COWEN
AND COMPANY

Biotechnology

Relypsa, Inc

Equity Research

Initiating Coverage

December 10, 2013

Price: $19.99 (12/9/2013)
Price Target: NA

OUTPERFORM (1)

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Key Data

Symbol	NASDAQ: RLYP
52-Week Range:	$21.40 - 11.00
Market Cap (MM):	$630.0
Net Debt (MM):	$0.0
Dil. Shares Out (MM):	27.7
Enterprise Value (MM):	$736.1
Dividend:	NA

FY (Dec)	2012A	2013E	2014E
Earnings Per Share			
Q1	$0.00	$(3.90)A	$(0.49)
Q2	$0.00	$(4.79)A	$(0.49)
Q3	$0.00	$(1.30)A	$(0.51)
Q4	$0.00	$(0.69)	$(0.61)
Year	$(11.94)	$(3.15)	$(2.10)
P/E	NM	NM	NM
Revenue (MM)			
Q1	0.0	0.0A	0.0
Q2	0.0	0.0A	0.0
Q3	0.0	0.0A	0.0
Q4	0.0	0.0	0.0
Year	0.0	0.0	0.0

Initiation: Potassium Too High? Patiromer Is Nigh

The Cowen Insight

We are initiating coverage on Relypsa with an Outperform rating. We believe patiromer for the treatment of hyperkalemia associated with chronic kidney disease (CKD) has U.S. sales potential of $500MM - $1B. We expect RLYP shares to outperform as the drug advances toward an NDA filing in 2014 and potential FDA approval in 2015.

Hyperkalemia: Potassium Gone Bad

Potassium, a chemical element that is essential for life, can reach dangerously high levels in CKD patients with impaired renal excretion. Cases of hyperkalemia are often aggravated by medications that are effective in treating CKD (ARBs or ACE inhibitors), but have the unfortunate property of further elevating serum potassium. Because a safe and effective means for controlling serum potassium is lacking, a majority of CKD patients receive sub-optimal doses of ARBs or ACE inhibitors, placing them at greater risk of disease progression.

Patiromer Binds, Without Gagging

Patiromer is a non-absorbed polymer that binds and removes potassium from the gut. Multiple clinical studies, including an SPA-sponsored Phase III trial, have shown that patiromer can effectively lower serum potassium to within normal ranges in the great majority of treated patients. Moreover, unlike prior generation potassium binders, patiromer is well tolerated (tasteless, free of GI issues) and safe for chronic administration. With patiromer's clinical development essentially de-risked, Relypsa is on track to submit an NDA for the drug in Q3:14.

A Large Market For KO'ing K+

Relypsa estimates that ~2.4MM CKD and heart failure patients with hyperkalemia might present to specialist physicians. The company intends to commercialize patiromer on its own in the U.S., and believes it can reach this market with a targeted salesforce of ~100 reps. Assuming annual pricing in the $6,000-$7,000 range, we believe patiromer could become a $500MM to $1B drug by penetrating just 4-9% of this market.

Stock Looks Like A Winner

Relypsa raised $78MM in a November IPO and is financed through patiromer's anticipated 2015 launch. We value RLYP on a sum-of-the-parts basis, ascribing value only to patiromer ($25/share) and net cash ($3/share), and view shares as 29% undervalued.

At A Glance

Our Investment Thesis

Relypsa plans to file an NDA on patiromer for the treatment of hyperkalemia in Q3:14. The addressable U.S. market opportunity is large, with over 2M moderate to severe hyperkalemia patients presenting to specialist physicians. We model sales ramping to nearly $1B over time assuming fairly modest market penetration estimates (~10% market share). We view RLYP shares as 29% undervalued based upon a sum of the parts methodology.

Forthcoming Catalysts

- Complete Phase I onset of action trial
- File patiromer NDA
- Possible FDA AdCom meeting on patiromer

Base Case Assumptions

- Patiromer is approved for treating hyperkalemia
- Patiromer achieves 2018 U.S. sales of $200MM

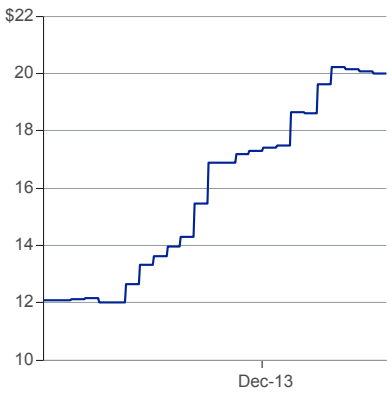
Upside Scenario

- Patiromer's launch proceeds better than expected
- Relypsa is able to monetize patiromer's value outside the U.S.
- Relypsa is able to generate other interesting drug candidates

Downside Scenario

- Patiromer encounters regulatory delays or setbacks
- Patiromer's side effect profile worsens
- Patiromer's launch falls short of expectations

Price Performance



Source: Bloomberg

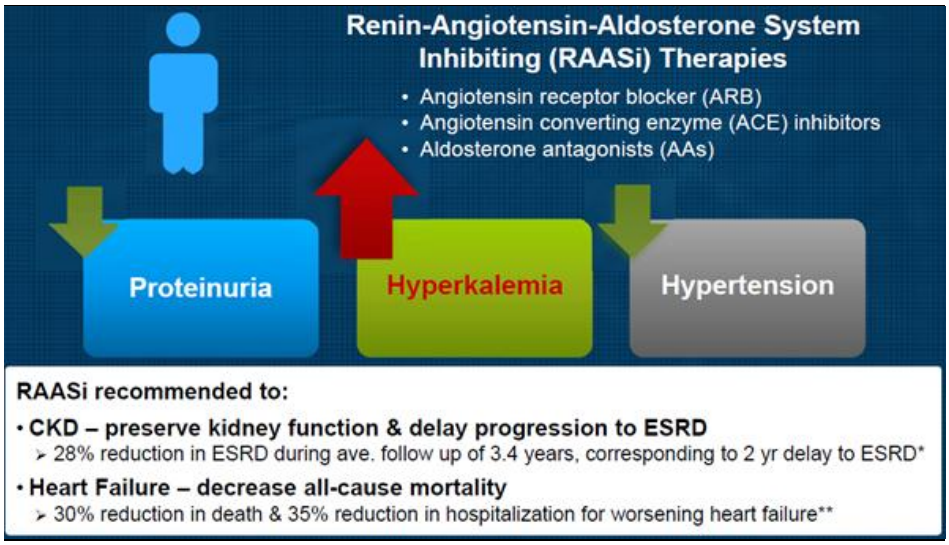
Company Description

Relypsa is developing patiromer for the treatment of hyperkalemia (high levels of potassium in the blood). Patients with chronic kidney disease and heart failure are known to have elevated levels of potassium, which carry risk of cardiac arrhythmia and sudden death. Unfortunately, RAASi therapies (ARBs, ACE inhibitors, AAs) that are the standard of care for treating these diseases further exacerbate the situation by increasing blood levels of potassium. As a result, RAASi therapies are often under-dosed, providing for sub optimal control of the underlying disease. Patiromer is a non-absorbed polymer that binds potassium in the gut and excretes it from the body. In an SPA-sponsored Phase III trial, patiromer reduced serum potassium to normal ranges in 76% of patients. Unlike other potassium lowering therapeutics, the drug appears well tolerated and safe for chronic use. Therefore, we believe patiromer represents an approvable therapy for an unmet need.

Hyperkalemia: A Vicious Cycle

Potassium is an element (chemical symbol "K") necessary for the function of all living cells. Approximately 0.2% of the human body is comprised of potassium cations (K+), which are important to nerve function and osmotic balance. Potassium is taken in through the diet and maintained at proper levels by the kidneys, which excrete excess potassium. Therefore, patients with kidney failure often retain potassium, and have serum levels above that which is considered normal (3.8 to 5.5mEq/L). If potassium levels in the serum rise above 5.5mEq/L, a state of hyperkalemia results, the consequences of which can be severe, including sudden death. A class of therapies called Renin-Angiotensin-Aldosterone System inhibitors (or RAASi) is recommended for use in patients with CKD and heart failure due to their ability to delay the progression of kidney disease and lower blood pressure. However, these therapies also have the effect of increasing serum potassium, placing patients further at risk of hyperkalemia. As a result, RAAS inhibitors are under-dosed in many patients or in some cases not utilized at all, leading to sub-optimal treatment of the underlying disease. The hope is that a safe and effective therapy capable of lowering serum potassium could break the cycle, and allow patients to receive more optimized RAASi therapy while reducing the risks associated with hyperkalemia. We believe Relypsa's patiromer addresses this unmet need.

RAAS Inhibitors Further Exacerbate Hyperkalemia



Source: Relypsa

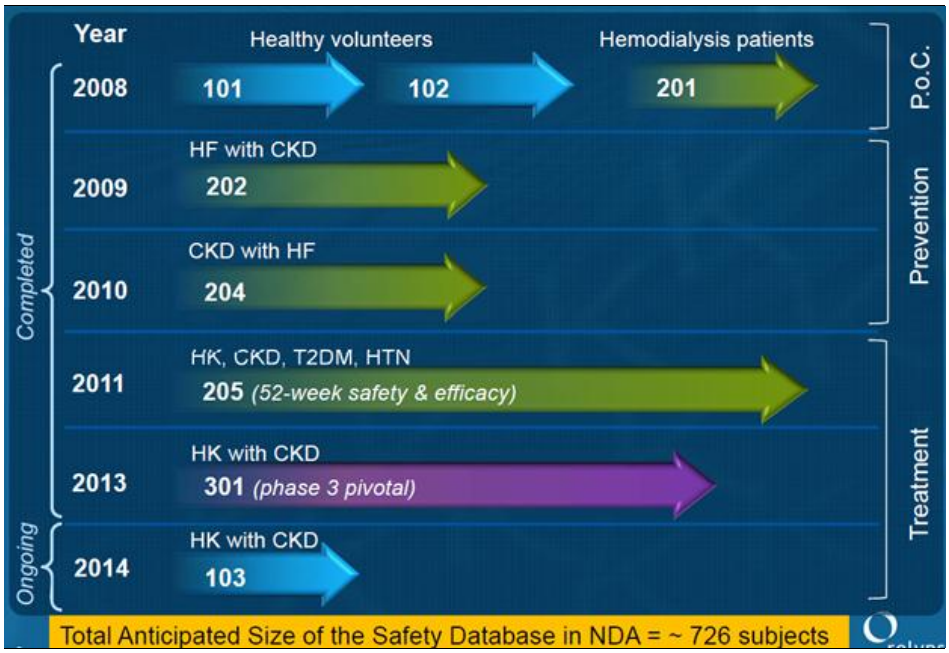
Patiromer To The Rescue

Patiromer is a non-absorbed polymer that binds potassium in the colon, where potassium is known to be elevated, and removes it from the body. The active potassium-binding agent within patiromer (flouroacrylate) was identified from a series of high and low throughput screens based upon its capacity for binding cations. Relypsa created a polymer of flouroacrylic acid, formulated the polymer into tiny spherical beads, and further cross-linked the polymer within the beads so as to prevent bead swelling. The resulting product (patiromer) has a high capacity for binding potassium, flows freely in solution (important for tolerability and GI mobility),

is stable at room temperature for 3-6 months, and essentially tasteless and odorless. Patiromer is formulated in dry 10g packets, which are reconstituted in water and dosed twice daily.

Clinical trials on patiromer were initiated in 2008 and over 700 subjects have been treated to date. The drug has been shown to normalize serum potassium in a majority of hyperkalemic CKD patients, and has also proven safe in this somewhat fragile patient population.

Patiromer's Clinical Trial Program



Source: Relypsa

More specifically, Relypsa has completed a large Phase IIb trial as well as an SPA-sponsored Phase III trial. The Phase IIb trial identified an optimal starting dose of patiromer for patients with milder and more severe forms of hyperkalemia, demonstrated statistically significant reductions in serum potassium, and indicated that patiromer was safe and well tolerated when dosed for up to one year. The Phase III trial confirmed the efficacy of patiromer by showing that the drug could reduce serum potassium by at least 0.7 mEq/L. On average, patiromer achieved a 1.01mEq/L reduction within four weeks. Patiromer was also shown to be critical for maintaining serum potassium levels within the target range, underscoring a need for chronic dosing. Based upon these data, we view patiromer as an approvable agent. Relypsa plans to submit an NDA to the FDA in Q3:14 (a Phase I time of onset study is rate limiting) and anticipates approval and commercial launch in H2:15.

The Market Is Wide Open For Patiromer

Most cases of hyperkalemia are managed by treatment options that are either cumbersome (hemodialysis), impractical (dietary restriction), or less than optimal (dose reductions in RAASi therapy). In the U.S. a single drug (sodium polystyrene sulfonate, Kayexalate) is available that removes K+ ions from the body. However, its utilization is substantially curbed by tolerability and safety issues. We expect patiromer

to displace Kayexalate from the market, and greatly expand the use of potassium binders in the large CKD and HF patient populations that present with hyperkalemia. Relypsa estimates that a specialty salesforce of 100 reps can cover a large fraction of the 2.4M U.S. patients who present to nephrologists and cardiologists. We assume patiromer pricing in the $6-7K/year range (on par with other novel CKD drugs), with penetration rates ramping up gradually over time. Though estimating patiromer's ultimate market share is challenging, we note that even modest adoption rates could provide for very meaningful sales.

Estimates For Patiromer's Market Share And Associated Value To Relypsa

2022 U.S. Market Share	2022 Sales	Net Present Value To RLYP
2.5%	$235MM	$0/share
3%	$350MM	$7/share
4%	$475MM	$17/share
5%	$590MM	$25/share
6%	$710MM	$35/share
7%	$825MM	$45/share
7.5%	$885MM	$55/share
8%	$945MM	$61/share

Note: Assumes peak sales of $960B in 2028, a 11% discount rate, and no terminal value

Patiromer is protected by a variety of patents covering the drug's composition, use, and formulation that expire in the 2025-2030 timeframe. Assuming the franchise retains exclusivity through 2028, we estimate that patiromer would break even on an NPV basis assuming 2022 sales of ~$235MM, and that the franchise could deliver significant shareholder value at higher sales levels.

Patiromer Makes RLYP A Stock Worth Owning

Relypsa netted $77.9MM via a November IPO. The company's pro-forma cash of nearly $95MM is expected to last well into 2015 and through patiromer's anticipated FDA approval.

RLYP shares have performed well in the public markets (+82% from their IPO price), and as of December 9 the company sports a market cap of approximately $630MM and enterprise value of roughly $535MM. We value Relypsa using a sum-of-the-parts methodology. Our analysis suggests shares may be 29% undervalued inclusive of the NPV of patiromer and Relypsa's cash. We would expect share to appreciate as investor appreciation for patiromer builds and the drug advances toward commercialization in 2015.

RLYP Sum-Of-The-Parts Valuation

Asset	Value/share
NPV of Patiromer's U.S. Opportunity	$25
Net cash/share	$3
Polymer platform and pipeline candidate RLY6002	$0
Total	$28

Source: Cowen and Company

Upcoming Relypsa Milestones

Event	Timing
Complete Phase I onset of action trial on patiromer	Q2:14
Submit patiromer NDA	Q3:14
Potential selection of additional polymer-based development candidates	2014-2015
Possible FDA advisory panel for patiromer	H1:15
U.S. approval and launch of patiromer	Q4:15

Source: Cowen and Company

Estimated NPV Of Patiromer

Financial Year End	12/31/2012
Valuation Date	12/9/2013
Discount Rate	11.0%
Perpetual Growth Rate	NA

Relypsa NPV

Valuation Date: Monday, December 09, 2013

$MM	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Patiromer U.S. Sales	0	0	5	50	125	200	300	400	500	590	673	747	814	871	923	960
Growth (%)				*900%*	*150%*	*60%*	*50%*	*33%*	*25%*	*18%*	*14%*	*11%*	*9%*	*7%*	*6%*	*4%*
Total Revenue	0	0	5	50	125	200	300	400	500	590	673	747	814	871	923	960
COGS	0	0	2	12	24	34	45	60	70	83	94	97	106	113	120	125
Gross Margin			*65%*	*76%*	*81%*	*83%*	*85%*	*85%*	*86%*	*86%*	*86%*	*87%*	*87%*	*87%*	*87%*	*87%*
R&D	64	46	46	50	54	57	50	45	45	40	40	35	35	30	30	30
R&D as a % of Revenues				*100%*	*43%*	*29%*	*17%*	*11%*	*9%*	*7%*	*6%*	*5%*	*4%*	*3%*	*3%*	*3%*
Sales and Marketing	-4	4	36	72	77	81	88	95	100	105	110	105	100	95	90	50
SG&A as a % of Revenues				*144%*	*61%*	*40%*	*29%*	*24%*	*20%*	*18%*	*16%*	*14%*	*12%*	*11%*	*10%*	*5%*
Operating Income	(60)	(50)	(78)	(84)	(29)	28	117	200	285	362	428	510	573	633	683	755
Operating Margin			*-1569%*	*-167%*	*-23%*	*14%*	*39%*	*50%*	*57%*	*61%*	*64%*	*68%*	*70%*	*73%*	*74%*	*79%*
Tax	0	0	0	0	0	0	0	10	43	127	150	178	201	221	239	264
Tax rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*5%*	*15%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Approx Free Cash Flow	(60)	(50)	(78)	(84)	(29)	28	117	190	242	236	278	331	372	411	444	491
Years	0.06	1.05	2.05	3.06	4.06	5.05	6.05	7.06	8.06	9.05	10.05	11.06	12.06	13.05	14.05	15.06
Discount Factor	0.99	0.90	0.81	0.73	0.65	0.59	0.53	0.48	0.43	0.39	0.35	0.32	0.28	0.26	0.23	0.21
NPV of Cash flows	(60)	(45)	(63)	(61)	(19)	17	62	91	104	92	98	104	106	105	102	102

Terminal Value Calculation

Final year FCF	491
Perpetual Growth Rate	NA
Terminal Value	**NA**
Discount Factor	0.21
Present Value of Terminal Value	**NA**
Present Value of Cash Flows	**781**
Enterprise Value	**781**
Fully Diluted Shares Outstanding	31.5
Value per Fully Diluted Share	**$24.78**

Source: Cowen and Company.

Kidneys: Too Important To Fail

Chronic kidney disease (CKD) patients experience a slow, progressive loss of renal function. Malfunctioning kidneys pose a tremendous threat to patients' well-being as they are responsible for removing wastes, maintaining blood pressure, and regulating the homeostasis of important minerals such as sodium and potassium. CKD is most commonly caused by diabetes or high blood pressure, and in turn, CKD patients are at higher risk of heart and vascular disease. Other health complications include anemia, osteoporosis, nerve damage, and hyperkalemia. When kidney disease progresses, it leads to kidney failure, or end-stage renal disease (ESRD). ESRD patients require dialysis or a kidney transplant in order to survive. Clinically, CKD is defined by a sustained reduction in the volume of fluid filtered through the kidney per unit time, known as glomerular filtration rate (GFR), or evidence of structural or functional abnormalities of the kidneys. The GFR is the most commonly used metric for assessing kidney function and determine the stage of disease progression. GFR is approximated (eGFR) by measuring the rate of creatinine clearance from the plasma. The US National Kidney Foundation established a five-stage classification system for the disorder.

Stages of Chronic Kidney Disease

Stages of CKD		GFR (mL per min per 1.73m^2)
At risk		≥60 (with risk factors for chronic kidney disease)
1.	Kidney damage with normal or increased GFR	≥90
2.	Kidney damage with mildly diminished GFR	60-89
3.	Moderately reduced GFR	30-59
4.	Severely decreased GFR	15-29
5.	End-stage renal disease (kidney failure)	<15

Source: Cowen and Company

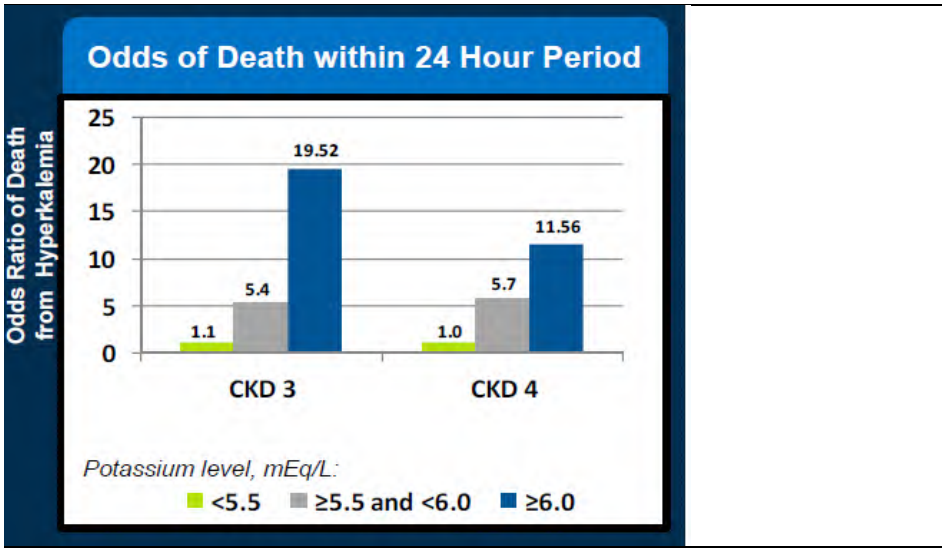
CKD – All Too Common, And Growing

Once a rare affliction caused mainly by genetic mutations, chronic kidney disease has become a global pandemic that diminishes a patient's quality of life and results in exorbitant medical costs. According to the National Kidney Foundation, approximately 26 million American adults have some form of CKD and millions of others are at increased risk. The costs of caring for patients with CKD in 2011 amounted to $45.5 billion, which accounted for 18% of total Medicare expenditures. In the U.S., the incidence of CKD is increasing most rapidly in people ages 65 and older. In this category, the incidence more than doubled between 2000 and 2008 (1.9-4.3% of the population). Based on the 2001-2008 National Health and Nutrition Examination Survey (NHANES), the prevalence of Stage 3 CKD in people ages 60 and older was 26% (~10M). Looking forward, the number of people suffering from CKD is expected to increase, given the widespread exposure to risk factors such as diabetes and an aging population.

Kidney Disease Is A Major Cause Of Hyperkalemia

One of the most important functions of the kidney is to maintain appropriate levels of sodium (Na+) and potassium (K+) in the blood. These minerals play numerous essential roles in regulating blood pressure, establishing membrane potentials, and controlling cell volume, to name a few. When filtering over 180 liters of plasma every day, the kidney has finely tuned mechanisms that manage the amount of electrolytes excreted into the 1.5-2 liters of urine produced. In CKD patients with impaired glomerular filtration rates, a particular cause of concern is the decreased ability of the kidney to excrete potassium. Elevated potassium levels cause symptoms ranging from malaise, muscle weakness, and paralysis to bradycardia (a type of arrhythmia) and sudden death. A 2009 retrospective study of patients with moderate-to-severe hyperkalemia found a 10-fold increase in their mortality rate within 24 hours.

Patients With Moderate-To-Severe Hyperkalemia Have A 10-Fold Increase In Mortality Rate



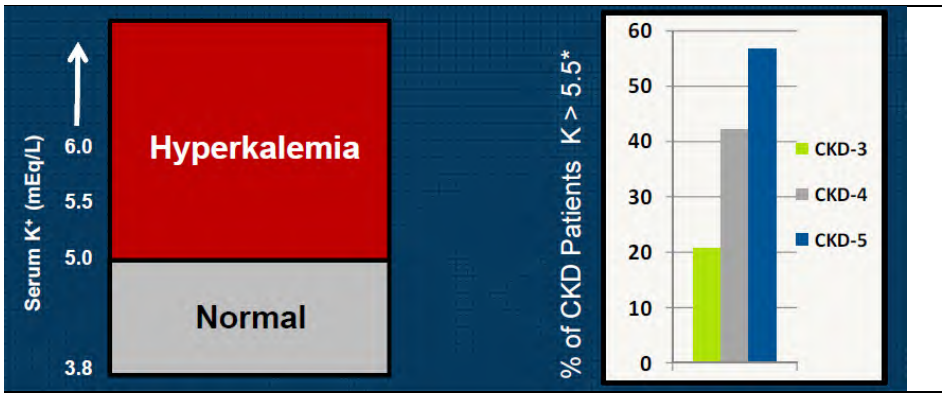
Source: Relypsa

In a healthy individual, the normal range for serum potassium is between 3.8 to 5.0 mEq/L. Concentrations of potassium above this threshold are characteristic of hyperkalemia. The great majority (approximately 98%) of potassium in the body resides inside cells, though potassium can shift back and forth from extracellular to intracellular compartments. In order to maintain a stable equilibrium of potassium, the body must balance the dietary intake of potassium with its renal excretion. Over 90% of dietary potassium is excreted through the kidney. While increased potassium intake on its own is not a common cause of hyperkalemia, when combined with renal deficiency, the risk is greatly increased. The ability of the kidney to excrete potassium decreases proportionally to the loss of glomerular filtration. Therefore, the more advanced the stage of chronic kidney disease, the higher the incidence of hyperkalemia. Between 20-40% of stage 3 and 4 CKD patients exhibit some form of hyperkalemia.

Owing to their poor cardiac output resulting in reduced renal blood flow, heart failure (HF) patients are another population at risk of developing hyperkalemia. In fact, the pathophysiologies of HF and CKD are interdependent and have sodium and potassium as key mediators. This is because in addition to filtering the blood, kidneys also play a

key role in the regulation of blood pressure. In response to decreased kidney blood flow, the kidney activates what is known as the renin-angiotensin-aldosterone system (RAAS). Activation of this system aids the kidney to elevate blood pressure by two main mechanisms: (1) vasoconstriction and (2) reabsorption of water to increase the circulating blood volume. Central to the first mechanism is angiotensin II, which is produced in a series of enzymatic reactions carried out by renin and angiotensin-converting enzyme (ACE). Angiotensin II causes blood vessels to contract, thus elevating the blood pressure and flow rate through the kidneys. The second mechanism employed by the kidney to control blood pressure relies on aldosterone and a gradient of sodium and potassium. Aldosterone, is a hormone secreted by the adrenal gland after stimulation by angiotensin II. Aldosterone establishes a gradient of potassium and sodium across specialized cells that line the collecting duct of the kidney. The movement of potassium ions from the blood into urine, and that of sodium ions from the urine into the blood triggers reabsorption of water into the blood. Reabsorption of water reduces the urine output and increases the circulating blood volume. An increase in the amount of blood pumped by the heart per minute raises blood pressure. Besides controlling blood pressure, aldosterone is principally responsible for eliminating potassium from the circulating blood and maintaining electrolyte homeostasis. The reliance of the body on the RAAS system to maintain potassium at normal levels in the blood explains why, when CKD and HF patients are treated with RAAS inhibitors, a further increase in blood potassium levels and hyperkalemia incidence is observed.

Hyperkalemia In Late Stage CKD Patients



Source: Relypsa

RAAS Inhibitors Are The Standard Of Care

The goal of CKD treatment is to reduce kidney damage and slow the progression to ESRD. The preferred class of drugs that accomplish this goal are the renin-angiotensin-aldosterone system (RAAS) inhibitors. Drugs within this class, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and aldosterone antagonists (AAs), are effective at slowing the progression of kidney disease and delaying the onset of ESRD. Their effectiveness in diabetic or non-diabetic chronic kidney disease patients was demonstrated in a number of clinical trials. Pooled data from 11 randomized control trials in non-diabetic CKD patients showed that in comparison to other hypertensive drugs, RAASi treatment reduced the risk of kidney failure by 40%. Two landmark studies in patients with nephropathy due to type 2 diabetes showed that treatment with an angiotensin-receptor blocker reduced the risk of doubling of serum creatinine or kidney failure. Notably, in the

REENAL trial that enrolled 1,513 patients with type 2 diabetes and nephropathy, the use of Losartan (an ARB) reduced the incidence of end-stage renal disease by 28%. Therefore, treatment with RAAS inhibitors confer considerable renal benefits to patients, and can delay the onset of ESRD by approximately two years.

Even though these drugs are commonly used in heart failure (HF) patients for the treatment of hypertension, their effects have been shown to benefit CKD patients without hypertension. RAASi are thought to work at multiple levels to slow progression of CKD:

1) **RAASi reduce blood pressure and glomerular intracapillary pressure.** Excessive glomerular pressure can damage the kidney filtration system. As detailed above, the renin-angiotensin-aldosterone system controls arterial blood pressure. In heart failure and CKD patients, RAASi can successfully reduce hypertension by decreasing the amount of water reabsorbed in the kidney. Decreased arterial pressure indirectly reduces glomerular pressure as well. RAASi also have more direct effect on the kidney as they have been shown to selectively dilate efferent glomerular arterioles.

2) **RAASi reduce proteinuria**. One of the first signs of chronic kidney disease is the appearance of large molecular weight proteins in the urine, or proteinuria, measured as albumin/creatinine ratio or ACR. Proteinuria is associated with a faster progression of kidney disease. This is likely due to the fact that when large proteins slip through the defective filter, their reabsorption causes injuries to the tissue, an event that triggers inflammatory signals. RAASi have been shown to reduce glomerular permeability to proteins, to limit proteinuria and protein-dependent inflammatory signals.

3) **RAASi reduce mesangial cell (MC) hypertrophy**. MCs are specialized cells around blood vessels in the kidney. Growth signals stimulated by Angiotensin II promote mesangial cell hypertrophy and extracellular matrix production, both prominent features of progressive glomerular injury.

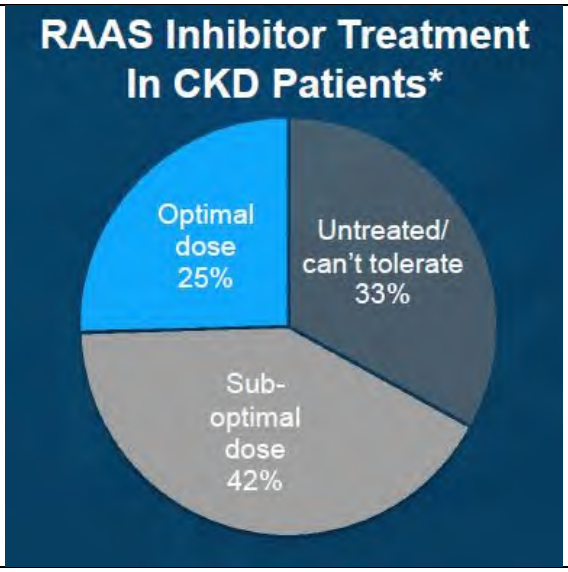
4) **RAASi may interfere with free radical formation in the kidney**. Angiotensin II has been implicated in the intracellular formation of reactive oxygen species (ROS). RAASi may protect the kidney from oxidative stress.

Given their effectiveness in slowing progression of chronic kidney disease, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and the American College of Cardiology and the American Heart Association (ACC/AHA) recommended the administration of RAAS inhibitors to patients at high risk of kidney and cardiovascular complications.

Unfortunately, treating HF and CKD patients with RAAS inhibitors exacerbates the already inefficient excretion of potassium and increases the risk of hyperkalemia. The possibility of developing such a life-threatening treatment complication discourages

many physicians from prescribing RAAS inhibitors. In addition, ACE inhibitors and ARBs are often dosed sub-optimally. In fact, market research shows that ~90% of nephrologists have hyperkalemia as a top concern when using RAASi medication, and consultants believe that over 40% of patients treated with RAASi take a suboptimal dose. Despite the great benefit demonstrated by RAAS inhibitors in slowing down renal disease and treating heart failure patients, their use is hindered by the sudden appearance of hyperkalemic complications that are hard to manage.

Percentage Of CKD Patients Treated With Suboptimal Doses of RAASi



Source: Relypsa

Much Unmet Need In Managing Hyperkalemia

Treating hyperkalemia has proven very challenging. Existing treatments have either a short duration of action, are inconvenient or poorly tolerated, or have debilitating side effects. In particular, there is a dearth of treatment options for the chronic management of hyperkalemia. The available alternatives include dietary potassium restrictions, potassium-wasting diuretics, or sodium polysterene suflonate (SPS). Dietary restrictions are hard to impose in this at risk population. Dietary fat, carbohydrate, sodium, and phosphorus intake tends to already be restricted in CKD patients. Since potassium is present in most foods, increasing dietary restrictions tends to be difficult. Diuretics are highly effective at removing potassium in patients with normal kidney function. In CKD patients, however, their effect is greatly reduced.

SPS is the only drug on the U.S. market approved for the treatment of hyperkalemia. Drugs that have sodium polystyrene sulfonate as an active ingredient and are prescribed to hyperkalemic patients include Kayexalate, Kionex, Kalexate and Marlexate. SPS is a cation-exchange polymer designed to take up K+ ions in the gastrointestinal tract and release Na+ ions. Even though, SPS is able to induce and maintain a lower plasma K+ concentration over longer periods of time, it is far from an ideal treatment. SPS, besides having a bad taste and needing to be administered up to 4x a day in some cases, is also associated with potentially severe side effects. Since the SPS polymer swells excessively in water, it can cause constipation. Despite the black box warning against co-administering sorbitol (laxative) with SPS, many doctors

don't have a choice, and in the U.S. there are still sorbitol and Kayexalate premixed solutions being sold. Moreover, some studies indicate that co-administration of sorbitol to induce diarrhea is necessary to achieve target potassium levels. In addition, SPS can induce intestinal necrosis, GI bleeding and perforation in some instances. This is caused by irregular polymer fines that result from the grinding up process used to create the SPS powder. These fines can be absorbed by GI epithelial cells and create dangerous accretions in the gut. Doctors are typically unwilling to prescribe SPS for longer than a few days at a time. Lastly, the exchange cation for SPS is sodium, which is reabsorbed by the kidney and can aggravate hypertension and fluid retention.

In the absence of effective therapies, long-term management of hyperkalemia typically means the discontinuation or dose reduction of drugs that increase retention of potassium such as RAAS-blocking agents. Cardiologists and nephrologists express frustration and concern at the fact that hyperkalemia is forcing them to withhold potentially life-saving medications from their HF and CKD patients. No doubt, there is a great need for products that can safely treat hyperkalemia long-term.

Patiromer Could Be The Obvious Choice In Managing Hyperkalemia

Patiromer is a novel, non-absorbed polymer for the chronic control of serum potassium in patients at risk of hyperkalemia. The drug acts in the gut to bind cations, including potassium, with high capacity and remove them from the body. Patiromer has demonstrated efficacy in multiple clinical trials, including an SPA sponsored Phase III study, and appears to have a vastly superior safety and tolerability profile relative to other potassium binders including Kayexalate. Moreover, data support the chronic administration of patiromer to CKD patients without interruption of their RAAS inhibitors. Given the positive pivotal clinical data, we think patiromer is likely to gain FDA approval in 2015.

Patiromer, Not Your Average Polymer

Patiromer is formulated as a dry, odorless powder that is easily suspendable in small amounts of water (~40 ml) for oral BID administration. The starting doses vary depending on the hyperkalemia level and all patients can be titrated up. For patients with serum potassium levels between 5.1 and 5.5 mEq/L, the starting dose is 8.4 g of patiromer (4.2 g twice a day). For those patients with potassium levels beyond 5.5 mEq/L, the starting dose is 16.8 g (8.4 g twice a day). The active pharmaceutical ingredient within patiromer is a polymer of fluoroacrylic acid, cross-linked with divinylbenzene and 1,7 octadiene. The fluoroacrylate monomer is the moiety responsible for binding potassium in the colon. It was selected following a screen of about 20,000 other moieties for its ability to bind high quantities of potassium, low molecular weight, ease of polymerization and amenability to crosslinking. In *in vitro* experiments conducted by Relypsa, patiromer bound considerably more potassium per gram of polymer as compared to SPS (8.5 mEq/g vs. 5.1 mEq/g). Patiromer's cross-linking minimizes swelling in water (swelling ratio of less than 1g of water per gram of polymer). Reduced swelling is key for optimal flow properties and good GI tolerability. Kayexalate, which swells excessively in water, is associated with poor flow properties and severe constipation. Thus far, while patients taking patiromer have experienced some level of gastrointestinal AEs, physician consultants feel these symptoms are far less severe and concerning compared to those seen in patients taking SPS. Another distinguishing factor that contributes to patiromer's better GI tolerability is the fact

that the cross-linked polymer is induced to assume a spherical shape, with an average diameter of about 100 microns, approximately 100x larger than epithelial cells. Patiromer's particle size prevents the beads from being absorbed into the body, while the spherical shape imparts good flow properties to patiromer. In contrast, the finely ground SPS polymer is made of smaller less regular particles that have the propensity to form crystals and become lodged in the gastric mucosa. An additional advantage to using patiromer is that the exchange cation is calcium, not sodium, as it is for SPS, and therefore it removes the risk related to fluid retention or hypertension caused by sodium. Taken together, the properties of patiromer offer much improved convenience and tolerability over current options.

Comparing and Contrasting Patiromer And Kayexalate Properties

Patiromer	Property	Kayexalate
Small MW K^+ binding units, synthesized by suspension polymerization process, significant K^+ binding capacity (in vitro)	Chemistry and Binding	Large MW K^+ binding units, synthesized by bulk polymerization process, moderate K^+ binding capacity (in vitro)
Nonabsorbed, well-tolerated	Safety and Tolerability	Intestinal necrosis warning, GI side effects
Spheres of uniform size, free-flowing polymer beads	Design/Active Pharmaceutical Ingredient	Irregular bulk gel material, sharp edges, non-uniform size and fines, clay-like consistency
Ca^{2+}/sorbitol–loaded	Counterion	Na^+–loaded
5 clinical studies with proven K^+ reduction and control	Proven Efficacy	No published efficacy data from prospective clinical trials (approval grandfathered in)
Lower dose, neutral taste	Dosing/ Compliance	Gritty, bad taste, up to 60 g TID

Source: Relypsa

Patiromer Has Been Tested In Five Clinical Trials

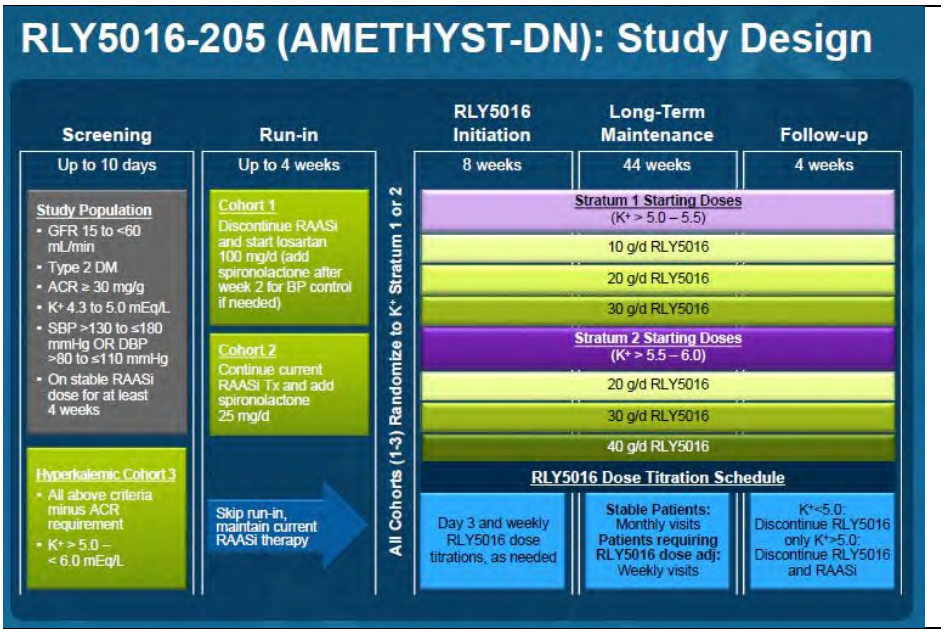
Relypsa kicked off the Patiromer development program with two Phase I studies in healthy volunteers designed to assess the safety and tolerability of different dosing regimens of the polymer. The drug was well-tolerated and led to a significant increase in fecal potassium excretion and a concomitant decrease in urinary potassium excretion. Next, Relypsa embarked on a phase 2a proof of concept study in hemodialysis (kidney failure) subjects. This trial established that patiromer was pharmacologically active in reducing serum potassium levels and was well-tolerated. The next two Phase II trials were designed to determine the safety and efficacy of patiromer in preventing hyperkalemia in heart failure patients both with and without CKD. To demonstrate that patiromer can prevent the development of hyperkalemia even when co-administered with a RAAS inhibitor, patients with normal serum potassium were enrolled. In these studies, not only did patiromer produce a statistically significant reduction in the incidence of hyperkalemia, it also allowed for a

significantly greater percentage of HF subjects to increase the RAASi dose, compared to placebo (91% vs. 74%, respectively, p=0.019). In one of the Phase II studies, the incidence of adverse events was higher in patiromer-treated subjects vs. placebo, with the majority of AEs being GI related. The adverse events, however, were mild or moderate, and the four serious adverse events (two in each arm) were evenly divided and likely not related to the study drug. Collectively, these studies suggested that patiromer exhibits adequate safety and it promises to reliably control serum potassium levels even in CKD patients taking RAAS inhibitors.

A Positive Phase IIb Set The Stage For The Pivotal Trial

A Phase IIb trial was conceived to evaluate the optimal starting dose, efficacy, and safety of patiromer in treating hyperkalemia. It enrolled 306 patients with diabetic nephropathy and chronic kidney disease (CKD) who were already on RAAS inhibitors. The trial design included an initial 4-week run-in period during which patients were treated with ARBs and aldosterone antagonist (AA) as required for diabetic CKD patients with uncontrolled hypertension. At the end of first four weeks, the level of hyperkalemia developed by these patients was quantified. At the beginning of the subsequent 8-week open label treatment phase of the study, patients were divided into two strata based on their baseline serum potassium level and given one of three different starting doses of patiromer depending on the stratum. Stratum 1 patients had potassium levels above 5.0 to 5.5 mEq/L, while serum potassium levels for stratum 2 patients were above 5.5 to less than 6.0 mEq/L. Unlike in clinical practice, where an increase in serum potassium levels triggers discontinuation of RAASi treatment, the patients in this Phase IIb trial were maintained on RAASi while co-administered patiromer. All subjects were titrated to an individual patiromer dose based on their serum potassium levels. The primary efficacy endpoint was the mean change from baseline in serum potassium levels, measured at the end of four weeks of treatment.

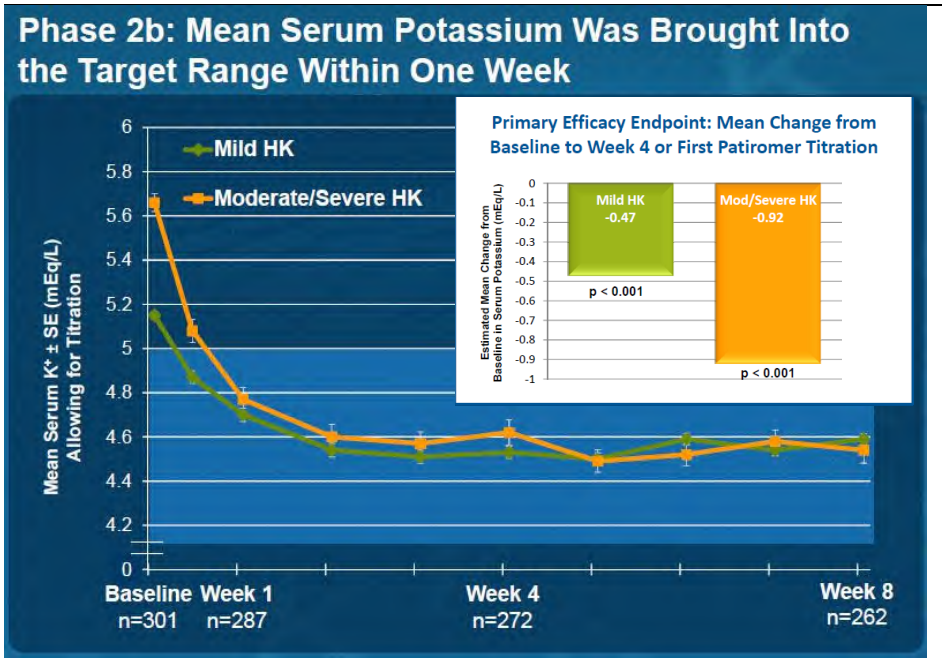
Patiromer Phase IIb Trial Design



Source: Relypsa

Results for the treatment phase of the trial showed that patiromer led to a statistically significant decrease in mean serum potassium level in all patients. Across the subjects with a baseline serum potassium above 5.0 to 5.5 mEq/L (stratum 1), the change from baseline was -0.47 mEq/L (95% CI -0.55, -0.44; p< 0.001). For subjects with baseline serum potassium 5.5 to less than 6.0 mEq/L (stratum 2), the change from baseline in serum potassium was -0.92 mEq/L (95% CI -1.07, -0.78; p<0.001). Statistically significant decreases from baseline were observed as early as two days after initiating treatment with patiromer and an optimal serum potassium level was maintained throughout the 8 weeks of study.

Statistically Significant Reduction In Mean Serum Potassium At 4 weeks



Source: Relypsa

All patients were permitted to advance into a 44-week long-term maintenance phase of the trial. Subjects continued to take patiromer, and by the end of the study they had been on the drug for up to one year. Throughout this second period, the mean serum potassium in both Strata remained in the target range (3.8 to 5.0 mEq/L). At week 52, the portion of patients with a serum potassium in the target range was 85.5% in Stratum 1 (95% CI 78.7%, 90.8%) and 89.8% in Stratum 2 (95% CI 77.8%, 9 6.6%).

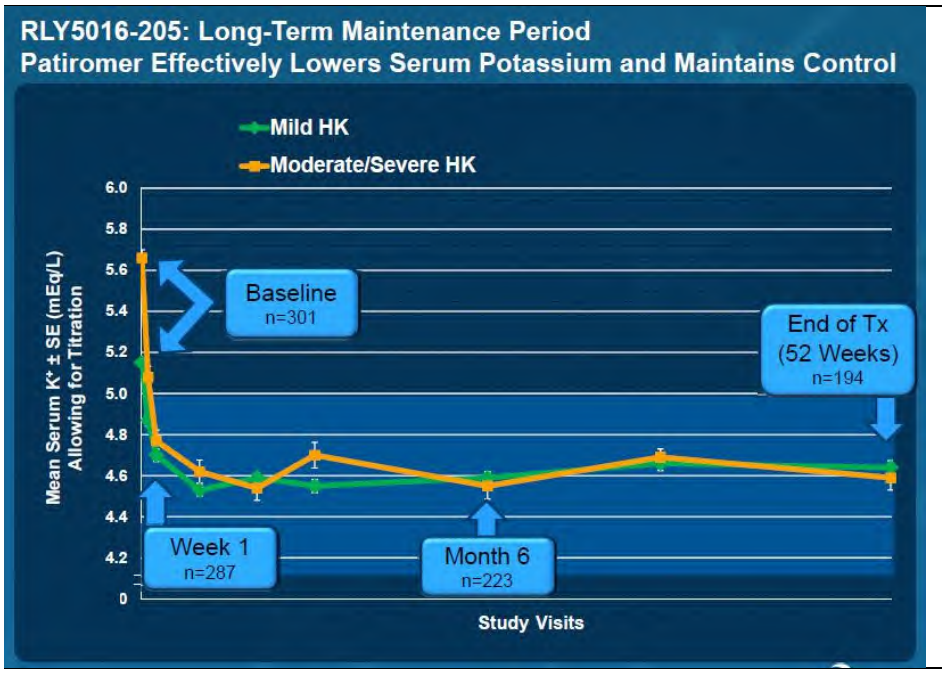
Built into the Phase IIb trial was a dose finding interim data analysis that was designed to identify the starting dose for the pivotal Phase III trial. The analysis was triggered by a pre-specified sample size of approximately 120 subjects who had completed the initial 8 weeks of treatment. Based on the stratum they fell under, subjects were given one of three different starting doses of patiromer which were titrated individually with most titrations taking place in the first two weeks. Each dose group in each stratum achieved statistically significant and clinically meaningful reductions in serum potassium levels. However, there was no concrete starting dose-dependent effect for most parameters. Lacking a clear starting dose-dependent response to patiromer, the lowest effective dose tested was designated as the appropriate starting dose for the Phase 3 trial. The starting doses used for the Phase 3 program were: 8.4 grams/day for

patients having a serum potassium level at baseline in the range of 5.1 to 5.5 mEq/L and 16.8 grams/day for patients having a serum potassium level at baseline above 5.5 mEq/L.

This dose finding study provided additional insight into the titration requirements of patiromer in these two patient populations. This is informative as we expect titration to be commonly used by doctors when dealing with a heterogeneous patient pool like that present in CKD. The study showed that in subjects with mild hyperkalemia (5.0 to 5.5 mEq/L) who were dosed starting at 8.4 g per day (4.2 g BID), 50% did not require any titration to get to the potassium target concentration, while 25% required one titration step (went to 16.8 g/day) and the rest 25% of subjects required more than one titration step. For subjects with mild hyperkalemia (5.0 to 6.0 mEq/L), who were initiated on 16.8 g per day (8.4 g BID), 30% did not require any titration to get to the target potassium concentration, 30% required only one titration (increased to 25.2 g/day), and the final 40% of subjects required more than one titration. Overall, a small number of subjects required the top doses of 42.0 g/day and 50.4 g/day.

In the Phase IIb trial, patiromer was well tolerated when dosed twice daily up to one year. Mild to moderate gastrointestinal symptoms were amongst the most common adverse events. Approximately 5-10% of patients experienced constipation and diarrhea. Chronic dosing did not increase the incidence of gastrointestinal adverse events. Only mild to moderate hypomagnesaemia was reported in less than 10% of patients. Other common adverse events reported in less than 10% of patients included hypertension and worsening of the underlying chronic renal failure. Serious adverse events were reported in 15% of patients, but were not deemed related to patiromer. Overall, the clinically meaningful results and the favorable safety and tolerability profile of patiromer support its twice daily dosing as an effective treatment for hyperkalemia.

Sustained Reduction In Serum Potassium Over 52 Weeks



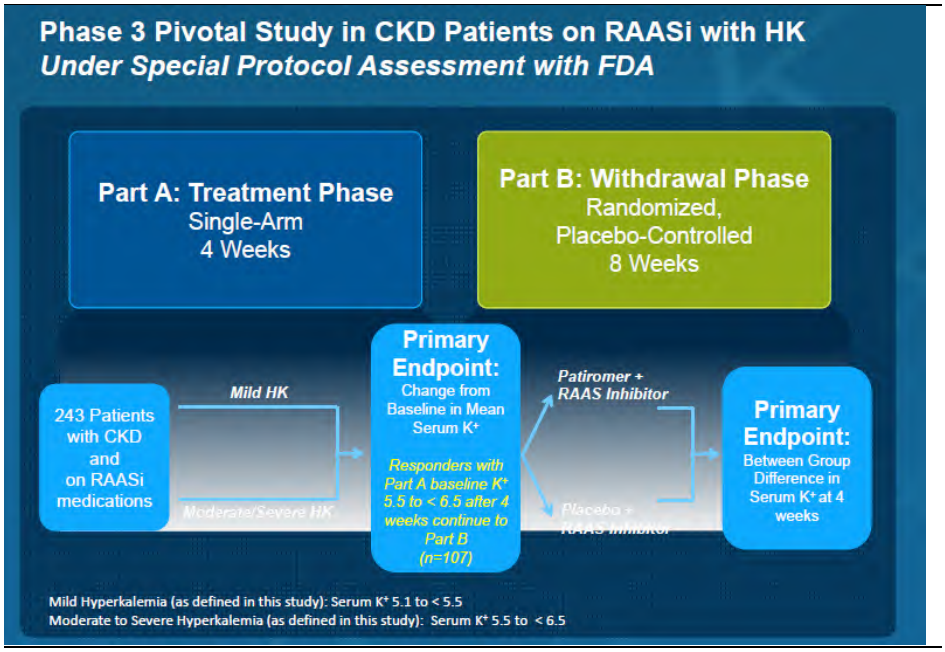
Source: Relypsa

Phase III Safety And Efficacy Data Seal The Deal

Under a special protocol assessment, Relypsa conducted a two-part Phase III trial, with each part serving as separate pivotal trial for regulatory purposes. Part A was designed to demonstrate the safety and efficacy of patiromer in the treatment of hyperkalemia. Part B was a withdrawal study designed to demonstrate that chronic administration of patiromer reduces the recurrence of hyperkalemia. Based on the starting doses obtained in the Phase IIb trial, subjects in Part A were placed in dosing Group 1 (starting dose 8.4 g/day) if their initial serum potassium was equal to 5.1 to less than 5.5 mEq/L, or in doing Group 2 (starting dose 16.8 g/day), if their serum potassium was found to range from 5.5 to less than 6.5 mEq/L.

Part A, in which all participants received patiromer, was a single-blind, single-arm trial enrolling 243 subjects who were hyperkalemic, had CKD, and were on RAAS inhibitors. The primary endpoint for Part A was the change from baseline to week 4 in mean serum potassium levels. A target reduction in serum potassium level of at least 0.7 mEq/L ($p< 0.05$) was agreed to with the FDA. The secondary endpoint was the proportion of subjects with a serum potassium level in the target range of 3.8 to < 5.1 mEq/L at week 4.

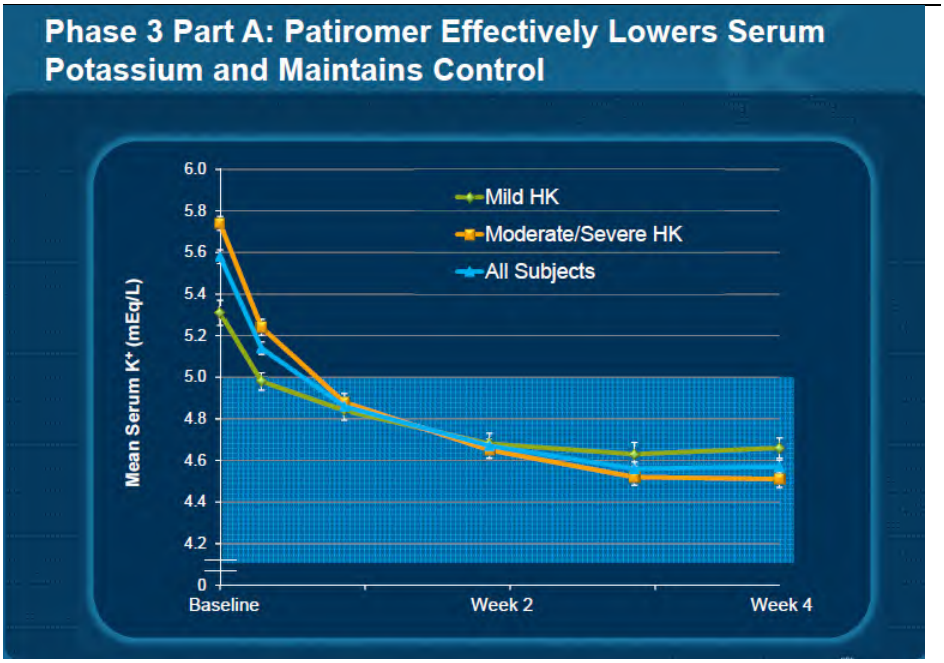
Phase III Pivotal Study Design



Source: Relypsa

The primary and the secondary efficacy endpoints were successfully reached. When all subjects were taken into account, the change in serum potassium from baseline to week 4 was a reduction of 1.01 mEq/L (95% confidence interval -1.07, -0.95), $p<0.001$. A statistically significant reduction in serum potassium was achieved within each dosing Group. In Group 1, the reduction in serum potassium was 0.65 mEq/L (95% confidence interval of -0.74, -0.55) and in Group 2 it was 1.23 mEq/L (95% confidence interval of -1.31, -1.61). At week 4 of this Part A trial, 76% of subjects had their serum potassium in the target range of 3.8 to <5.1 mEq/L (95% CI 70, 81).

Statistically Significant Reduction In Mean Serum Potassium At 4 Weeks

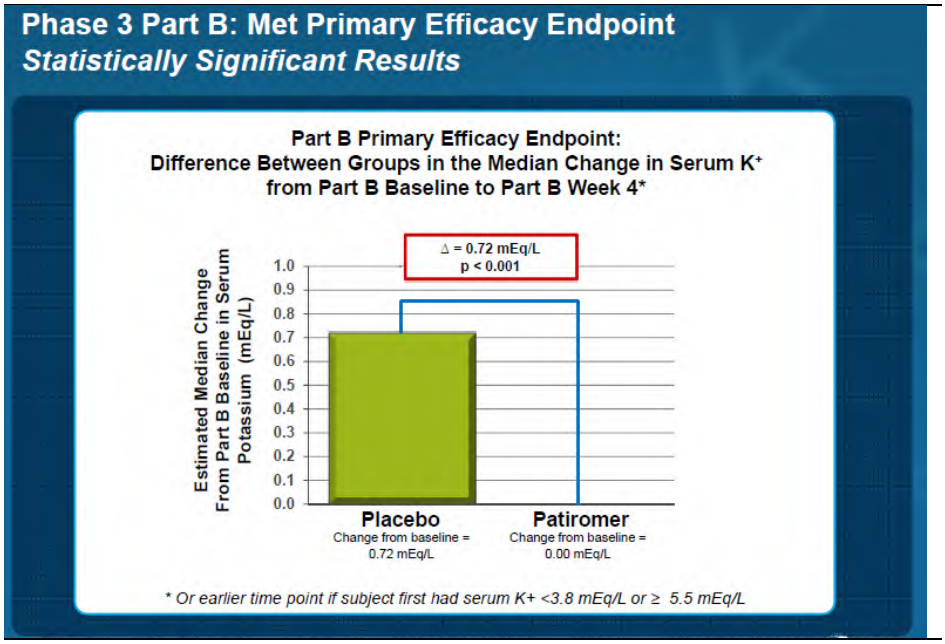


Source: Relypsa

Part B of the study was a placebo controlled randomized withdrawal trial designed to provide additional evidence of the efficacy of patiromer in treating hyperkalemia and to assess the impact of chronic dosing. The use of a placebo control arm in the Part A of the study was deemed unethical and unsafe as all subjects were hyperkalemic at study entry. A placebo arm was used in Part B to provide a comparator for safety data evaluation and continued control of serum potassium level. This was possible since the subjects' serum potassium levels were controlled upon randomization into Part B. Out of the 243 subjects from Part A, 107 patients whose baseline serum potassium level was greater than or equal to 5.5 mEq/L at enrollment and whose serum potassium level was controlled at week 4 were eligible to advance to Part B. The primary endpoint for Part B was the difference between the patiromer and the placebo groups in the change in serum potassium levels from the start of Part B to week 4, or earlier, if changes to patiromer or RAAS inhibitor therapy were required to control for rising serum potassium levels. If subjects developed recurrent hyperkalemia (serum potassium ≥ 5.1 mEq/L) during the second four weeks of part B, then those randomized to patiromer had their dose of patiromer increased, while those randomized to placebo decreased the RAAS inhibitor dose. If this strategy failed and the serum potassium level continued to increase, then the RAAS inhibitor therapy was withdrawn, much like it's done in current clinical practice.

Part B of the trial met its primary endpoint, with the difference between the placebo and the patiromer groups in the median change from Part B baseline in serum potassium equal to 0.72 mEq/L (95% CI 0.46, 0.97), $p < 0.001$. These results emphasize the importance of chronic administration of patiromer in managing kyperkalemia. Further support for chronic dosing comes from physician clinical experience with the drug. According to a consultant who was a PI on this trial, patients who were not compliant had a "rebound" of serum potassium.

Patients Develop Hyperkalemia Once Patiromer Is Removed



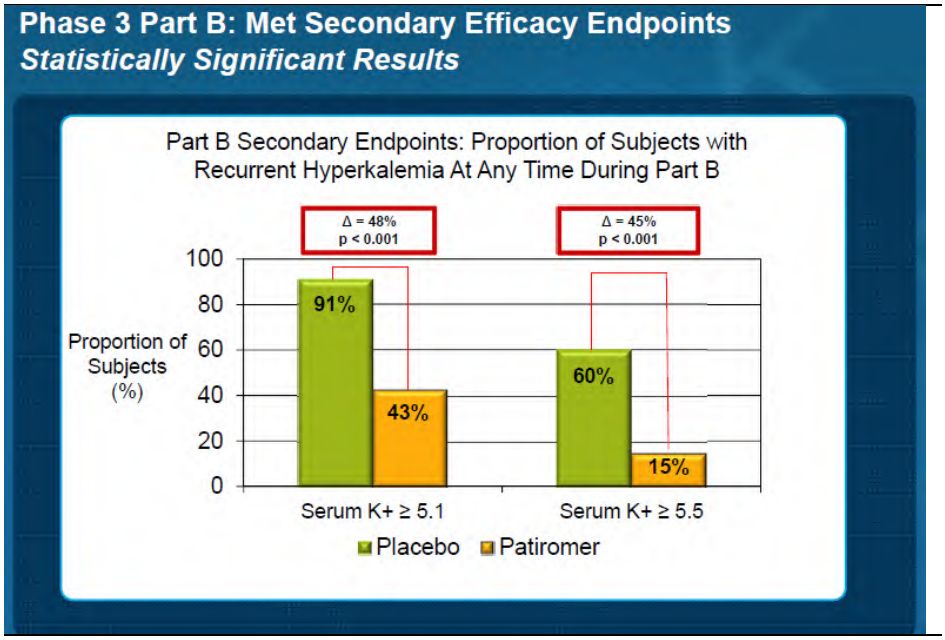
Source: Relypsa

Similarly impressive results pointing to patiromer's effectiveness were obtained when analyzing the proportion of subjects with recurrent hyperkalemia between patiromer and placebo group, a secondary endpoint. For this analysis, the subjects were divided into two groups, those who developed recurrent hyperkalemia with serum potassium levels between 5.1 and 5.5 mEq/L, and those with levels above 5.5 mEq/L. A significantly higher percentage of placebo patients (91%) developed recurrent hyperkalemia (K+ ≥ 5.1 mEq/L) at any time during Part B than patiromer subjects (43%). This 48% difference between groups was statistically significant (95% CI 33, 63, $p < 0.001$). The same trend was present when looking at recurrent hyperkalemia with higher serum potassium concentration ≥ 5.5 mEq/L. More placebo subjects (60%) than patiromer subjects (15%) developed recurrent hyperkalemia at any time during Part B, a difference that was statistically significant, $p < 0.001$ (95% CI 29, 61). Whether this level of control over serum potassium levels translates into more optimal dosing of RAAS inhibitors or a lower incidence of cardiovascular events remains to be determined. Even though the study was not powered for outcomes data, adjustment of RAASi dosing was an exploratory endpoint of Part B of the trial. Data related to this endpoint may be released to the public in 2014.

In terms of adverse events, since patiromer is not absorbed by the body, it would be unlikely to cause off target adverse events outside of potential gastrointestinal problems. This supposition was confirmed by safety data from Part A and B of the pivotal trial. While there were no reports of severe gastrointestinal events, in Part A, 19% of subjects did report mild to moderate gastrointestinal symptoms. In Part B, twice as many patiromer subjects (13%) as placebo (6%) reported gastrointestinal adverse events. Constipation, diarrhea and nausea were each reported in 4% of patiromer subjects, with no placebo subjects reporting these symptoms. One PI on the trial reported that he was satisfied with the tolerability levels he witnessed. He also confirmed that the gastrointestinal issues with patiromer, while present, were considerably milder than those experienced with alternative hyperkalemia therapies. Importantly, there were no severe cases of hypomagnesemia reported. Since

patiromer is able to also bind magnesium, not only potassium, there is some concern this property might lead to negative side effects. In this study, however, mild to moderate hypomagnesemia was balanced between the placebo and the drug-treated group with 2% of subjects in each group developing some level of hypomagnesemia. Other AEs were headaches (8% placebo, 4% patiromer), increase in hepatic enzymes (4% placebo, 2% patiromer), chronic renal failure (2% placebo, 2% patiromer). All serious adverse events were assessed as unrelated to patiromer by study investigators and by Relypsa. The size of the safety database that patiromer has gathered through its clinical trials (approximately 726 subjects) has been discussed with the FDA and management indicated that it will be sufficient for approval.

A Significantly Higher Percentage Of Placebo Patients Developed Hyperkalemia



Source: Relypsa

Data Should Position Patiromer For FDA Approval

Relypsa expects to file an NDA with the FDA in the second half of 2014. The rate limiting factor is the completion of one last Phase I trial. This 20-patient trial is designed to investigate the time of onset of action of patiromer, and is expected to read out in the first half of 2014. The FDA requested this trial to establish how quickly patiromer can impact hyperkalemia and whether the drug might be useful in acute hyperkalemic patients that require more urgent reductions of serum potassium. Currently, patients with ECG changes that need to reduce their potassium levels within minutes are put on dialysis and are administered insulin-glucose, which push potassium ions into cells. This Phase I trial is limited to only 20 patients, and will be conducted in the hospital in-patient setting with frequent blood monitoring. Given the success of the pivotal Phase III trial and the dearth of chronic treatments for hyperkalemia, the results of this trial should have little bearing on the approvability of patiromer for chronic treatment. The FDA indicated to Relypsa that patiromer may be approved solely based on its ability to reduce serum potassium levels, no outcomes data was requested.

Manufacturing Considerations

Compared to small molecule drugs, polymeric drugs require the production of larger volumes for commercialization. Patiromer is packaged as a powder formulation in 10 gram packets. The product is expected to have a ~3 year shelf-life at 2-8C, and a stability of 3-6 months at room temperature. Therefore, patiromer ought to be fairly convenient to store and transport.

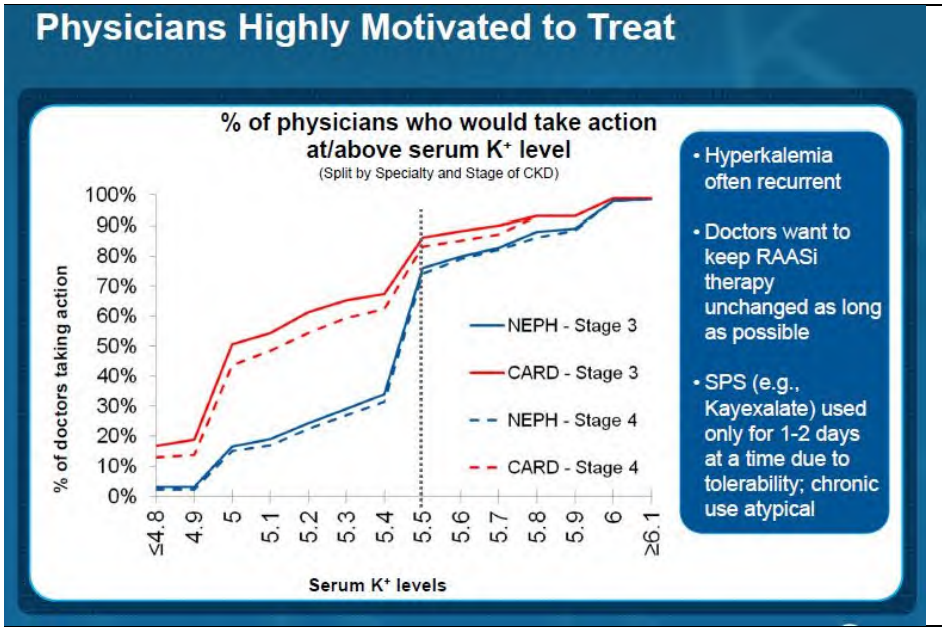
Relypsa relies on third-party manufacturers to produce bulk drug substance and drug product. At peak sales, Relypsa plans for 3-4 suppliers of drug substance. For the purpose of the initial NDA filing, Relypsa has named Saltigo, an experienced polymeric drug manufacturer as the supplier of the active pharmaceutical ingredient (API). Saltigo produced the API used by Relypsa in some of its clinical trials. Relypsa has not provided details regarding the quantities of patiromer needed for the launch. However it believes that its suppliers are well positioned to meet launch requirements. Polymeric drugs such as Renagel/Renvela and Welchol are manufactured at multi-hundred metric ton levels per year. Therefore, following the successful adoption, Relypsa plans to apply for approval of at least one other drug substance supplier. In the first year of commercialization, the cost of producing patiromer is likely to be around $6 for a packet containing 10 grams of drug. Assuming that on average, a patient undergoing chronic treatment for moderate hyperkalemia (between 5.1 and 5.5 mEq/L) takes one 10g pack each day and the yearly price per patient is $6400, then we model GMs to be 65% at launch. Overtime, increasing scale and technology improvements are expected to reduce the cost of starting materials and drive down COGS to perhaps $1.5 per 10g pack within 5 years of launch. Combined with price increase, this would push Relypsa's GMs up to 83% by 2020.

Patiromer's Commercial Outlook: A Large Market Waiting To Be Created

Relypsa plans to commercialize Patiromer on its own in the U.S. market. The company believes a targeted sales force calling on specialists (nephrologists and cardiologists) can cover the majority of >3 million CKD and HF patients that present with hyperkalemia. Of the roughly 7,000 U.S. nephrologists who are treating CKD patients, focus will be placed on those most likely to prescribe patiromer, as identified through market analysis. Relypsa also intends to target around 1,000 major U.S. centers that treat heart failure patients. Based on the company's estimates, a 100-person specialty sales force should be sufficient to cover these physician audiences. The sales force will be complemented by a marketing team and an account management team covering managed care customers.

Our checks with nephrologists suggest much unmet need in the treatment of hyperkalemia, and indicate that patiromer could represent a very meaningful advance. As discussed above, existing treatment options leave much to be desired, particularly in terms of the chronic treatment of hyperkalemia. Nephrologists report strong discomfort and even dislike toward Kayexalate, and recognize that a drug like patiromer could offer unique and superior attributes. One consultant maintains that the threat of malpractice suits has doctors "paranoid" about serum potassium levels. He believes that any treatment directed at alleviating this anxiety will be well received. Patiromer is also recognized as an agent that could improve the overall care of CKD patients by permitting nephrologists to continue dosing RAASi through elevations in serum potassium.

Nephrologists And Cardiologists Are Highly Motivated To Treat Hyperkalemia



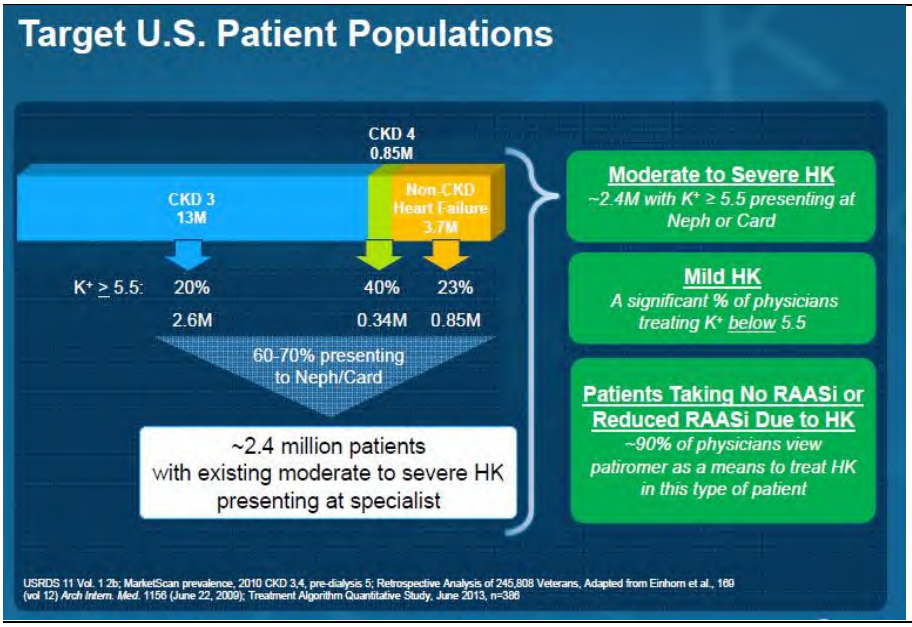
Source: Relypsa

On the other hand, there are reasons to expect that patiromer might witness a somewhat gradual adoption curve. While awareness of hyperkalemia is high, consultants indicate that some physicians will need to be educated about patiromer's benefits, including its potential to maintain RAASi dosing. In the absence of data on outcomes, one consultant believes that Relypsa will face some challenges in making the treatment of hyperkalemia a high priority, and moving physicians away from the current treatment paradigm of responding to hyperkalemia by reducing RAASi dosing. In addition, patiromer's formulation (a reconstituted powder, not a small white pill) is not ideal in terms of convenience. Furthermore, CKD patients are not known to be particularly compliant with any medication, so Relypsa may have some educational work to do on this front, too. Many novel CKD drugs (Renagel, Sensipar) have started off slowly, but grown into large franchises.

Modest Market Share Could Translate Into Big Sales Gains

Chronic kidney disease represents a large and rapidly growing patient population driven by rising rates of obesity and diabetes. In the U.S., of the estimated 26 million CKD patients, roughly 13 million are categorized as stage 3 patients, while 0.85 million are diagnosed as stage 4. Studies show that approximately 20% of stage 3 CKD patients and 40% of stage 4 CKD patients have serum potassium levels above 5.5 mEq/L. These patients represent the core target pool for patiromer. The size of the hyperkalemia market further includes non-CKD, heart failure patients, 0.85 million of which are believed to be hyperkalemic. Based on its market research, Relypsa assumes that the number of U.S. patients presenting to specialists with moderate to severe hyperkalemia is approximately 2.4 million today. Given that the prevalence of CKD is growing at approximately 4% per year, we would expect this figure to increase over time.

Patients With Modest-To-Severe Hyperkalemia Have A 10-Fold Increase In Mortality Rate



Source: Relypsa

We assume that patiromer will be launched in the second half of 2015. We project it will capture 0.6% of its U.S. opportunity in 2016, growing to 5.0% by 2022. In light of the known compliance issues encountered in the target population, we built into our projections a compliance rate of 50%. We estimate pricing for patiromer at $6,400 per year, inclusive of a ~15% gross to net discount. U.S. sales are expected to reach $400 million by 2020.

Patiromer Hyperkalemia Revenue Model

U.S. Patiromer Revenue Model	2015	2016	2017	2018	2019	2020	2021	2022
# patients with existing modetrate to severe HK (000s)	2,448	2,473	2,497	2,522	2,548	2,573	2,599	2,625
population growth	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
% of patients prescribed patiromer (market penetration)	*0.1%*	*0.6%*	*1.5%*	*2.2%*	*3.1%*	*3.9%*	*4.5%*	*5.0%*
# patients prescribed Patiromer (000)	1.6	15.3	36.5	55.6	79.4	99.9	117.8	131.1
% compliance rate with daily patiromer treatment	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Effective # of patients on full daily dose of patiromer	0.8	7.7	18.2	27.8	39.7	49.9	58.9	65.6
patiromer annual price per	$6,400	$6,528	$6,854	$7,197	$7,557	$8,010	$8,491	$9,000
Patiromer U.S. sales ($MM)	**$5**	**$50**	**$125**	**$200**	**$300**	**$400**	**$500**	**$590**

Source: Cowen and Company

We note that according to Symphony Health, today's market for treating hyperkalemia is quite small. Each month there are approximately 20,000 prescriptions written for sodium polystyrene sulfonate (sold as Kayexalate and generic versions). At branded pricing this would represent an approximate $100MM U.S. market. However, SPS is very poorly tolerated, and therefore commonly used for just a few days or weeks at a time. We expect patiromer to drive a major increase in the number of scrips written for hyperkalemia based upon its potential for chronic dosing.

Not Much In The Way Of Competition

Based upon our physician checks, we are convinced that there is much unmet need in the treatment of hyperkalemia, and that patiromer should have first mover advantage in addressing this opportunity. As this market is currently wide open, and our assumptions for patiromer's market share are fairly modest, we would expect any subsequent therapeutics to expand the market rather than compete with patiromer for share. Regardless, we are only aware of one other drug in later stages of development for treating hyperkalemia. ZS Pharma's ZS-9 is an inorganic crystal that also binds potassium in the GI tract. A Phase 2 proof-of-concept study investigated ZS-9 for the acute treatment of hyperkalemia, and produced data showing that ZS-9 reduced mean serum potassium levels by 0.92 mEq/L at 38 hours, four hours after the last dose ($p < 0.0001$). In addition, ZS Pharma is expected to announce data from a Phase III pivotal trial that enrolled 753 hyperkalemic patients and looked at once-daily dosing for 12 days in the near term. While data on ZS-9's ability to be used chronically are lacking, ZS Pharma appears to be slowly heading in that direction with plans to kick off another Phase III in early 2014 that looks at 28 days of administration. A key risk to this program is the potential for safety issues with a heavy-metal based potassium binder to accumulate over time. ZS Pharma has stated that it intends to file an NDA before the end of 2014, though it would appear that the company will not have much experience with chronic dosing by that time.

Relypsa's R&D Pipeline

Therapeutic Class/Product	Indication	P-C	I	II	III	FILING	MKT	Comments
Metabolic disease								
Patiromer	Hyperkalemia in CKD				▪			Positive Phase III, NDA filing expected in Q3:14
RLY6002	Type 2 diabetes	▪						Polymer designed to improve glycemic control
Total Drugs In Development		1	0	0	1	0	0	
Redwood City, CA	**Investor Relations Contact: Kristine Ball (650) 421-9503**							

Source: Cowen and Company

Relypsa Quarterly P&L Model ($MM)

	Q1:13A	Q2:13A	Q3:13A	Q4:13E	2013E	Q1:14E	Q2:14E	Q3:14E	Q4:14E	2014E
Relypsa Revenue	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total Revenue	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**
Y/Y growth										
COGS	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GMs										
R&D	16.3	19.6	12.2	16.0	64.1	11.5	11.0	11.5	12.0	46.0
SG&A	2.0	3.5	2.7	3.0	11.2	3.5	4.0	4.5	7.0	19.0
Total Expenses	**18.3**	**23.1**	**14.8**	**19.0**	**75.3**	**15.0**	**15.0**	**16.0**	**19.0**	**65.0**
Operating Income/Loss	**(18.3)**	**(23.1)**	**(14.8)**	**(19.0)**	**(75.3)**	**(15.0)**	**(15.0)**	**(16.0)**	**(19.0)**	**(65.0)**
Non-Operating Income	(2.5)	(2.5)	(10.8)	(0.3)	(16.1)	(0.4)	(0.4)	(0.4)	(0.4)	(1.6)
Pre-tax Income/Loss	**(20.8)**	**(25.6)**	**(25.6)**	**(19.3)**	**(91.4)**	**(15.4)**	**(15.4)**	**(16.4)**	**(19.4)**	**(66.6)**
Tax rate (%)	0%	0%	0%	0%	0%	0%	0%	8%	0%	0%
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss)	**(20.8)**	**(25.6)**	**(25.6)**	**(19.3)**	**(91.4)**	**(15.4)**	**(15.4)**	**(16.4)**	**(19.4)**	**(66.6)**
GAAP EPS	**($3.90)**	**($4.79)**	**($1.30)**	**($0.69)**	**($3.15)**	**($0.49)**	**($0.49)**	**($0.51)**	**($0.61)**	**($2.10)**
Diluted Shares	5.3	5.3	19.7	27.7	29.0	31.5	31.7	31.9	32.0	31.8

Source: Cowen and Company

Relypsa Annual P&L Model ($MM)

	2012A	2013E	2014E	2015E	2016E	2017E	2018E
Relypsa Revenue	0.0	0.0	0.0	5.0	50.0	125.0	200.0
Total Revenue	**0.0**	**0.0**	**0.0**	**5.0**	**50.0**	**125.0**	**200.0**
Y/Y growth		0%	0%	0%	900%	150%	60%
COGS	0.0	0.0	0.0	1.8	11.9	23.5	34.0
R&D	36.1	64.1	46.0	56.0	60.0	64.0	67.0
SG&A	7.3	11.2	19.0	51.0	84.5	90.0	95.0
Total Expenses	**43.3**	**75.3**	**65.0**	**108.8**	**156.4**	**177.5**	**196.0**
Operating Income/Loss	(43.3)	(75.3)	(65.0)	(103.8)	(106.4)	(52.5)	4.0
Non-Operating Income	(19.1)	(16.1)	(1.6)	(1.6)	(2.0)	(2.0)	(2.0)
Pre-tax Income/Loss	(62.4)	(91.4)	(66.6)	(105.4)	(108.4)	(54.5)	2.0
Tax rate (%)	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Provision for income taxes	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net Income (Loss)	(62.4)	(91.4)	(66.6)	(105.4)	(108.4)	(54.5)	2.0
GAAP EPS	**($11.94)**	**($3.15)**	**($2.10)**	**($2.85)**	**($2.85)**	**($1.40)**	**$0.05**
Diluted Shares	5.2	29.0	31.8	37.0	38.0	39.0	41.0

Source: Cowen and Company

Valuation Methodology And Risks

Valuation Methodology

Biotechnology:

In calculating our 12-month target price, we employ one or more valuation methodologies, which include a discounted earnings analysis, discounted cash flow analysis, net present value analysis and/or a comparable company analysis. These analyses may or may not require the use of objective measures such as price-to-earnings or price-to-sales multiples as well as subjective measures such as discount rates.

We make investment recommendations on early stage (pre-commercial) biotechnology companies based upon an assessment of their technology, the probability of pipeline success, and the potential market opportunity in the event of success. However, because these companies lack traditional financial metrics, we do not believe there are any good methodologies for assigning a specific target price to such stocks.

Investment Risks

Biotechnology:

There are multiple risks that are inherent with an investment in the biotechnology sector. Beyond systemic risk, there is also clinical, regulatory, and commercial risk. Additionally, biotechnology companies require significant amounts of capital in order to develop their clinical programs. The capital-raising environment is always changing and there is risk that necessary capital to complete development may not be readily available.

Risks To The Price Target

Addendum

Stocks Mentioned In Important Disclosures

Ticker	Company Name
RLYP	Relypsa, Inc

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Outperform (1): The stock is expected to achieve a total positive return of at least 15% over the next 12 months

Market Perform (2): The stock is expected to have a total return that falls between the parameters of an Outperform and Underperform over the next 12 months

Underperform (3): Stock is expected to achieve a total negative return of at least 10% over the next 12 months

Assumption: The expected total return calculation includes anticipated dividend yield

Cowen and Company Rating System until May 25, 2013

Outperform (1): Stock expected to outperform the S&P 500

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Underperform (3): Stock expected to underperform the S&P 500

Assumptions: Time horizon is 12 months; S&P 500 is flat over forecast period

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Hold – The fundamentals/valuations of the subject company are neither improving nor deteriorating and the investment return is expected to be in line with the general market return

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Rating	Count	Ratings Distribution	Count	IB Services/Past 12 Months
Buy (a)	394	58.72%	54	13.71%
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Sell (c)	22	3.28%	1	4.55%

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Legend for Price Chart:

I = Initation | 1 = Outperform | 2 = Market Perform | 3 = Underperform | UR = Price Target Under Review | T = Terminated Coverage | $xx = Price Target | NA = Not Available

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