricing and reimbursement support for Buphenyl was marginal and so there is some fear regarding access. We believe that Hyperion's patient hub and reimbursement center should shield patients from paying large sums out of pocket. Moreover, Hyperion has been working closely with the UCD foundation to get information to patients, and the foundation's leadership appears encouraged that all patients will be able to access the drug

We segment the market for Ravicti into three buckets:

- **Current Buphenyl patients**. About 500 patients are currently taking Buphenyl and we believe these patients are the low hanging fruit – they are already engaged in treatment and Ravicti would represent a major improvement in disease management, tolerability and quality of life. About 20% of this group has been involved in Ravicti clinical trials (75 from the U.S.). We believe the high retention rate in the clinical studies and patient outcomes from the extension trial suggest that penetration into this segment of the patient population could be relatively rapid.

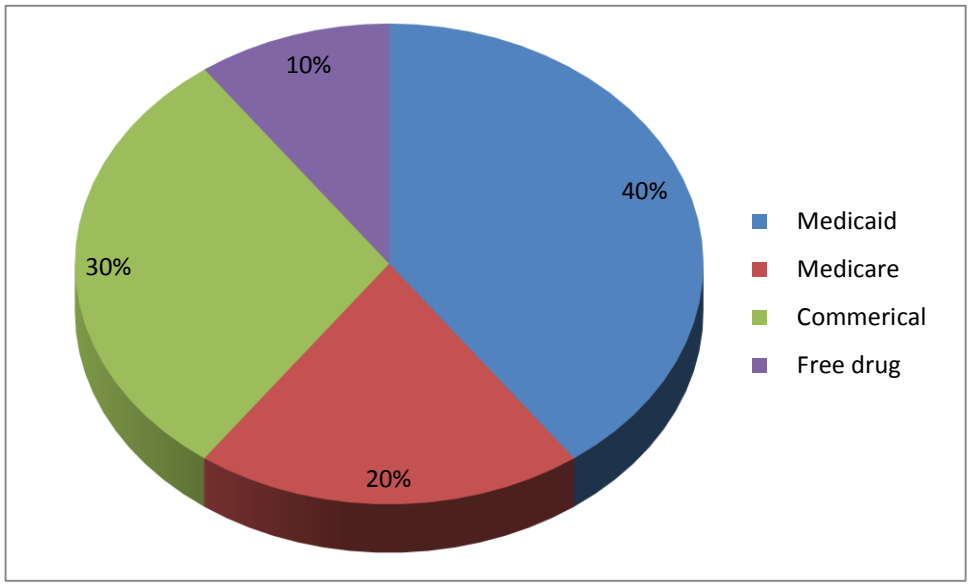
- **Newly diagnosed.** We also believe that a significant number of newly diagnosed patients (about 30 a year) will likely start Ravicti therapy.
- **Untreated.** Patients not currently on Buphenyl will be more difficult to target. The majority of these patients (80-90%) cannot control their disease by diet alone and 40% of these patients suffer from frequent hyperammonemic crises and many have learning disabilities. We believe Hyperion may gain some traction in this group as individuals present to physicians with an acute crisis and may be amenable to trying to control their disease with a medicine that is potentially more tolerable than Buphenyl. We estimate penetration into this segment (of newly diagnosed and not treated patients) at 10% at peak, although we believe this will take time.

Payor mix reflects a poor patient population

Feedback from payors suggests a continued level of price insensitivity for drugs to treat rare diseases

A larger proportion of patients with UCD are managed through Medicaid, followed by private payors and Medicare (Figure 18). Feedback from payors suggests a continued level of price insensitivity for drugs to treat rare diseases and is confident that most patients will not have any issues with reimbursement over the long term. To address any near term hurdles securing reimbursement, Hyperion may provide free drug in the first six to nine months to some patients on Medicaid until reimbursement is established, which we applaud. Our model reflects this level of support.

FIGURE 18. Payor Breakdown



Source: Company communications and JMP Securities LLC

Option to buy Buphenyl

We believe Hyperion will likely exercise its option to purchase Buphenyl and Ammonul from Valeant for $22M. However, if Valeant chooses to keep Ammonul, which appears increasingly likely, the transaction for Buphenyl will become a $13M net gain in cash for Hyperion. Once acquired, we anticipate that Hyperion will increase the price of Buphenyl, currently sold for $65,000 per patient per year, to be more competitive with the price of Ravicti. We expect that Buphenyl use will decrease dramatically in the coming year as patients switch to Ravicti.

EU filing coming

Hyperion is preparing to submit a dossier for approval in the E.U. and the initial assessment suggests that the regulatory path should be relatively straightforward. The bigger issue is pricing and reimbursement. With the current reference pricing system used in Europe, Ravicti is at risk for pricing levels similar to Buphenyl and sodium benzoate. The price per patient per year in Europe ranges from about $30,000-42,000 depending on the country and we anticipate similar pricing for Ravicti, with the potential for a slight premium in some countries if the pharmacoeconomic argument for fewer hospitalizations due to hyperammonemic crises resonates with European payors. Nonetheless, Sobi, the European distributor of Buphenyl, has a right of first refusal for Europeans distribution and we believe it is conceivable the Sobi and Hyperion will come to an agreement on terms this year. Beyond Europe, Hyperion is exploring distributor relationships in other geographies including the Middle East (selling via a named patient program at prices similar to U.S. pricing is feasible).We include ex-U.S. revenue that at $30M in 2018.

Competitive landscape

To our knowledge, there are no other urea surrogate medicines in development. There is one product in Europe, Pheburane, from Lucane Pharma that has recently received a positive CHMP ruling. Pheburane is a formulation of Buphenyl that masks the taste. However, we believe the other attributes of Ravicti set it apart from this compound. Sigma has a generic version of the powdered formulation of sodium phenylbutyrate that it is making available in the U.S.; however, this is closer to Buphenyl then to Ravicti.

NEXT UP - HEPATIC ENCEPHALOPATHY

The neurological symptoms associated with HE are similar to those associated with UCD

As a scavenger of ammonia, Ravicti may have a role in the treatment of hepatic encephalopathy – a disease characterized by high ammonia levels. We note that the neurological symptoms associated with HE are similar to those associated with UCD. To test its hypothesis that Ravicti could provide a benefit to patients with HE, Hyperion conducted a Phase 2 proof-of-concept study in patients and in November at the AASLD meeting, released some intriguing results. Key opinion leaders we have spoken with view the results from the Phase 2 study as a validation of this theory and we are optimistic that Ravicti can secure a place in the treatment paradigm alongside lactulose and Xifaxan.

What is HE?

Hepatic encephalopathy (HE) is a serious neuropsychiatric syndrome brought on from liver impairment most commonly from either cirrhosis, a condition resulting from chronic liver diseases such as hepatitis, or from acute liver failure. Hepatic encephalopathy is the result of nitrogenous substances from the gut, such as ammonia which is normally detoxified by the liver, that enter the bloodstream and adversely affect the brain. When liver function is impaired it either fails to detoxify blood flow from the gut or a shunt develops allowing blood to bypass the liver. When gut-derived nitrogenous substances enter systemic circulation and eventually the brain, they adversely affect neurotransmission and induce intracranial pressure. HE results in a wide spectrum of neuropsychiatric complications including

confusion, disorientation, impaired memory, delirium, and dementia. Patients can experience agitation, dysfunctional movement, and speech impairment. The disease severely limits quality of life and severe patients often cannot live without assistance. Following diagnosis of a patient's first acute episode of HE, the one-year survival rate is 42% and the three year survival rate is 23%.

The World Congresses of Gastroenterology in 1998 classified HE into three types. They are HE associated with acute liver failure, portal-systemic bypass in the absence of liver disease, and cirrhosis (Figure 19).

FIGURE 19. Classes of HE

Type A	Acute	Acute liver failure (ALF) ALF is a rapid onset of deterioration of the liver, where a majority of liver function is lost. It is commonly brought on by drug overdose, drug reaction,or liver disease. Coma may result from ALF.
Type B	Bypass	Portal-systemic bypass in the absence of liver disease. Systemic shunting allows substances from the gut to byass liver and directly enter systemic circulation. Shunting may occur in people with healthy livers.
Type C	Cirrhosis	Clinical manifestations of HE in cirrhotic patients can be classified as: Episodic HE : rapid but reversible disease progression characterized by disturbance in consciousness. Episodes usually triggered by certain precipitating factors. Persistent HE : neurological deficits that are not completely reversible Minimal HE : mild symptoms that are only detected with certain psychological tests.

Source: Ferenci et al. Hepatic Encephalopathy—Definition, Nomenclature, Diagnosis, and Quantification: Final Report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998. HEPATOLOGY 2002; 35:716-721.

In type C, where HE is associated with cirrhosis, the disease is chronic. Disease progression in cirrhotics can be measured using the West Haven grading system based on grades 0-4, referred to as a Conn Score (Figure 20).

FIGURE 20. West Haven Grading System

Conn score 0	No personality or behavioral abnormality detected
Conn score 1	Trivial lack of awareness, euphoria or anxiety; shortened attention span; impairment of addition or subtraction
Conn score 2	Lethargy; disorientation for time; obvious personality change; inappropriate behavior
Conn score 3	Somnolence to semi-stupor, responsive to stimuli; confused; gross disorientation; bizarre behavior
Conn score 4	Coma; unable to test mental state

Source: FDA Advisory Committee Meeting, Xifaxan

Current therapeutic options for chronic HE include lactulose and Xifaxan

Current therapeutic options for chronic HE include lactulose and Xifaxan. Lactulose is a synthetic, non-digestible sugar available as an oral solution. It has been established as the standard of care for HE even though it is not officially approved and is available in generic form. Physicians perceive lactulose to be moderately efficacious but burdened with GI side effects, leaving significant room for improvement. Nonetheless, given its low cost, isn't widely utilized.

A new entrant, Xifaxan from Salix Pharmaceuticals, was approved in 2010 for the treatment of HE. Xifaxan is a non-absorbed antibiotic and as such, kills colonic bacteria responsible for ammonia production in the gut, and thereby reducing circulating nitrogen levels. As the only treatment option to lactulose, Xifaxan is gaining significant traction in HE and we estimate it has achieved about 30% penetration (JMP estimate). Xifaxan sales reached $515M in 2012 and we expect continued strong growth considering the dearth of treatment options and good safety and efficacy profile for Xifaxan.

Ravicti Phase 2 proof of concept study in HE

Hyperion conducted a Phase 2 that randomized 178 HE patients to Ravicti or placebo for 16 weeks. To be included in the study, patients needed to have cirrhosis, have experienced ≥2 HE events in the past six months or ≥1 HE event in the past three months (if on Xifaxan, ≥1 HE event after at least four weeks was required) and patients had to be stable on standard of care medication. The primary endpoint was the percentage of patients with at least one HE events during the study. Secondary endpoints included total HE events and HE-related hospitalizations.

Fewer patients on Ravicti experienced a HE event and there were about 40% fewer HE events, and half as many HE hospitalization and hospitalization days

Results of the study were intriguing and suggestive of a statistically significant benefit, particularly when one considers the baseline patient characteristics. Fewer patients receiving Ravicti experienced a HE event (36% versus 21% p=0.021) (Figure 21) and there were about 40% fewer (p=0.035) HE events throughout the 16 weeks. Particularly noteworthy was the observation of fewer HE hospitalization and hospitalization days, each lowered by about half, which could be the beginning of a strong pharmacoeconomic argument for usage. Lower ammonia levels were observed in patients without an HE event, further supporting the role of ammonia in the pathophysiology of HE (Figure 22). In our view, these data warrant further study and support Hyperion's choice to move forward into Phase 3.

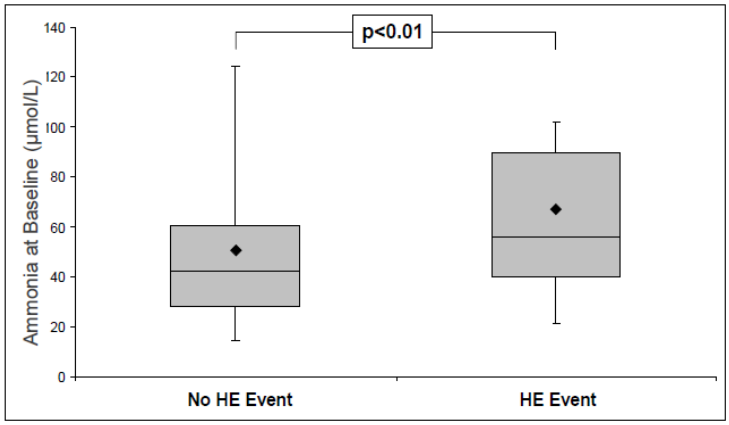
FIGURE 21. Summary of Phase 2 Results for Ravicti in HE

	Placebo N=88	GPB N=90	% Reduction	p value
Primary Efficacy Endpoint % of patients with ≥ HE event (No. of subjects)	36% (32)	21% (19)	41%	0.021
Total HE events	57	35	39%	0.035
NH_3 (time normalized AUC, µmol/L)	58	46	21%	0.036
Subjects with a symptomatic day *	27	13	52%	0.015
Total HE hospitalizations	25	13	48%	0.064
Total HE hospitalization days	134	66	51%	NS
Subjects reporting AEs (%)	76%	79%	NA	NS

* Symptomatic day defined as CHESS Score ≥3
NS = Not significant

Source: Company Reports

FIGURE 22. Risk of an HE Event and Baseline Ammonia



Horizontal line = Median, Dot = Mean, Box= 25th-75th percentiles, Whiskers = 5th-95th percentiles; p value derived from t-test

Source: Company reports

The benefit of Ravicti in Xifaxan failures is unclear

To explore the activity of Ravicti in patients 'failing' Xifaxan, the study specifically enrolled and stratified patients on Xifaxan at baseline and maintained these patients on Xifaxan for the duration of the study. The criteria for enrollment for this subgroup were more stringent: patients had to have at least one HE event during the four weeks preceding the study while on Xifaxan therapy, selecting for a more difficult to treat group. This subgroup, which represented about one-third of patients in the study, did not reach a statistically significant benefit for the primary endpoint between Ravicti (+Xifaxan) cohort and placebo (+Xifaxan) (Figure 23).

Superficially, this suggests that Ravicti (GBP) does not provide a benefit in this population, however, there may be other underlying explanations for a lack of benefit in this population including a more difficult to treat population and 2x higher ammonia levels in the Xifaxan subgroup which seems to lead to worse outcomes (Figure 22). We point out that there were more Child Pugh C patients, reflecting more advanced liver disease, in the Ravicti arm than in the placebo arm, which would support this thesis, however, management has indicated that Child's Pugh status does not appear to have impact the endpoint, at least in this study. Moreover, there were trends to a decrease in hospitalizations and days in the hospital when Ravicti was given in this subgroup, which we believe is compelling.

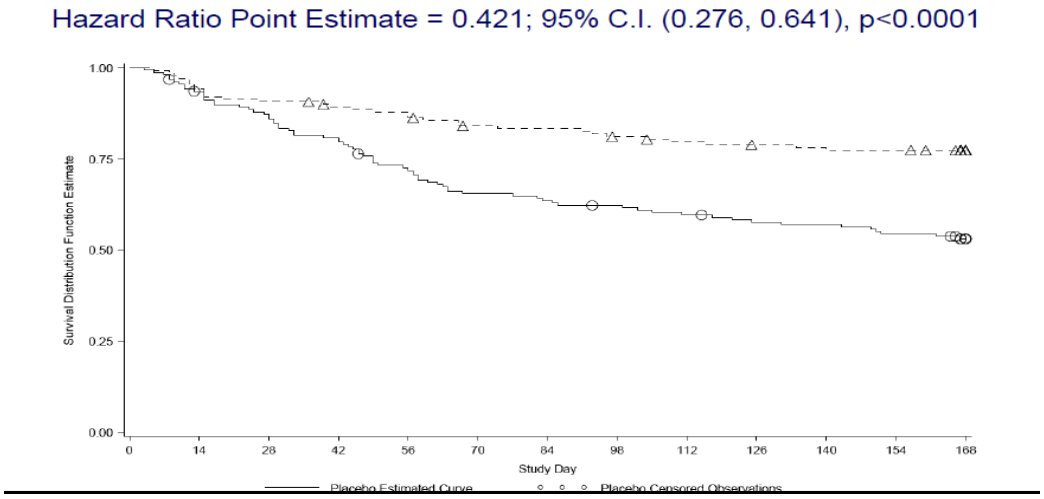
FIGURE 23. Phase 2 HE Subgroup data

	GBP	Placebo	
Rifaximin naïve (N= 119)	**60**	**59**	
Patients with at least one HE event	10%	32%	0.003
Patients with an HE event, WH ≥ 2	5%	28%	0.001
Total HE events	6	19	0.0002
Rifaximin at baseline (N= 59)	**30**	**29**	
Patients with at least one HE event	13	13	0.909
HE Hospitalizations	11	20	0.095
HE Hospital days	57	90	0.06

Source: Company reports

Comparing these data to the Phase 3 Xifaxan study, suggests that Ravicti may have efficacy similar to Xifaxan. In the Xifaxan naïve cohort, we observe a 10% event rate versus about 20%. For the six month Phase 3 study for Xifaxan, HE breakthrough events occurred in 22.1% and 44.9% of patients on Xifaxan and placebo, respectively. We are cautious in our expectations for superiority, even though numerically Ravicti appears superior, given the relatively small sample size of the Phase 2 Ravicti dataset relative to the Xifaxan Phase 3 program and the lighter placebo arm in the Ravicti study, despite more Child Pugh C patients in the Ravicti. Each therapy appears to decrease the placebo rate by about 50%.

FIGURE 24. Time to First Breakthrough Overt HE Episode (Xifaxan Pivotal Study)



Source: Company reports

Safety analysis

We see no major safety concerns for Ravicti in HE

Adverse events were similar to placebo (Figure 25) and included serious adverse events such as GI bleeding, urinary tract infection, hepatic and renal failure and anemia. Aminotransferase enzyme levels (ALT and AST) and MELD scores remained steady over time in both the placebo and Ravicti groups. We see no major safety concerns for Ravicti in this population.

FIGURE 25. AEs for Ravicti (GPB) excluding HE events

Adverse Events (AE) *	Placebo (N = 88)	GPB (N = 90)
Subjects Reporting at Least One AE	67 (76%)	71 (79%)
Grades 1-3 (Mild - Severe)	60	65
Grade 4-5 (Life-Threatening - Fatal)	7	6
Possibly or Probably Related	31	35
Serious Adverse Events (SAE) */**		
Subject Reporting at Least One SAE	12 (14%)	20 (22%)
Possibly or Probably Related	4	1

* Does not include HE events

** SAEs are defined as life-threatening or fatal AEs, AEs requiring/prolonging hospitalization, or AEs associated with a significant medical event. Most common SAEs irrespective of treatment included: GI bleeding (4), urinary tract infection (3), ascites (2), bacterial peritonitis (2), hepatic failure (2), renal failure (2), dyspnea (2), anemia (2), hyper- or hypoglycemia (2 each in patients with IDDM).

Source: Company Reports

Hyperion is planning to develop the HE indication under the auspices of a SPA towards initiating Phase 3 in mid-2014

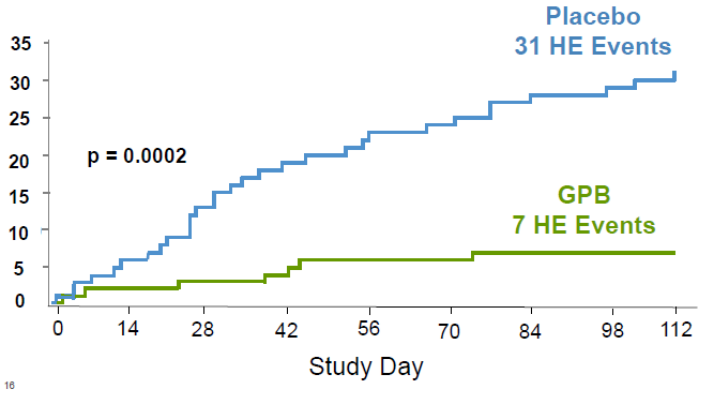
Next steps

Hyperion is planning to develop the HE indication under the auspices of a special protocol assessment (SPA) towards initiating Phase 3 in mid-2014. The reason for the delay is that the FDA GI division is revamping the West Have scoring system following criticism for being imprecise, insensitive to milder forms of HE and too subjective. As such, the FDA hopes to "operationalize" the Conn Score, attempting to put more emphasis on objective endpoints, such as orientation of place and time, in lieu of more subjective measures such as irritability. Hyperion believes these discussions should wrap up in 2013, after which the company will submit a SPA that reflects the most updated measures of efficacy.

Hyperion is anticipating one pivotal trial targeting enrollment of 500 patients with overt HE. The study will include a six-month blinded phase, followed by a six-month open label extension. We point out several changes from the Phase 2 design that we believe could help demonstrate a larger treatment effect of Ravicti: 1) longer duration of therapy (24 versus 16 weeks in the Phase 2 where the curves appear to be separating and therefore could show a great difference over time (Figure 26); 2) slightly earlier stage patients as the patients on Xifaxan will not have to be 'failing'; 3) balanced disease severity – recall there were disproportionately more patients in the Ravicti arm with Child Pugh C scores.

Conservatively assuming a 12-month enrollment period and a 12-month study, we target mid-2016 for results from this Phase 3 study.

FIGURE 26. Total HE Events (Xifaxan Naïve)



Source: Company reports and JMP Securities LLC

SIGNFICANT MARKET OPPORTUNITY IN HEPATIC ENCEPHALOPATHY

Assuming the Phase 3 data confirm the efficacy observed in Phase 2, we believe Ravicti could be worked into the paradigm of first line therapy after lactulose as an alternative to Xifaxan. In our view, the systemic exposure of Ravicti and the direct ammonia lowering effect will resonate with physicians. We also believe the decrease in observed in number of hospitalizations, if confirmed, will give Hyperion a good pharmacoeconomic argument to justify formulary adoption and premium pricing. We currently estimate a 35% share of Xifaxan naïve patients with peak sales of $525M in 2024. We believe there would be room for upside if Ravicti can demonstrate a benefit in patients receiving Xifaxan.

Potential niche opportunity for patients with Child Pugh C

Ravicti may be able to carve out the Child Pugh C patients

We believe Ravicti may be able to carve out the Child Pugh C patients – a sub-group for which Xifaxan bears cautious language. If confirmed in Phase 3, this attribute could help move Ravicti into first-line therapy after lactulose. The Xifaxan label warns the drug should be used with caution in patients with severe (Child Pugh C) hepatic impairment, as Xifaxan is a non-absorbable antibiotic with increased systemic exposure in patients with greater liver dysfunction leading to a higher risk of death.

We believe this may not be an issue with Ravicti and we are encouraged that Hyperion conducted a safety study of Ravicti in cirrhotic patients in a single dose compared to Buphenyl and then in a two week open label study compared to healthy controls. Our analysis shows that there was no correlation between adverse events and the Child Pugh score (Figure 27) though the number of exposures is small. The drug was dosed at 100mg/kg on day one, twice a day at 100mg/kg for days 8-14, and 100mg/kg on day 15. Most notable side effects were a drop in platelets and a feeling of warmth that was not accompanied by fever (Figure 27). The 100mg/kg BID dose corresponds to about 12.7mL per day for a 70kg adult, similar to the 6mL BID dosing in the HE study.

As noted previously, 23% of patients in the Ravicti arm of the Phase 2 study had severe hepatic impairment, and yet the AE profile was similar to placebo. If these trends hold in the year-long study, we believe this could help Ravicti market penetration.

FIGURE 27. AEs from Study in Cirrhotic Patients

UP 1204-002	Child-Pugh A	Child-Pugh B	Child-Pugh C	Healthy volunteers	All
Abdominal discomfort	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)
Abdominal pain (upper)	2 (2)	0 (0)	2 (4)	0 (0)	4 (6)
ALT increased	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)
Blood glucose increased	0 (0)	1 (1)	0 (0)	1 (2)	2 (3)
Body temp increased	2 (4)	5 (8)	3 (5)	0 (0)	10 (17)
Diarrhea	0 (0)	1 (3)	1 (1)	0 (0)	2 (4)
Dyspepsia	2 (2)	0 (0)	0 (0)	1 (1)	3 (3)
Headache	2 (2)	1 (1)	2 (4)	2 (2)	7 (9)
Nausea	1 (1)	2 (3)	0 (0)	0 (0)	3 (4)
Pharyngolaryngeal pain	1 (1)	0 (0)	1 (1)	0 (0)	2 (2)
Platelet count decreased	4 (4)	0 (0)	0 (0)	1 (1)	5 (5)
Tachycardia	0 (0)	2 (2)	1 (3)	0 (0)	3 (5)
Throat irritation	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)
Data is presented as number of subject (No of AE)					

Source: HEPATOLOGY 2010;51:2077-2085)

Patent strategy

Hyperion has filed a provisional patent for coverage of usage in HE (method of use patent) which, if granted, would provide coverage until 2032. In addition, if Ravicti is designated as an orphan drug for HE by the FDA, it would afford seven years of exclusivity following approval.

MANAGEMENT TEAM

Hyperion's management team has many members from CoTherix, who commercialized Ventavis for PAH. The team has experience with both regulatory and clinical development and marketing of products.

FIGURE 28. Management Team

Name	Position	Previous Company
Donald Santel	CEO	CoTherix
Jeffrey Farrow	CFO	Evotec, Renovis
Bruce Scharschmidt MD	CMO	Novartis, Chiron
Klara Dickinson	VP Regulatory	CoTherix, Scios
Christine Nash	COO	CoTherix
Dion Coakley, Pharm D	VP Clin Op	Virobay, Gilead
Masoud Mokhtarani, MD	VP Clin Dev	Limerick, Pfizer

Source: Company Reports and JMP Securities LLC

FIGURE 29. Hyperion Board

	Since	Affiliation
James Healy, MD, PhD	2006	Sofinnova Ventures
Donald Santel	2007	CEO Hyperion
Gaurav Aggarwal, MD	2009	Investor Growth Capital
David Gryska	2010	Myrexis, Celgene
Bo Jesper Hansen MD, PhD	2011	Swedish Orphan Biovitrum
Robert Hopfner, PhD	2010	Bay City Capital
Jake Nunn	2009	New Enterprise Associates
Dijan Salehizadeh, MD	2007	NaviMed Capital Advisors
Lota Zoth	2008	MedImmune
Daniel Welch	2012	InterMune

Source: Company Reports and JMP Securities LLC

FINANCIALS

Hyperion ended 2012 with $50M in cash as has $103M in cash *pro forma* after a recent financing. We believe this cash is sufficient to launch Ravicti in UCD, support a Phase 3 study in HE and get the company to profitability in 2014. Hyperion has the option to purchase Buphenyl and potentially Ammonul at a price of $22M which will be financed by a loan from the seller and paid back in eight installments with an interest rate of 9%. However, if Valeant retains Ammonul, which appears increasingly likely, Hyperion will gain $13M in cash from the transaction and will not require a loan. We have modeled the latter scenario. We assume an increase in R&D spend in 2014 and 2015 to finance a Phase 3 study in HE. With the small footprint needed to support the Ravicti launch, we believe the company can reach profitability next year.

FIGURE 30. Projected Income Statement for Hyperion Therapeutics (000's)

	FY11A	Mar-12A	Jun-12A	Sep-12A	Dec-12A	FY012A	Mar-13E	Jun-13E	Sep-13E	Dec-13E	FY013E	FY014E	FY015E	FY016E	FY017E	FY018E	FY019E	FY20E	FY21E	FY22E	FY23E	FY24E
Revenues:																						
Buphenyl						0	0	0	4,261	3,333	7,594	8,469	8,625	6,779	4,871	0	0	0	0	0	0	0
Ractivi							331	1,866	3,870	8,436	14,502	67,301	81,451	99,276	121,777	6,966	7,694	8,151	8,635	9,147	9,690	10,265
HE Market											0	0	0	0	0	49,702	106,462	171,032	244,233	326,967	420,219	525,063
Total product revenue	**0**					**0**	**331**	**1,866**	**8,131**	**11,769**	22,096	**75,770**	**90,076**	**106,055**	**126,648**	**56,668**	**114,156**	**179,182**	**252,868**	**336,115**	**429,909**	**535,329**
Total revenue	**-**					**-**	**331**	**1,866**	**8,131**	**11,769**	**22,096**	**77,999**	**106,901**	**126,418**	**151,467**	**87,112**	**120,868**	**191,752**	**272,009**	**362,697**	**464,893**	**579,773**
Operating expenses:																						
COGS	0	0	0	0	0	0	68	237	467	969	1,741	9,802	11,796	14,173	17,210	9,067	18,265	28,669	40,459	53,778	68,785	85,653
R&D	17236	8902	2732	2372	3033	17,039	3000	2500	2500	2500	10,500	25,000	35,000	25,000	20,000	30,000	15,000	10,000	8,000	8,000	8,000	8,000
G&A	8162	2077	1469	1541	2450	7,537	2500	2600	2600	2600	10,300	10,920	11,466	12,039	12,641	13,273	13,937	14,634	15,366	16,134	16,941	17,788
Sales and Marketing	761	246	554	845	2312	3,957	2500	2700	3000	3000	11,200	12,600	13,230	13,892	25,000	35,000	36,750	38,588	40,517	42,543	44,670	46,903
Total operating expenses	**26159**	**11225**	**4,755**	**4,758**	**7,795**	**28,533**	**8068**	**8,037**	**8,567**	**9,069**	33,741	**58,322**	**71,492**	**65,104**	**74,851**	**87,340**	**83,952**	**91,891**	**104,341**	**120,455**	**138,396**	**158,343**
											0											
Loss from operations	**(26,159)**	**(11,225)**	**(4,755)**	**(4,758)**	**(7,795)**	**(28,533)**	**(7,737)**	**(6,171)**	**(436)**	**2,700**	(11,645)	**19,677**	**35,409**	**61,314**	**76,616**	**(228)**	**36,916**	**99,862**	**167,668**	**242,242**	**326,497**	**421,430**
Interest expense	(2554)	(588)	(2410)	(214)	(491)	(3703)	(548)	(548)	(548)	(548)	(2,192)	(1140)	(118)	(87)	(55)	(24)	0	0	0	0	0	0
Other, net	(731)		0	(39)		(39)		8000	0		8,000											
Total other income (expense)	**(3257)**	**(584)**	**(2407)**	**(250)**	**(490)**	**(3731)**	**19**	**7487**	**(481)**	**(416)**	6,608	**(653)**	**925**	**1724**	**3434**	**6701**	**12963**	**24987**	**48163**	**92837**	**178950**	**344937**
											0											
other	-												-									
Income Taxes											-	-	-	*3,152*	*4,002*	*324*	*2,494*	*12,485*	*32,375*	*67,016*	*149,107*	*226,078*
Tax rate											0%	0%	0%	5%	5%	5%	5%	10%	15%	20%	30%	30%
Net loss	**$ (29,416)**	**$ (11,809)**	**$ (7,162)**	**$ (5,008)**	**$ (8,285)**	**$ (32,264)**	**$ (7,718)**	**$ 1,315**	**$ (918)**	**$ 2,284**	$ (5,037)	**$ 19,024**	**$36,335**	**$ 59,886**	**$ 76,047**	**$ 6,150**	**$ 47,384**	**$112,364**	**$183,456**	**$268,063**	**$356,340**	**$540,288**
Loss per Share basic	**$ (62.68)**	**$ (25.16)**	**$ (15.26)**	**$ (0.44)**	**$ (0.50)**	**$ (4.45)**	**$ (0.44)**	**$ 0.07**	**$ (0.05)**	**$ 0.11**	$ (0.31)	**$ 0.96**	**$ 1.79**	**$ 2.87**	**$ 3.26**	**$ 0.26**	**$ 1.95**	**$ 4.52**	**$ 7.24**	**$ 10.37**	**$ 13.52**	**$ 20.12**
Shares outstanding, basic	469	469	469	11,327	16,613	7,257	17,364	19,968	20,018	20,068	19,355	19,855	20,355	20,855	23,355	23,855	24,355	24,855	25,355	25,855	26,355	26,856

Liisa A. Bayko 312-768-1789

Source: Company reports and JMP Securities LLC estimates

Company Description

Hyperion Therapeutics is a San Francisco-based biopharmaceutical company focused on the development of Ravicti, a delayed release formulation of buphenyl, an ammonia scavenger approved for use in UCD with the potential to be used in other diseases characterized by ammonia toxicity, notably HE.

Investment Risks

Clinical risk. Ravicti is currently being evaluated for use in children under age 2. Should a safety issue arise, ramifications could include approval extension into this age group and potentially for the broader age group. Ravicti could underperform in forthcoming clinical studies in hepatic encephalopathy (HE) or safety issues could arise.

Regulatory risk. The FDA is currently revising endpoints for HE. We expect the process to wrap up by year end, but it is conceivable that it could take longer, which would push back the start of pivotal studies for Ravicti in this indication. Hyperion has indicated that it will pursue a special protocol assessment (SPA) in advance of starting its pivotal program and it is possible that the FDA may disagree with development plans for Ravicti in HE.

Intellectual Property risk. The composition of matter patent for Ravicti expires in 2015, with market exclusivity extended to 2018 with Hatch Waxman. Hyperion may or may not receive orphan designation, which, if granted, would extend the exclusivity period until 2020. Hyperion recently received notice that new patents will be allowed which cover instructions on how to monitor and adjust dosing, which management believes will extend protection until 2028. It is possible that a generic competitor could attempt a work around to these patents, which could put Ravicti revenue at risk, as early as 2018.

Commercial risk. As a small company, Hyperion may not be able to maximize the marketplace and bring non-treated UCD patients on board. Insurers may provide more push-back than anticipated in allowing patients to switch from Buphenyl to Ravicti. Patients may chose other alternatives such as generic sodium phenylbuterate powder or a tasteless formulation currently moving through the European regulatory process. Newer technological breakthroughs may occur rendering Hyperion's compound obsolete. Hyperion may have a harder time gaining traction in HE given the dominance of lactulose and Salix’s Xifaxan in the marketplace.

Sector risk. Valuation of biopharmaceutical stocks is subject to both investors' assessments of the prospects of the underlying companies, as well as investor tolerance for risk and confidence in the prospects of pharmaceutical stocks as a group. Therefore, Hyperion's stock price may fall even while the company meets or exceeds investor expectations.

JMP FACTS AND DISCLOSURES

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JMP Securities currently makes a market in the security of Hyperion Therapeutics, Inc.

JMP Securities was manager or co-manager of a public offering for Hyperion Therapeutics, Inc. in the past 12 months.

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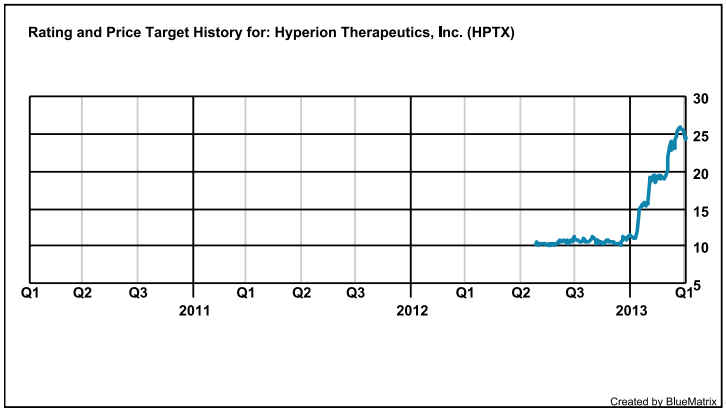
MARKET OUTPERFORM	Buy	212	*59.22%*	Buy	212	*59.22%*	63	*29.72%*
MARKET PERFORM	Hold	140	*39.11%*	Hold	140	*39.11%*	15	*10.71%*
MARKET UNDERPERFORM	Sell	6	*1.68%*	Sell	6	*1.68%*	0	*0%*
TOTAL:		358	*100%*		358	*100%*	78	*21.79%*

Stock Price Chart of Rating and Target Price Changes:

Note: First annotation denotes initiation of coverage or 3 years, whichever is shorter. If no target price is listed, then the target price is N/A. In accordance with NASD Rule 2711, the chart(s) below reflect(s) price range and any changes to the rating or price target as of the end of the most recent calendar quarter. The action reflected in this note is not annotated in the stock price chart. Source: JMP Securities.



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