Ardelyx Inc. (ARDX)

Initiating Coverage with an OUTPERFORM and $31 PT - Trust the Gut, Systemic Efficacy without Systemic Toxicity

- **ARDX is developing non-absorbed small-molecule drugs that act locally in the GI tract for mineral imbalance, GI and metabolic disorders.** These drugs have minimal systemic exposure, likely resulting in a benign safety profile and enhancing efficacy.
- **Tenapanor, a potent NHE3 inhibitor currently in Phase II studies, selectively inhibits sodium and phosphorus uptake from the GI tract.** Excess sodium and phosphorus exacerbate kidney disease, and current treatments are only marginally effective or are poorly tolerated. The diversion of sodium into the stool also draws water into the bowel, which can help treat constipation.
- **The lead indication for tenapanor is treating hyperphosphatemia in end-stage renal disease (ESRD), which has a relatively straightforward path to approval (lowering of phosphate levels).** In Phase I trials, tenapanor diverted dietary phosphorus into stools at the same rate as the approved non-absorbed phosphate binder sevelamer (Renagel), despite the latter's being administered at a dose level 500 times that of tenapanor.
- **Tenapanor is also in a Phase IIb trial in patients with irritable bowel syndrome with constipation (IBS-C), with data expected in Q4:14.** In clinical trials, tenapanor has produced improvements in multiple constipation-related measures, while not increasing the incidence of diarrhea, a key limitation of currently marketed products.
- **Tenapanor has been partnered with AstraZeneca, in a deal that reduces financial risk and should provide a consistent stream of non-dilutive funds to ARDX.** Given the low (or no) cash burn going forward, additional financings are likely to be limited and opportunistic.
- **With large market opportunities and partners financing the development for their lead programs, we view ARDX shares at current levels as having an attractive risk/reward in the small-cap biopharma space.**
- **Initiating coverage with an OUTPERFORM and $31 price target.** Our price target of $31 is derived by applying a 6 multiple to ARDX's share of 2022 tenapanor sales in the US, added to a 15 multiple of the royalty ARDX is expected to receive in 2022 for ex-US sales of tenapanor.

FYE Dec	2013A	2014E			2015E		
REV	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	8.6A			15.3E		NA
Q2 Jun	--	11.2E		NA	17.3E		NA
Q3 Sep	--	11.5E		NA	23.8E		NA
Q4 Dec	--	11.8E		NA	25.8E		NA
Year*	**28.9A**	**43.0E**		**NA**	**82.2E**		**NA**
Change	--	49%			91%		
	2013A	2014E			2015E		
EPS	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	--	($2.44)A		--	$0.21E		NA
Q2 Jun	--	$3.86E		NA	$0.14E		NA
Q3 Sep	--	$0.11E		NA	$0.25E		NA
Q4 Dec	--	$0.10E		NA	$0.21E		NA
Year*	**($5.82)A**	**$1.06E**		**NA**	**$0.81E**		**NA**
P/E	--	--			--		
Change	--	118%			-23%		

Consensus estimates are from Thomson First Call. ** Numbers may not add up due to rounding.*

July 14, 2014

Price
$16.60

Rating
OUTPERFORM

12-Month Price Target
$31

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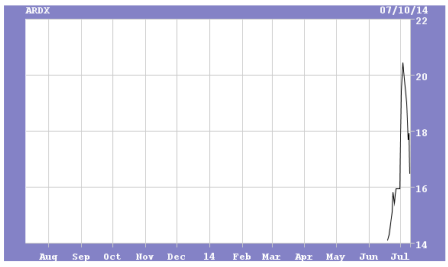
Company Information	
Shares Outst (M)	18.5
Market Cap (M)	$307.6
52-Wk Range	$14.05 - $21.60
Book Value/sh	$-3.86
Cash/sh	$5.30
Enterprise Value (M)	$209.4
LT Debt/Cap %	0.0
Cash Burn (M)	$0.0

Company Description

Ardelyx Inc. is developing small-molecule drugs for the treatment of cardio-renal, GI and metabolic diseases. Its lead product candidate, tenapanor, is in three ongoing Phase II trials for ESRD, CKD and IBS-C.



Source: Thomson Reuters

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Investment Thesis

Ardelyx (NASDAQ:ARDX) is a clinical-stage company focused on developing small-molecule drugs that act locally within the gastrointestinal (GI) tract for the treatment of cardio-renal, GI and metabolic disorders. Its lead drug candidate, tenapanor, is an oral, non-absorbed inhibitor of NHE3, a sodium transporter expressed in the GI tract. Tenapanor is being developed to treat hyperphosphatemia in end-stage renal disease (ESRD) patients and late-stage chronic kidney disease (CKD), as well as constipation-predominant irritable bowel syndrome (IBS-C). Clinical studies have demonstrated tenapanor's ability to reduce the absorption of dietary sodium and phosphorus and to increase the frequency of bowel movements, key factors in reducing the progression of kidney disease and alleviating the symptoms of IBS-C. AstraZeneca has licensed worldwide rights to tenapanor, while Ardelyx is eligible for milestones and royalties and retains US co-promotion rights.

Valuation

We arrive at our $31 price target by applying a 6 multiple to ARDX's share of 2022 tenapanor sales in the US, added to a 15 multiple of the royalty ARDX is expected to receive in 2022 for ex-US sales of tenapanor.

Risks

Risks to the achievement of our price target include clinical or regulatory failure for tenapanor and failure to achieve sales or earnings estimates.

Key Points

- ARDX focuses on developing small-molecule drugs that act locally in the GI tract and are not absorbed into the bloodstream. The minimal systemic exposure results in a favorable safety profile, as evidenced by the lack of any drug-related SAEs in the over 750 patients who have been administered tenapanor.
- Tenapanor, in its clinical studies to date, decreases absorption of dietary sodium, sparing the cardiovascular and renal system from excess sodium and fluid accumulation, key factors in the progression of kidney disease.
- Tenapanor also reduces the absorption of dietary phosphorus, an attribute that can help treat hyperphosphatemia, a condition that develops in a majority of patients with kidney failure and which is associated with increased cardiovascular complications. Phosphorus is not readily removed by dialysis, and currently-approved phosphate binders (the only approved treatments for hyperphosphatemia) require doses that are difficult to administer. If approved, tenapanor would have the lowest pill burden of any available phosphate binders, which should improve tolerability and patient compliance.
- Tenapanor's ability to divert sodium into stools increases the water content in the bowel, which can help improve the symptoms of IBS-C. In clinical studies, tenapanor has increased the frequency of bowel movements without increasing the incidence of diarrhea, a key limitation of other available IBS-C treatments.
- ARDX's lead programs have been financially de-risked through partnerships. Tenapanor has been partnered with AstraZeneca, which, in 2012, licensed exclusive, worldwide development and commercialization rights in an $870M deal. The deal gives ARDX an option to co-promote tenapanor in the US and to partially fund Phase III costs in exchange for an increased royalty rate. ARDX is eligible for $237.5M in development milestones, of which $40M has been received, and $597.5M in commercial milestones.
- ARDX's preclinical NaP2b inhibitor program (RDX002) was exclusively licensed by Sanofi earlier this year in a potential $198M deal, including up to $196.75M in development and regulatory milestones. We believe the fact that ARDX has managed to partner both tenapanor and RDX002 so early in development is a validation of the science that underpins its platform and the large market opportunity for its drug candidates.
- The capital-efficient partnerships ARDX has established should leave the company with little cash burn going forward. With its partners covering the development costs for the lead programs, and assuming regular milestone payments, ARDX may not require further capital raises. We expect ARDX to receive $70M in non-dilutive funds in 2015.

Ardelyx Overview

Ardelyx is based in Fremont, California and is developing tenapanor, an oral NHE3 inhibitor in three ongoing Phase II trials for ESRD, CKD and IBS-C. The company also has RDX002, a portfolio of NaP2b inhibitors, and three other small-molecule drug programs in preclinical development for cardio-renal, GI and metabolic diseases. Ardelyx has partnerships with AstraZeneca for tenapanor and Sanofi for RDX002.

Upcoming Milestones

Q4:14	Data from Phase IIb trial to treat IBS-C
H1:15	Data from Phase IIb trial to treat hyperphosphatemia in ESRD patients
H2:15	Data from Phase IIa trial to treat late-stage CKD
H2:15	Potential start of pivotal Phase III trial(s) of tenapanor in hyperphosphatemia
H2:15	Potential start of Phase IIb trial of tenapanor to treat CKD

Figure 1: Ardelyx Pipeline

Product	Description	Partner	Indication/Field	Stage of Development
Tenapanor (RDX5791, AZD1722)	NHE3 inhibitor	AstraZeneca	Hyperphosphatemia in ESRD	Phase IIb
			IBS-C	Phase IIb
			CKD	Phase IIa
RDX002	NaP2b inhibitors	Sanofi	Hyperphosphatemia in ESRD	Preclinical
RDX009	TGR5 agonists	-	IBD	Preclinical
RDX013	Potassium channel modulators	-	Hyperkalemia	Preclinical
RDX020	Chloride channel modulators	-	Fluid overload	Preclinical

Source: Wedbush Securities, Inc.

Drug Discovery Platform

Background: Gastrointestinal Tract

The gastrointestinal (GI) tract is the organ system responsible for digestion, nutrient absorption and excretion. The GI tract is generally divided into an upper section, which includes the stomach, and a lower section (also called the gut) which includes the small and large intestines. The small intestine, which is divided into the duodenum, jejunum and ileum, is a long thin tube that is responsible for extracting about 90% of the nutrients from food. The large intestine, which consists of the cecum, colon and rectum, is a shorter and thicker tube whose main task is to absorb water and pass waste from the body.

The lumen (inner channel) of the small intestine is lined by a layer of epithelial cells on protrusions called villi, which increase the surface area for absorption. The predominant epithelial cell type in intestines are enterocytes, also known as absorptive cells, which specialize in nutrient absorption from the apical (exposed) membrane and nutrient export across the underlying basal membrane into capillaries. The surface area for absorption is further increased by the protrusion of dense microvilli from the apical surface of enterocytes. Scattered in the epithelium are goblet cells, which secrete mucus to help protect the cell lining and aid in motility, and endocrine cells which secrete various hormones. The lining is maintained by stem cells located at the base of the villi which continually divide to produce new cells in the epithelium. The large intestine lacks villi, but has a larger supply of goblet cells and glands to help pass material through and aid in water absorption.

APECCS

ARDX's drug discovery platform, APECCS (Ardelyx Primary Enterocyte and Colonocyte Culture System), is designed to discover therapies that target receptors, enzymes and transporters in the GI tract. The platform involves taking biopsies of the gut and growing the cells collected under proprietary conditions that maintain cell integrity and functionality. These cells are then used to measure ion and nutrient transport across epithelial cells and to screen for promising new compounds and drug targets. The platform allows for more efficient phenotypic screening as the cell lines used are a better representation of GI tissue in comparison to traditional screening which uses transformed cell lines that express recombinant targets. ARDX has identified over 3,800 proteins that line the GI tract and this knowledge base is being used to identify targets for the treatment of cardio-renal, GI and metabolic disorders. ARDX intends to use a portion of the IPO proceeds to expand the capabilities of APECCS, including the ability to grow cells from multiple animal species and from human tissues derived from a variety of disorders.

The benefits of producing a local effect within the gut are many. The risk of systemic toxicity associated with small molecules that are absorbed into the bloodstream can be avoided, and drug design is faster since the competing concerns of adequate bioavailability and minimal off-site toxicity is not as significant. Multiple indications can also be targeted, since a variety of therapeutic effects can be achieved by modulating any one of the many natural functions of the gut. The gut is also readily targeted with oral therapies, providing greater convenience for patients and the ability to easily modify dosage if symptoms fluctuate.

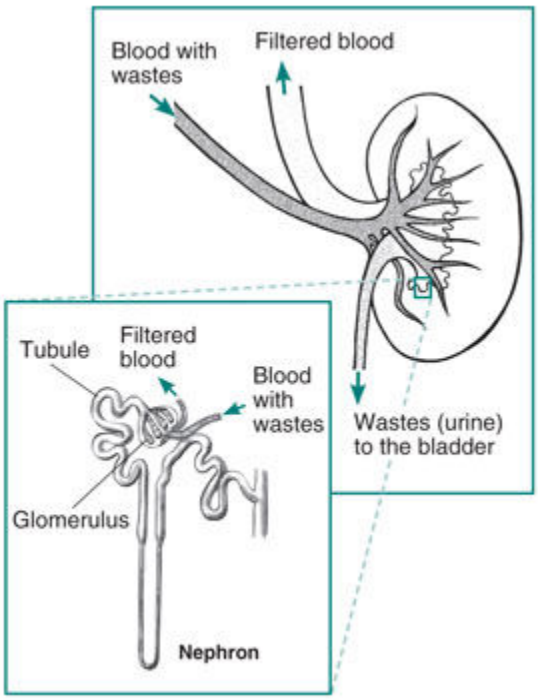
Background: Kidneys and Electrolyte Balance

Electrolytes are electrically charged minerals that help maintain homeostasis in the body. Important roles that are partially regulated by electrolytes include heart and neurological activity and fluid balance within the body. The most common electrolyte disorders include:

- Hyper/hypocalcemia: serum calcium (Ca^{+2}) levels outside the normal range of 9-10.5 mg/dL
- Hyper/hypochloremia: serum chloride (Cl^{-}) levels outside the normal range of 96-106 milliequivalents per liter (mEq/L)
- Hyper/hypokalemia: serum potassium (K^{+}) levels outside the normal range of 3.5-5.0 mEq/L
- Hyper/hyponatremia: serum sodium (Na^{+}) levels outside of the normal range of 135-145 mEq/L
- Hyper/hypophosphatemia: serum phosphate ($PO4^{-3}$) levels outside the normal range of 2.5-4.5 mg/dL.

Kidneys are the primary regulators of electrolyte imbalance, and kidney dysfunction or a lack of water intake can cause various electrolyte disorders. The kidneys maintain electrolyte concentrations through filtration of the blood and by excreting excess amounts into the urine. Each day the kidneys filter about 190L of blood, with the excess fluid and wastes excreted as urine and the cleansed blood returning to the heart for recirculation.

Figure 2: Illustration of Kidney

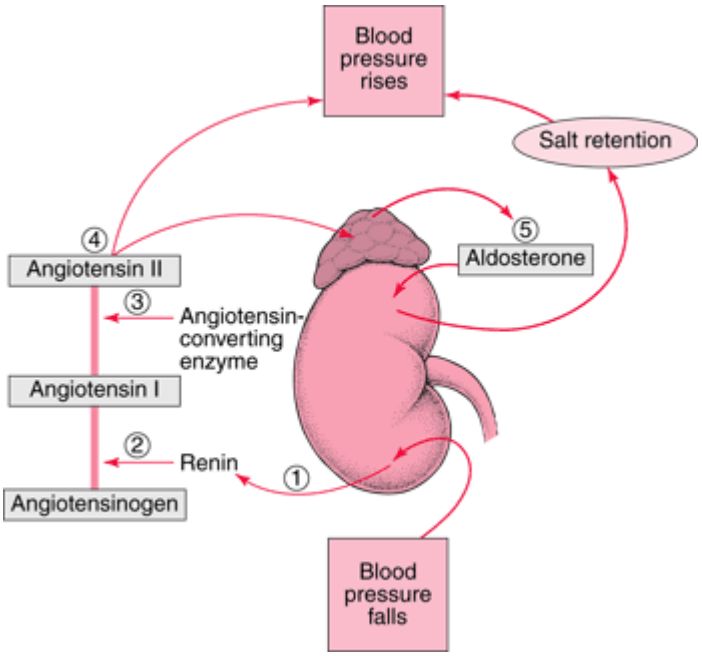


Source: NIH

Each kidney is made up of about a million filtering units known as nephrons, which contain a filter called the glomerulus and a tubule which takes the filtered fluid and returns useful minerals back to the bloodstream and emits the remaining waste to the bladder. The vast majority of filtered fluid is reabsorbed, with less than 2% excreted as urine.

The kidneys also regulate blood pressure through sodium excretion and production of the renin enzyme. Secretion of renin by the kidneys into the bloodstream activates the renin-angiotensin-aldosterone system (RAAS), a series of reactions that helps regulate blood pressure. Renin, released by the kidneys when blood pressure is low, triggers a signal transduction pathway that results in the production of the hormone angiotensin II (see Fig. 3). Angiotensin II increases blood pressure by causing vasoconstriction and stimulating the release of aldosterone from the adrenal glands and the antidiuretic hormone vasopressin from the pituitary gland, which causes the kidneys to retain sodium and water and excrete potassium (which further increases blood pressure due to increased blood volume).

Figure 3: The Renin-Angiotensin-Aldosterone System (RAAS)



Source: Merck Manual

Cardiovascular treatments that target the RAAS system include diuretics, which reduce blood volume by increasing the amount of water excreted in urine, and angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB).

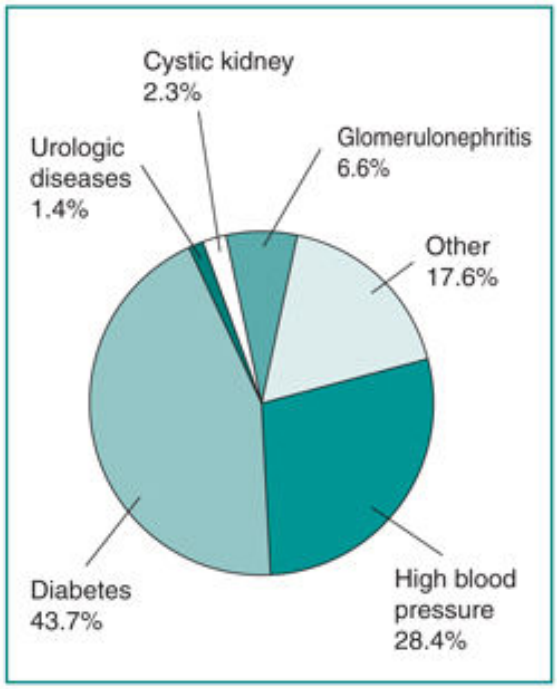
Kidney disease

The most common cause of electrolyte imbalances is renal failure. Failing kidneys become less efficient at blood filtration, and the resulting electrolyte imbalance results in fluid retention as the body seeks to maintain osmolarity. Fluid overload can lead to higher blood pressure and worsening heart and kidney function, and has been shown to be a predictor of mortality in CKD and ESRD patients.

Renal function can be assessed by measuring the glomerular filtration rate (GFR), which describes the volume of fluid that is filtered through the glomeruli each minute. GFR is widely accepted as the best overall biomarker of kidney function. Healthy young adults have a GFR of 120-130 mL/min/1.73m2, and the rate typically declines by about 1mL/min/1.73m2 after the age of 40. Irreversible kidney damage with progressive reduction in renal function (GFR < 90mL/min/1.73m2) is classified as chronic kidney disease (CKD). There are five stages of CKD, with stage 3 and 4 (GFR < 45mL/min/1.73m2) classified as late-stage. If GFR < 15mL/min/1.73m2 then kidney disease has progressed to the final stage known as end-stage renal disease (ESRD), where kidney function is completely lost and dialysis or a kidney transplant is required. CKD is often not diagnosed until it is advanced, since the symptoms (including fatigue, headaches, itchy skin, and nausea and weight loss) are non-specific.

Diabetic nephropathy is the leading cause of kidney failure, with approximately one-third of adult diabetics developing CKD. The damage diabetes causes to the kidneys is not immediate, and oftentimes will take over a decade to manifest. The first sign will be microalbuminuria, as the high sugar levels in the blood damages the kidneys and allows the protein albumin to pass into urine. With disease progression macroalbuminuria will develop as the kidney's ability to filter waste further degrades. The second leading cause of CKD is hypertension, which also increases the risk of comorbidities like cardiovascular disease. Notably, more CKD patients die from CV disease than progress to ESRD status. Together, diabetes and hypertension is responsible for over 70% of renal failure cases in the US.

Figure 4: Causes of Kidney Failure in the US



Source: CDC

In some patients, the cause of renal failure may be the administration of drugs that adversely affect renal function, such as NSAIDS and antibiotics, or some other contributing cause such as urinary tract infections. In these patients transitioning away from certain drugs or treating the underlying condition should reverse the decline in kidney function.

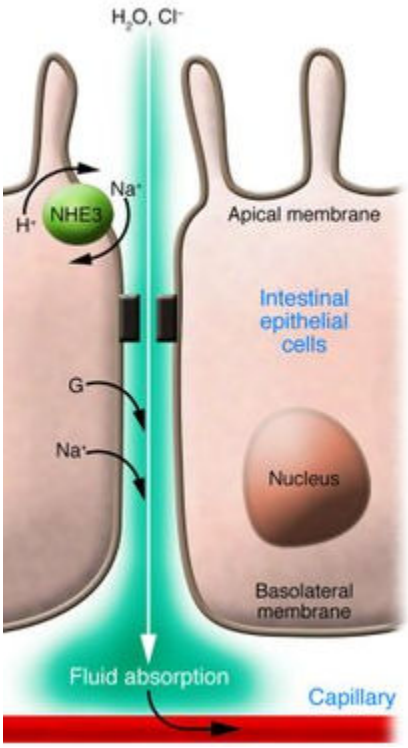
The general treatment strategy for CKD is based around slowing the progression of the disease by controlling blood pressure and proteinuria. Dietary restrictions are recommended for early-stage patients, but non-compliance is high. Pharmacological methods include the use of ACE inhibitors and ARBs, and patients may also be prescribed diuretics to help reduce extracellular fluid and blood pressure. Other complications that can arise from CKD, such as anemia (caused by reduced erythropoietin production by the kidney), can be treated with the use of iron replacement therapy or erythropoiesis-stimulating agents. Hypertriglyceridemia and other lipid abnormalities can also occur in CKD patients, and is generally treated with statins.

In patients that progress to ESRD, the gold standard of treatment is a kidney transplant, which is associated with improved survival and quality of life when compared to dialysis. However, the demand far exceeds supply, with over 90,000 patients on the waiting list in the US and an average wait time of about four years. Patients who are waiting or who are not good candidates for transplant must go on dialysis, which has a significant quality-of-life impact. Hemodialysis, the most common form, typically requires a visit to a clinic at least three times a week for a 3-5 hour session. Peritoneal dialysis, which is used by less than 10% of patients in the US, requires surgery and the placement of a permanent tube in the abdomen.

Tenapanor

Tenapanor (RDX5791, AZD1722) is a small-molecule inhibitor of NHE3, a sodium proton (Na+/H+) exchanger located on the plasma membrane of intestinal epithelial cells and nephrons. The NHE3 protein is responsible for the majority of salt absorption in the intestine and kidney, and acts to regulate the sodium levels that are absorbed and secreted by the body (see Fig. 5). NHE3 is stimulated and inhibited during normal digestive physiology, and its function is upregulated in diabetic nephropathy and downregulated in diarrhea.

Figure 5: NHE3 Function in Intestinal Epithelial Cells



Source: Adapted from Field, Michael. *Journal of Clinical Investigation* (2006).

When administered orally, tenapanor selectively inhibits sodium uptake in the lower GI tract, resulting in increased sodium levels along with increased water retention in the large intestine. This was established in preclinical studies and a Phase I trial in healthy volunteers, where tenapanor significantly diverted dietary sodium into the stool. *In vitro* studies have also shown that tenapanor is specific for NHE3 versus NaP2b and other members of the NHE family.

Tenapanor is designed to act locally within the GI tract, with little systemic exposure observed in both animals and humans. In rats, approximately 98% of radiolabeled tenapanor was detected unchanged in the feces, indicating that no substantial metabolism occurred. In addition, tenapanor was detected in the blood in only 0.7% of the more than 2,000 serum samples that have been collected from humans administered tenapanor, and even then, drug amounts were at low levels (< 1.5 ng/mL). The non-systemic effect of tenapanor gives it a good safety profile, with no drug-related SAEs observed in the over 765 patients that have been administered tenapanor thus far. This tolerability has been seen even in patients administered tenapanor for a period of up to three months at 100 mg per day and single doses of up to 900 mg, far greater than the maximum target dose of 90 mg per day.

Effect on Phosphorus Absorption

Tenapanor has been found to reduce phosphorus absorption in the GI tract, although the exact mechanism of action is not well understood (there is no direct inhibition of phosphate transporters like NaP2b or PiT-1). As with sodium, patients with failing kidneys develop elevated phosphorus levels, leading to hyperphosphatemia (serum phosphorus levels > 5 mg/dL) unless corrective efforts are made. Hyperphosphatemia is associated with adverse outcomes in ESRD patients, including increased cardiovascular complications and mortality. Elevated phosphorus levels can also lead to increases in parathyroid hormone, which can cause a bone disease called renal osteodystrophy (also known as chronic kidney disease–mineral and bone disorder, or CKD-MBD) that is characterized by uneven bone growth and demineralization. Achieving a normal phosphate balance in ESRD patients is a challenge, however, as dialysis does not readily eliminate phosphorus and dietary restriction is ineffective due to the widespread presence of phosphate in foods. Pharmacological methods of correcting excess phosphorus, such as the use of phosphate binders, have a high medication burden and low tolerability.

Tenapanor's ability to inhibit phosphorus absorption has been demonstrated in preclinical and in-human studies, including in a rat model of CDK where tenapanor caused significant reductions in urinary and serum phosphorus while improving renal status, with the animals also demonstrating reductions in aortic and gastric calcification and improved survival. In humans, tenapanor has demonstrated the ability to inhibit absorption of dietary phosphorus in four separate clinical trials, as measured by diversion into stool

and/or a decrease in urinary phosphorus levels. The increase in fecal phosphorus with tenapanor during Phase I testing is similar to that seen in a 1997 Phase I trial for the leading phosphate binder sevelamer, despite sevelamer being administered at a dose 500 times larger than tenapanor (5g TID vs. 15mg BID).

Partnership

In 2012, AstraZeneca licensed exclusive worldwide development and commercialization rights to ARDX's small molecule NHE3 inhibitors, including tenapanor and any potential follow-on compounds, with ARDX retaining an option to co-promote in the US. ARDX received $35M upfront and became eligible for $237.5M in development milestones, of which $40M has been received. ARDX is also eligible for $597.5M in commercialization milestones and tiered royalties ranging from the high single-digits to high teens. ARDX also has the option to co-fund the first Phase III program for tenapanor by paying $20M, $30M or $40M, which would increase its royalty percentage by 1%, 2% or 3%, respectively.

Based on the current development timeline for tenapanor, we expect ARDX will receive an additional $70M in milestone payments in 2015 from AstraZeneca. We expect ARDX to exercise its option for US co-promotion rights once positive Phase III results are released, and to build a specialty sales force with an initial focus on the CKD and ESRD applications. Currently ARDX is conducting the Phase II trials in CKD and IBS-C on AstraZeneca's behalf, with AstraZeneca reimbursing ARDX for all expenses. From the signing of the license agreement in October 2012 through Q1:14, ARDX has received $24.5M in reimbursement from AstraZeneca.

ARDX has one issued patent in the U.S. (No. 8,541,448) and Japan covering the composition of tenapanor, both of which will expire in 2029. The company also has two patent applications pending in the U.S. covering the composition of or methods of using tenapanor, and related patent applications pending in Europe, Asia and other territories. These patents have been exclusively licensed to AstraZeneca as part of their partnership.

ARDX has relied on third-party CMOs for manufacturing tenapanor, and is currently supplying the drug for use in clinical testing. ARDX is in the final stages of transferring the manufacturing process for tenapanor to AstraZeneca, which is responsible for manufacturing all future supplies for clinical and commercial use.

Clinical Studies

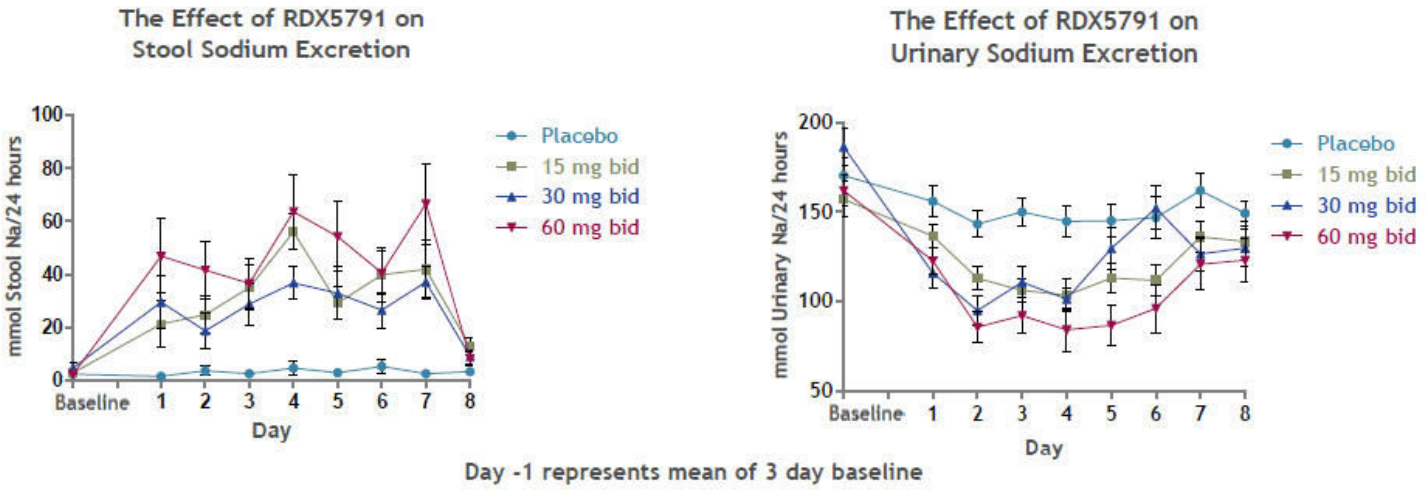
Preclinical testing in rats showed that tenapanor improved measures of cardio-renal function and prevented increases in markers of renal injury, both in healthy rats and a rat model of CKD. In addition, rats treated with a combination of tenapanor and the ACE inhibitor enalapril demonstrated an improvement in arterial stiffness and cardiac diastolic dysfunction compared to animals treated with enalapril alone. A long-term carcinogenicity study of tenapanor in rats, required for regulatory approval, is currently being conducted, with results expected by end of 2016.

Clinical Studies

Tenapanor has completed eight clinical trials (six Phase I trials and two Phase II trials) and is currently being evaluated in a Phase I PK study and three Phase II trials, including one in CKD and another in ESRD.

Results from the completed Phase I trials show tenapanor was safe and well tolerated, even at single doses of up to 900 mg and 100 mg QD for four weeks. Early signs of efficacy were also seen, with sodium and phosphorus levels rising in the stool and falling in urine in healthy adults administered tenapanor. About 20-50 mmol of sodium was diverted per day from the urine into stool with tenapanor use (see Fig. 6), a meaningful amount that on the high end matches the effect of adopting a sodium-restricted diet (CKD patients are recommended to reduce their sodium intake to <100 mmol/day from the average American intake of 150 mmol/day). A rapid onset of action was observed, and the effect was maintained during use of tenapanor. Over the course of the week tenapanor reduced sodium intake by about 280-350 mmol, equivalent to about 2-2.5L of extracellular fluid.

Figure 6: Change in Stool and Urinary Sodium Excretion for Various Tenapanor (RDX5791) Doses in a One-Week Phase I Trial



Source: Company data

Results from one of the Phase I studies show the activity of tenapanor was not affected by the addition of the phosphate binder sevelamer (Renvela). The open-label PK/PD study was evaluating tenapanor BID with/without Renvela for four days in healthy adults. Results show that changes in phosphorus levels in urine and stool and urinary potassium and creatinine levels were similar between the two arms (the study was not powered to demonstrate statistical significance). The combination was safe, with no tenapanor detected in blood plasma. The lack of drug-drug interactions in the study is important as ESRD patients will likely be using tenapanor concomitantly with other medications.

While tenapanor did not meet the primary endpoint of interdialytic weight gain (IDWG) in a Phase IIa pharmacodynamic study in 88 ESRD patients with fluid overload, we note that drug activity was confirmed by an increase in sodium in the stool of patients receiving tenapanor. The double-blind, placebo-controlled, dose-finding study evaluated IDWG after four weeks of treatment with either 5-90 mg doses of tenapanor or placebo. We note that IDWG is a measure of sodium and water intake between dialysis sessions and the results could have been affected by the infusion during dialysis of saline with a high sodium concentration. It is also possible that the kidney's role in regulating sodium levels in the body is not as predominant as once believed, at least in the short term. Recently published research from Dr. Jens Titze, Professor of Medicine at Vanderbilt University, found that reserves of sodium are stored for short durations in the muscles and skin (Titze et al. *Cell Metabolism*, 2013), perhaps as an evolutionary adaptation to maintain homeostasis for periods when sodium-rich food was unavailable. Although the research is still early, the results may point to the need to run clinical studies for a longer time-frame to show a stronger relationship between reduced sodium absorption and fluid elimination. Importantly, we note that the relevant FDA approvable endpoint in a Phase III study for hyperphosphatemia should be actual reduction of phosphorous levels.

Tenapanor is currently being evaluated in a double-blind, placebo-controlled Phase IIb study in 150 patients with ESRD on hemodialysis. The study is designed to find the minimum effective dose, with the primary endpoint being change in serum phosphate levels at the end of the four-week treatment period. Data is expected in H1:15, and if positive, AstraZeneca could begin either one or two pivotal Phase III trials in H2:15, with the Phase IIb trial potentially being accepted as a pivotal study.

Tenapanor is also being evaluated in a double-blind, placebo-controlled Phase IIa trial in 140 stage 3 CKD patients with Type II diabetes, albuminuria and high blood pressure. The study is evaluating the effects of tenapanor on markers of kidney disease and fluid status in patients who are not yet on dialysis. Specifically, the study will measure the changes in urine albumin to creatinine ratio (UACR), a measure of urinary protein excretion that correlates to the severity of kidney disease. In addition, the study will assess the safety, tolerability and pharmacodynamics of tenapanor in the late-stage CKD patient population. Results from the ongoing study are expected to be available in H2:15. If an improvement in UACR is seen, AstraZeneca could begin a Phase IIb trial in CKD patients evaluating the long-term benefit of systemic sodium and fluid reduction. AstraZeneca could also begin a large Phase III study in CKD, evaluating tenapanor's ability to delay disease progression, as measured by GFR, percent of patients who progress to ESRD, cardiovascular events and survival.

Recent guidance also indicates that the requirements for approval in CKD could be changed, possibility resulting in shorter development time for CKD drug candidates. A 2012 scientific workshop convened by the FDA and the National Kidney Foundation recommended a 30-40% decline in GFR as an acceptable surrogate endpoint for a pivotal CKD trial, a reduction from the prior

requirement of a 50% decline in GFR as a kidney failure endpoint. This could reduce the time for demonstrating a delay in kidney disease progression during a clinical trial from 3-4 years to 2 years.

Competition in CKD and ESRD

Current Treatment of Hyperphosphatemia in ESRD

The current management of ESRD involves hemodialysis or peritoneal dialysis to filter toxins from the blood. ESRD patients with elevated phosphorus levels are also assigned low phosphorus diets and prescribed oral phosphate binders since dialysis is unable to efficiently eliminate excess phosphorus.

Phosphate binders control elevated phosphate levels by absorbing phosphate in the GI tract and reducing its uptake. The most widely used binders have a calcium base and bind to the phosphate ionically. Although effective and inexpensive, calcium based binders (such as calcium carbonate and calcium acetate) can cause hypercalcemia and its performance can be affected by other medications the patient is taking. The former is a major concern, as patients on ESRD are already likely to have elevated calcium levels. Binders that contain lanthanum are an alternative, as it has lower systemic absorption and fewer drug-drug interactions. Treatment with lanthanum is more expensive, however, and it carries the risk of metal accumulation. Lanthanum carbonate is currently marketed by Shire (not covered) under the brand name Fosrenol, while calcium-based binders are available in multiple generic formulations.

Sevelamer, introduced in 1997 under the brand name Renagel by Genzyme (acquired by Sanofi), is a non-absorbed phosphate-binding resin that avoids the systemic toxicity issues associated with prior phosphate binders. A newer version introduced by Genzyme, called Renvela, uses a carbonate counter-ion that avoids the acidosis associated with the older chloride-based version. Sevelamer is widely used, but its low binding capacity results in a high pill burden, with patients having to take eight or more pills a day.

Due to the toxicity and pill burden associated with available phosphate binders, patient compliance is low, which reduces treatment efficacy. In general, less than half of dialysis patients are able to achieve and maintain the target serum phosphorus level of 5.5 mg/dL. The EVOLVE trial, sponsored by Amgen, found that baseline serum phosphorus levels in 2,618 ESRD patients on hemodialysis in the US and Europe was 6.4mg/dL, despite 89% of patients being medicated with phosphate binders at study start (Chertow et al. *Nephrology Dialysis Transplantation*, 2012).

Iron-containing compounds have recently emerged as an alternative phosphate binder that could potentially have greater tolerability than currently available treatments. In contrast to the toxicity associated with other binders, absorption of iron could be beneficial in kidney disease patients who often have concurrent anemia. Iron-based phosphate binders include Zerenex (ferric citrate) from Keryx Biopharmaceuticals (KERX, not covered) and Velphoro (sucroferric oxyhydroxide) from Galenica Group and dialysis provider Fresenius. Zerenex is currently under FDA review, with a September 7, 2014 PDUFA date, while Velphoro was approved in the US in late 2013. Clinical testing has shown iron-based binders have a similar efficacy to sevelamer, with Velphoro demonstrating similar phosphate control to Renvela (-0.71 mmol/L vs. -0.79 mmol/L from baseline to week 12) in a large Phase III trial (Floege et al. *Kidney International*, 2014).

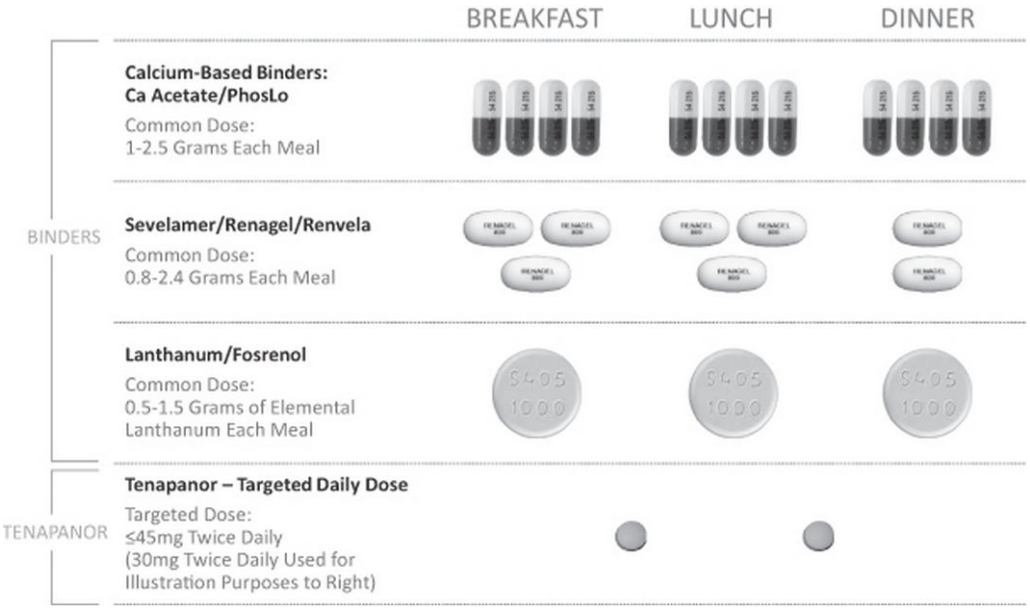
Figure 7: Comparison of Tenapanor to Marketed Treatments for Hyperphosphatemia

Treatment	Market Share*	Annual Cost in US ($)	Pill Burden (mg/day, max)	Advantages	Disadvantages
calcium acetate and calcium carbonate	51%	~$900	7500 mg (12 pills)	Inexpensive	Risk of hypercalcemia and other side effects
Fosrenol	18%	~$7,500	7200 mg (3 pills)	Highly effective	Metal toxicity and GI side effects
Renagel/Renvela	36%	~$7,600	4500 mg (8 pills)	Moderately effective	High pill burden, GI side effects
Velphoro	N/A	~$12,000	1500 mg (3 pills)	Moderately effective	Expensive
tenapanor	--	--	90 mg (2 pills)	Safe and effective, low pill burden	

Source: Company data, MedImpact, Wedbush Securities, Inc. *Note:* market share exceeds 100% due to combination use

Tenapanor, if approved, would likely have lowest pill burden of any marketed drugs for hyperphosphatemia, a key benefit since ESRD is one of the most medication-burdened of all chronic illnesses due to the high prevalence of co-morbidities. A study in a group of chronic dialysis patients found that the median daily pill burden was 19, with phosphate binders accounting for about half (Chiu et al. *Clinical Journal of the American Society of Nephrology*, 2009). Tenapanor has the potential to alleviate this burden, which should improve tolerability and patient adherence, while minimizing the risk of adverse events or medication errors.

Figure 8: Size Comparison of Tenapanor to Marketed Phosphate Binders



Source: Company data. *Note:* image does not reflect actual size, but is to scale

CKD Treatments in Development

There is a significant need for treatments that can slow the progression of CKD and delay dialysis initiation. No drugs currently exist that can reverse kidney damage once it has occurred, and the treatments available today for delaying kidney disease progression (such as diuretics and RAAS inhibitors) are only moderately successful.

Competitive treatments in development for CKD that have demonstrated promise in delaying kidney decline include CLP-1001, from Sorbent Therapeutics (private), and CTP-499, from Concert Pharmaceuticals (CNCE, not covered). CLP-1001 is an oral, non-absorbed polymer that is currently in Phase II testing in heart failure patients with CKD. CLP-1001 binds water and Na+ and K+ ions in the GI tract, and results from a Phase IIa trial show CLP-1001 increased fecal sodium and improved multiple heart function-related parameters. However, the mean daily increase in fecal sodium content seen with 15g of CLP-1001 administered daily for one week in heart failure patients was only 635.1mg, or 27.5 mmol/day (Dittrich et al. *Journal of the American College of Cardiology*, 2013). This figure is below the mean daily increase seen with 60 mg twice-daily tenapanor in the one-week Phase I study in healthy volunteers, despite the CLP-1001 dose being >100 times larger. CTP-499 is an oral multi-subtype selective phosphodiesterase inhibitor being developed to slow the progression of kidney disease in patients with Type II diabetes. CTP-499 is currently being evaluated as an additive to current standard of care (ACE inhibitor or ARB) in a Phase II extension study. Results from the Phase II study show that CTP-499 slowed the decline of kidney function at 48 weeks, although it missed the primary endpoint as measured by change in UACR at 24 weeks.

Market

ESRD

We expect the most expeditious path to approval for tenapanor is in hyperphosphatemia in ESRD, due to the need for treatments with greater tolerability and the acceptability of surrogate endpoints (the relatively straightforward measurement of serum phosphate) for approval. We expect a regulatory submission in ESRD to occur in late 2017 once the pivotal trial completes and results from the long-term carcinogenicity study in rats become available. We forecast US approval for tenapanor in the space in mid- to late 2018, and EU and Japanese approval to follow in late 2018 and early 2019, respectively.

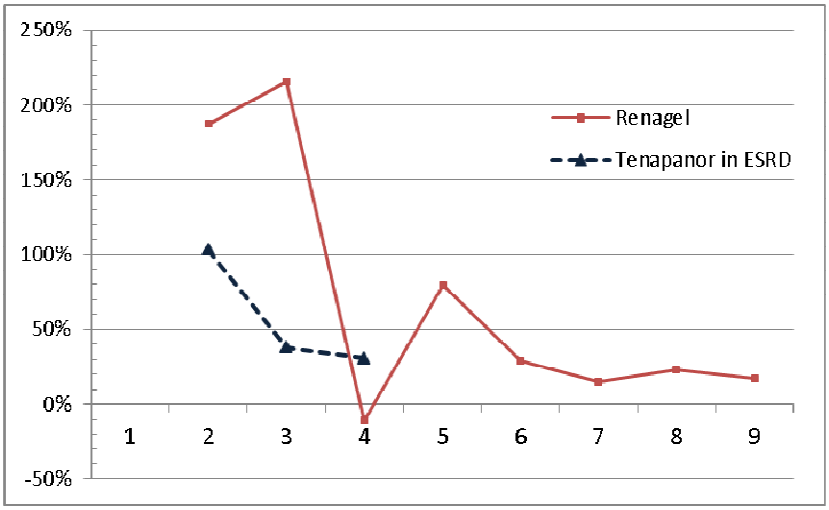
International dialysis provider Fresenius estimated that there were 2.5M ESRD patients worldwide at the end of 2013, including 1.1M in the major markets of US, Europe and Japan (2013 Annual Report, Fresenius Medical Care). Based on phosphate binder utilization, ARDX has estimated the number of ESRD patients with hyperphosphatemia to be 270k, 215k and 220k in the US, Europe and Japan

respectively. The worldwide market for phosphate binders is projected to be $2.3B in 2015, which breaks down to an annual cost of ~$2,300 per patient in major markets (assuming US, EU and Japan make up 70% of the worldwide market). We forecast tenapanor to be priced at $4 per pill in the US and $3 per pill in the EU and Japan, which at twice-daily use works out to be ~$2,900 and ~$2,200 per year per patient, respectively. Although priced at a premium to generic competition, it is a discount to the cost of branded Fosrenol, Renagel/Renvela and Velphoro. We expect the latter to be a key issue that will prevent Fresenius from favoring Velphoro in its clinics. Fresenius co-owns Velphoro under a joint venture with Galenica Group's Vifor Pharma subsidiary.

Recently passed legislation also removes concerns over phosphate binders being placed under the Medicare payment bundle for dialysis treatment, which would have capped the price of tenapanor. Oral-only medications used by patients on dialysis were expected to fall under the bundled model in 2016, but legislation passed earlier this year extended that deadline to 2024. Patients in the US with ESRD, irrespective of age, begin to receive Medicare coverage after three months of dialysis.

We forecast tenapanor will achieve $139M in worldwide sales in the hyperphosphatemia indication in 2019 (its first full year of sales), which we expect will rise to $506M in 2022, our last forecasted year. Beyond that, we expect the year-over-year growth to decline to the low double-digit range, similar to what was seen with Renagel five years after its launch (see Fig. 9). Renagel/Renvela, the leading phosphate binder, posted worldwide sales of EUR 750M (~$1B) in 2013.

Figure 9: Year-over-Year Growth (%) in Worldwide Sales Post-Launch for Tenapanor in ESRD (projected) vs Renagel



Source: Wedbush Securities. *Note:* Year 1 refers to first full year of sales after launch - 1999 for Renagel, 2019 (expected) for tenapanor

CKD

Although hyperphosphatemia occurs in late-stage CKD patients, we do not expect AstraZeneca to pursue approval in that indication in the near future. Unlike with ESRD, where a reduction of serum phosphorus is an approvable endpoint, in the broader CKD population approval would require a clinical outcomes study (based on FDA guidance from the Cardiovascular and Renal Drugs Advisory Committee meeting on October 16, 2007). This necessitates a large and long-running study for tenapanor to gain approval in pre-dialysis patients. Phosphate binders are approved in the EU and Japan for treating hyperphosphatemia in late-stage CKD patients.

We estimate 10% of the population in the US, EU and Japan has CKD, and we project that figure to rise in concordance with the aging population. ARDX is focused on treating the subpopulation that suffers from both Type II diabetes and late-stage (GFR < 45 mL/min) CKD, a group that has particularly adverse clinical outcomes. ARDX has estimated the number of patients with late-stage CKD and Type II diabetes to be 1.8M in the US, and 1.7M and 0.6M in Europe and Japan, respectively.

We expect the peak penetration of tenapanor in CKD to be less than ESRD, due to the less urgent patient population and the presence of competing treatments in development. Although it is too early to directly compare tenapanor to CLP-1001 and CTP-499, we expect that the phosphate level reduction seen with tenapanor would serve to differentiate it from the competition. We also note that the CKD market is large enough to accommodate multiple treatment options. We expect approval in CKD to occur in late 2019, a year after ESRD approval is achieved due to the larger pivotal trial that would have to be run.

Background: IBS

Irritable bowel syndrome (IBS) is a disorder affecting the large intestine that is characterized by a collection of symptoms, including abdominal pain, cramping, gas, and altered bowel habits. IBS is a functional GI disorder, associated with no known cause or physical damage to the intestine. The disorder has previously been referred to as 'nervous colon', a reflection of previously held beliefs that the disorder was a purely psychosomatic condition. IBS is currently thought to be driven by a combination of physical and mental factors that affect the function of the large intestine.

The main function of the large intestine is to absorb water and remaining nutrients from the partially digested food that is passed from the small intestine. Once most of the water is absorbed in the colon, the semi-solid waste (stool) is moved to the rectum, where it is stored until a bowel movement occurs. Motility within the large intestine occurs due to a series of intestinal muscle contractions, which is controlled by nerves and hormones within the muscle. Abnormal contractility is thought to be a possible cause of IBS, with delayed passage of material (excessive water absorption) associated with constipation and rapid passage (insufficient water absorption) associated with diarrhea. IBS affects over twice as many women than men, likely due to gender differences in hormones or pain sensitivity.

IBS is diagnosed when a patient has altered bowel habits and unexplained abdominal pain or discomfort at least three times a month for three months. Depending on the nature of the altered bowel habits, IBS can be classified under two large subtypes:

- IBS with constipation (IBS-C): at least 25% of bowel movements are characterized by infrequent and hard stools.
- IBS with diarrhea (IBS-D): at least 25% of bowel movements are characterized by frequent and watery stools

IBS can also be classified as mixed, where both of the above criteria are met, or unsubtyped, if neither of the above criteria is met. The treatment strategy for IBS will depend on which subtype the patient suffers from, with a treatment to improve motility (like tenapanor) likely to improve symptoms in IBS-C patients but not in IBS-D patients. It is worth noting that IBS-C is separate from chronic idiopathic constipation (CIC) due to the presence of abdominal pain in IBS-C patients, although the treatment strategy for both conditions is similar.

When presented with a patient exhibiting signs of IBS, physicians will likely conduct blood and other diagnostic tests to rule out more serious conditions like colon cancer or celiac disease. The tests will also ensure patients are not suffering from other related conditions such as colitis, an inflammatory bowel disease (IBD) that is characterized by physical inflammation of the colon.

Treatment

The treatment strategy for IBS depends upon the specific disorder subtype and severity of symptoms. Patients with mild IBS symptoms that have little impact on quality of life are generally treated with dietary and lifestyle modifications, while patients with moderate-to-severe symptoms are treated pharmacologically. For example, patients with moderate-to-severe IBS-D are treated with antidiarrheal agents, with loperamide (Imodium) regarded as standard of care.

For IBS-C patients, the recommended initial treatment strategy involves the use of a bulking agent like soluble fiber (i.e., Metamucil) or a laxative like polyethylene glycol (PEG). Although inexpensive, these treatments generally do not treat the abdominal pain IBS-C patients suffer from. For patients whose constipation does not improve with the use of fiber supplements or laxatives, two available treatments approved for IBS-C are lubiprostone (Amitiza) and linaclotide (Linzess). Both treatments have been found to relieve abdominal pain and increase the frequency of bowel movements in IBS-C patients, although the FDA only approved Amitiza in women due to a lack of demonstrated effect in men. Amitiza is a chloride channel activator that is marketed by Sucampo (SCMP, not covered) and Takeda, while Linzess is a guanylate cyclase agonist marketed by Ironwood (IRWD, NEUTRAL) and Forest Laboratories (not covered). Tegaserod (Zelnorm), a serotonin agonist from Novartis, was approved for IBS-C in 2002, but later pulled from the market in in 2007 due to cardiovascular side effects.

Tenapanor in IBS-C

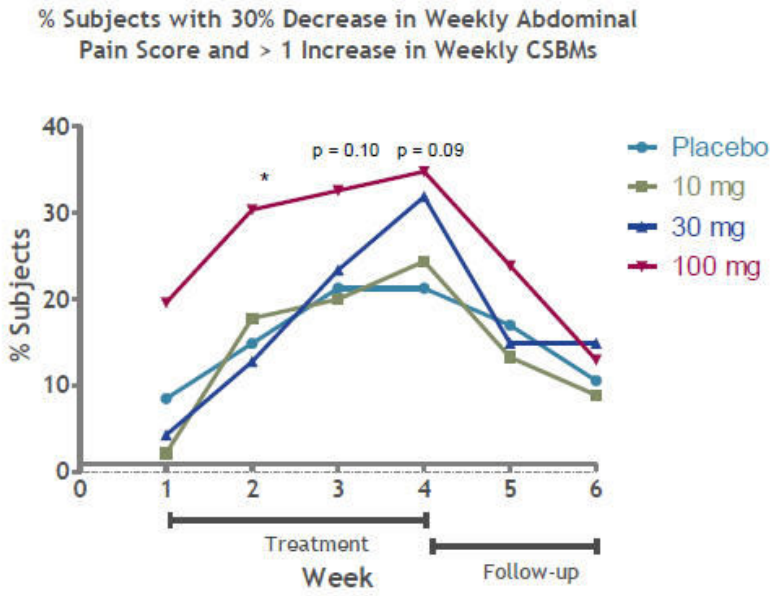
Preclinical data supported the development of tenapanor in IBS-C, with tenapanor increasing fecal water content, fecal form score (higher score correlates to looser stools) and intestinal motility in a dose-dependent manner in multiple animal models. Tenapanor also demonstrated efficacy in a rodent morphine-induced constipation assay, with intestinal transit time increasing to almost the same extent as with the opioid antagonist naltrexone.

Early signs of efficacy were seen in the Phase I trials in healthy adults, with tenapanor producing improvements in multiple constipation-related measures such as median time to bowel movement, stool consistency and stool weight. The increase in stool consistency and weight is a reflection of water retention in the intestines, a sign that sodium absorption was being inhibited. Increases in fecal sodium

were also observed, consistent with the drug's mechanism of action. In all of the studies of tenapanor the change in fecal form correlated with the amount of sodium that was diverted into the stool.

Based on these results, ARDX advanced tenapanor into a placebo-controlled Phase IIa trial in 186 patients with IBS-C. Tenapanor was generally well tolerated at all doses evaluated (10, 30 and 100mg QD for four weeks), with an incidence of diarrhea no different from that of placebo. The latter is a key differentiating factor, as diarrhea is the most common side effect of available IBS-C treatments like Amitiza and Linzess. The primary endpoint of change in the frequency of complete spontaneous bowel movements (CSBM) from baseline was not met, although the 30 and 100 mg tenapanor doses demonstrated activity. The two high-dose groups did demonstrate significant improvement in stool consistency scores vs placebo at all study weeks. Improvements were also seen with tenapanor in straining scores, abdominal pain and patient satisfaction, although results were not significant.

Figure 10: Tenapanor Activity in Dual Endpoint of Phase IIa Trial



Source: Company data

We believe the reason for the primary endpoint miss in the four-week Phase IIa study was due to underpowering due to the dose-finding nature of the study, and we expect positive results from the 12-week Phase IIb trial due to a doubling in patient enrollment and an optimized dosing regimen that will evaluate more frequent administration over a longer period. A pharmacodynamic analysis of Phase I results demonstrated improved response with twice-daily dosing, with a greater diversion of sodium into stool occurring at higher and more frequent doses. An ongoing placebo-controlled Phase IIb trial is evaluating the twice-daily dosing effect of 5, 20 and 50 mg tenapanor on frequency of bowel movements in 371 IBS-C patients. The primary endpoint is percent of responders with an increase of at least one CSBM in six of the 12 weeks of the study. The trial has completed enrollment with data expected in Q4:14, and if positive, could cause AstraZeneca to proceed with pivotal Phase III trials. Based on the registration trials for Linzess in IBS-C, which included two Phase III trials in more than 1,600 patients, we would expect the pivotal studies for tenapanor to be large and to have a dual endpoint of increase in CSBM and decrease in abdominal pain.

IBS-C Market

The IBS-C market is a large and growing one, currently accounting for 20-50% of referrals to gastroenterologists. According to the American College of Gastroenterology, an estimated 10-15% of the American population is thought to suffer from IBS, although only about half of that figure has been formally diagnosed. ARDX has provided more conservative estimates of disease prevalence, with 4.4M (1.4%) affected individuals in the US and 1.0M of them diagnosed. The company has also estimated European and Japanese prevalence to be 6.6M and 3.4M, respectively.

Insufficient clinical data exists for a direct comparison between tenapanor and the available IBS-C treatments. We believe tenapanor can be competitive, however, since currently available treatments have limited efficacy and tolerability issues. In its pivotal trials, the difference in Linzess and placebo patients who reached the primary endpoint was only 20%, while the drug caused diarrhea in 11-17%

more patients than placebo (diarrhea-related discontinuation was 4% higher than with placebo). Amitiza is also associated with side effects, including nausea and diarrhea in 7-37% of patients, and the drug has not demonstrated efficacy in men.

In contrast, during the Phase IIa trial the incidence of diarrhea with tenapanor was similar to placebo. We believe physicians would view tolerability as the most important feature for an IBS-C treatment, since the disease is not life-threatening and does not cause tissue damage. An additional benefit of tenapanor is the potential for dose and dose frequency to be adjusted for optimal effect, an important differentiating factor since the severity of IBS-C symptoms can vary suddenly.

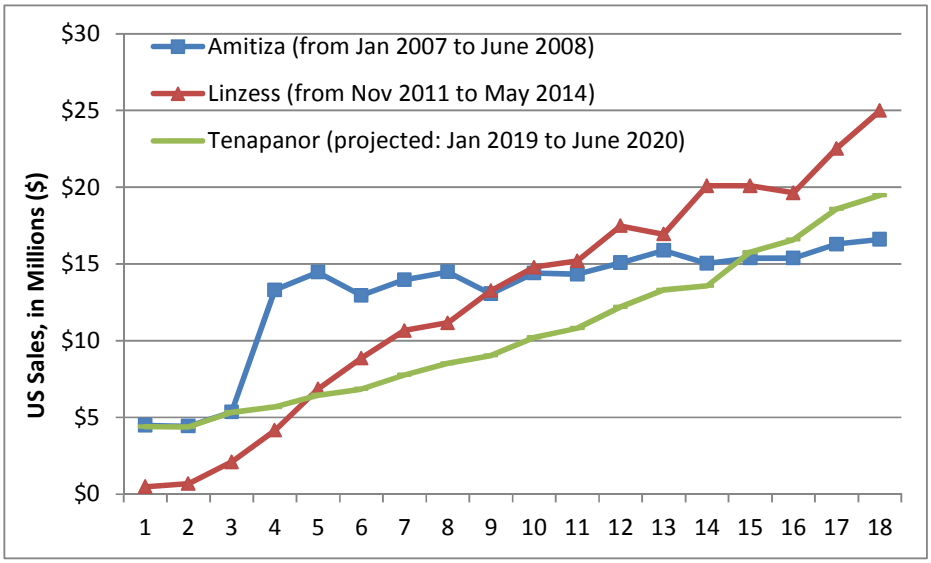
We expect the results from the Phase IIb trial to be positive, and for AstraZeneca to continue development of tenapanor in IBS-C. We believe AstraZeneca views IBS as a growing global market, as evidenced by the company licensing the Chinese rights to linaclotide from Ironwood. We also note that AstraZeneca has historically been a market leader in the GI space, having produced blockbuster treatments such as Nexium and Prilosec. Assuming tenapanor follows a similar development path as Linzess, we can expect 1-2 large Phase III trials to be conducted that will assess the change in abdominal pain and CSBMs during 12 weeks of treatment, followed by a one-year safety observation period. We currently expect approval in the US in early 2019 and in Europe and Japan six and 18 months later, respectively.

We currently forecast a tenapanor launch in IBS-C in early 2019, and expect the drug to be priced in line with available pharmacological treatments. We project tenapanor will be priced at $240 for a 30-day supply in the US, comparable to the $250-$300 average wholesale price of Linzess and Amitiza per month. We believe this price is reasonable considering the quality-of-life impact and economic cost of IBS, which can include healthcare treatments and worker absenteeism. ARDX has estimated the economic burden of IBS-C to be at least $1,500 per year in direct costs and $800 per year in indirect costs.

We estimate tenapanor will achieve a modest 20% peak penetration rate in the IBS-C market due to increased competition in the market. In addition to Linzess and Amitiza, we expect additional competition from promising compounds currently in mid-stage development. These compounds include elobixibat, an inhibitor of the ileal bile acid transporter from Ferring Pharmaceuticals and Albireo AB, and plecanatide, a uroguanylin analog from Synergy Pharmaceuticals (SGYP, not covered). Both drugs have completed Phase II trials and demonstrated statistically significant increases in CSBM frequency, but as with Linzess and Amitiza, both elobixibat and plecanatide are associated with increased rates of diarrhea. In Phase II trials, diarrhea occurred in 11% more elobixibat-treated patients than placebo and 8% more plecanatide-treated patients than placebo.

Despite the competitive space, we expect IBS-C to be the largest commercial opportunity for tenapanor due to the large patient population. We expect first full-year sales of $92M for tenapanor in 2019, compared to $119M in sales for Linzess in 2013. We note that Linzess is also approved for CIC, which we believe contributes about 1/3 of sales. We also note that even if all of ARDX's other programs are overlooked, ARDX's current market cap is about 1/6 of IRWD's ~$2B market cap.

Figure 11: Projected Tenapanor Sales in First 18 Months Post-Launch vs. Amitiza and Linzess Launches



Source: Symphony Health Solutions, Wedbush Securities.

Note: Amitiza launched in Q2:06, sales data available beginning Jan-07. Amitiza is approved for CIC and OIC in adults and IBS-C in women. Amitiza and Linzess sales based on wholesale acquisition cost, prior to discounts and rebates.

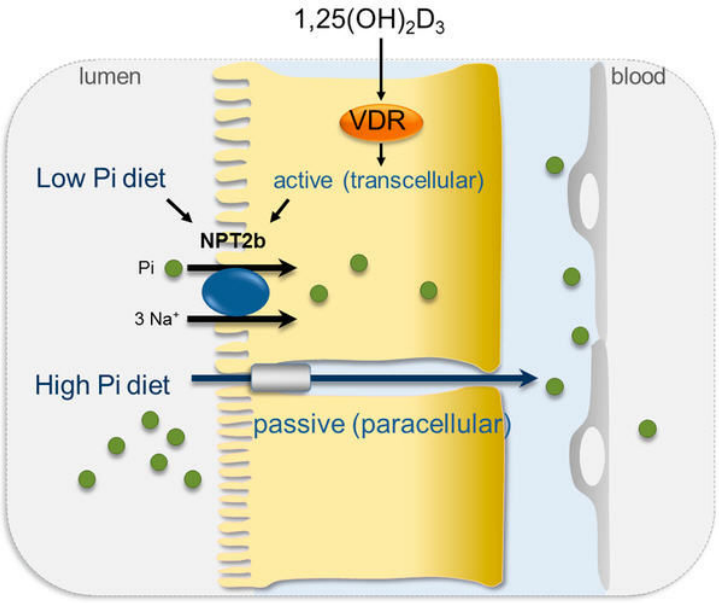
Preclinical Candidates

Outside of tenapanor, ARDX has a pipeline of candidates in preclinical development for cardio-renal, GI and metabolic disorders. Due to the early status, we are not forecasting sales from any of these preclinical programs, but we expect revenue from partnerships (as with RDX002) to be a source of non-dilutive funds for the company going forward. ARDX plans to use $15-$20M of its IPO proceeds to fund continued discovery and development efforts for its preclinical programs.

RDX002

The RDX002 program includes a portfolio of small-molecule inhibitors of the intestinal phosphate transporter NaP2b (also known as NaPi2b, Npt2b and SLC34A2). NaP2b is a sodium-dependent phosphate co-transporter expressed in the intestinal epithelium that is believed to mediate about half of dietary phosphate uptake (the remainder is taken up by passive diffusion). The role of NaP2b increases in importance in ESRD since dietary phosphate restriction (which is recommended for patients) upregulates NaP2b expression through a vitamin D pathway (see Fig. 12). As a result, NaP2b inhibition could have potential utility in the treatment of hyperphosphatemia in ESRD patients.

Figure 12: Upregulation of NaP2b (NPT2b) Expression on Intestinal Epithelial Cells due to Dietary Phosphorus Restriction



Source: Christakos, Lieben, Masuyama & Carmeliet. *BoneKEy Reports* (2014).

Preclinical testing in rats showed that certain RDX002 compounds were able to reduce urinary excretion of phosphorus to a greater extent than commercial phosphate binders like sevelamer, despite the latter being administered at a ~8x larger dose. Serum phosphorus was also reduced and a survival improvement was seen in a rat model of CKD following administration of RDX002. An additive benefit was also demonstrated when RDX002 was administered with sevelamer, which indicates combination use could potentially provide greater phosphate control and reduced pill burden compared to phosphate binders alone.

Earlier this year ARDX granted Sanofi exclusive research rights for the RDX002 program and an option to obtain exclusive global development and commercialization rights, with ARDX retaining an option to co-promote in the US if Sanofi exercises its commercialization option. Sanofi must exercise its option within 45 days after the filing of an IND for a NaP2b inhibitor. Sanofi is responsible for all preclinical costs, and if it exercises its option is responsible for all clinical, commercial and manufacturing costs. ARDX received a $1.25M upfront payment and is eligible for $196.75M in development and regulatory milestones.

Although it is too early to assess how the NaP2b inhibitors compares to tenapanor in controlling phosphate, we believe it is likely the former is superior, considering the lack of mechanistic explanation for tenapanor's inhibition of phosphorus absorption. We are forecasting the Sanofi partnership to provide an average of ~14M million in non-dilutive cash per year from 2016 through 2022. We expect an additional year of preclinical evaluation, with a RDX002 compound advanced into clinical advancement in 2016.

ARDX has five pending U.S. patent applications related to its RDX002 program, which is exclusively licensed to Sanofi and if issued is expected to expire in 2031.

RDX009

The RDX009 program is evaluating small-molecule oral compounds that stimulate TGR5, a membrane-bound bile-acid activated receptor that is highly expressed in the intestine and gall bladder. When TGR5 is stimulated it increases the secretion of glucagon-like-peptides-1 and 2 (GLP-1 and GLP-2), hormones which affects multiple metabolic processes. GLP-1 is the more widely known hormone due to its role in glucose homeostasis and its potential in diabetes therapy. GLP-2 is involved in intestinal growth and the maintenance of intestinal function, as well as the suppression of macrophage functions which could reduce inflammation.

ARDX is developing TGR5 agonists for the increased production of GLP-2, which could have therapeutic benefits in inflammatory bowel disease (IBD) and other disorders affecting the GI tract. IBD is an autoimmune disorder that is characterized by an abnormal immune response to food and bacteria in the gut which results in damage to the intestinal lining. IBD is a grouping of chronic inflammatory conditions, with the most common types being ulcerative colitis (UC) and Crohn's disease. UC primarily affects the colon while in Crohn's disease inflammation can occur anywhere along the GI tract, although both disorders present with similar symptoms.

ARDX is currently screening TGR5 agonists that can stimulate GLP-2 in rodent models of IBD. These product candidates have demonstrated low systemic exposure with no excess gallbladder filling in animal models. Excess gallbladder filling is a key limitation of systemic TGR5 agonists due to the increased risk of gallstones.

TGR5 agonists in development are often combined with dipeptidyl peptidase (DPP) IV inhibitors due to a synergistic benefit. DPP IV inhibition results in increased GLP-2 levels in circulation since DPP IV degrades GLP-2. When combined with a DPP IV inhibitor, ARDX's TGR5 agonists have demonstrated greater activity in animal models of IBD and a significant reduction in various measures of disease severity in animal models of colonic inflammation.

There is a large unmet need in both Crohn's and UC, with many patients requiring surgery that leaves them with a significantly reduced quality of life. ARDX has estimated that in the US there are 435,000 patients with Crohn's and 400,000 patients with UC, with about 60% of Crohn's and 15% of UC patients having the disease progress to surgical resection of the colon or affected intestinal segment.

ARDX's TGR5 agonists could also show benefit in short bowel syndrome (SBS), a condition in which malabsorption occurs because of the physical loss or loss of function of a portion of the intestines. SBS may be congenital or acquired as a result of disease or surgical resection. Patients with SBS are typically dependent on life-long IV parenteral nutrition. GLP-2 has demonstrated efficacy in SBS, as seen by the approval of Gattex (teduglutide) from NPS (NPSP, OUTPERFORM). Gattex is an injected recombinant GLP-2 analog that improves intestinal absorption of fluids and nutrients and reduces patient dependence on parenteral nutrition.

Due to the early status of the RDX009 program, we are not forecasting when a TGR5 agonist will enter the clinic. As the most advanced wholly-owned product candidate in its pipeline, we believe ARDX could seek to develop the program internally. If the company decides to partner it instead, we expect the stronger financial position of the company post-IPO should result in better terms compared to their prior licensing agreements.

RDX013

The RDX013 program is evaluating small-molecule oral drug candidates for the treatment of hyperkalemia, a common clinical problem in CKD patients that is characterized by potassium retention. Hyperkalemia is currently treated with potassium binders, which carries a high pill burden similar to phosphate binders. The RDX013 drug candidates are designed to target potassium transporters in the GI tract in order to enhance potassium secretion in the colon. These drug candidates could be used as a single agent or in combination with potassium binders for enhanced effect and reduced pill burden.

We note that Relypsa (RLYP, OUTPERFORM) is developing patiromer, a non-absorbed oral potassium binder to treat hyperkalemia. Patiromer has demonstrated efficacy in a Phase III trial in CDK patients with elevated serum potassium levels. We expect RLYP to submit an NDA for patiromer in Q3:14.

RDX020

The RDX020 program is evaluating small-molecule oral drug candidates that modulate chloride transport in the GI tract. ARDX is currently screening compounds that are non-systemic and can target transporters on the surface of the intestines that are responsible for moving chloride from the lumen of the small intestine to within the intestinal mucosa and moving bicarbonate ions in the opposite direction. The goal of the program is to identify a lead candidate that can limit the uptake of dietary chloride while limiting the loss of bicarbonate, which could result in reduced fluid overload and an improvement in metabolic acidosis in CKD patients.

Management

Figure 13: Executive Team

Title	Biography
Michael Raab, President and CEO	Mr. Raab has been President and CEO of ARDX since 2009. Previously, he was partner at New Enterprise Associates. Prior to that he spent 15 years in commercial and operating leadership roles in the biopharma industry. This experience includes serving as a SVP of Therapeutics and GM of the Renal Division at Genzyme (now Sanofi), where he launched and oversaw the sales growth of sevelamer. Mr. Raab has a B.A. from DePauw University.
Dominique Charmot, CSO	Mr. Charmot is a co-founder of ARDX and has served as CSO since 2007. Mr. Charmot has over 30 years of experience in the chemical and life sciences industries. This experience includes co-founding Ilypsa in 2003 (acquired by Amgen in 2007). Mr. Charmot has a M.S. in Chemical Engineering from Chimie ParisTech and a Ph.D. in Polymer Chemistry from ESPCI ParisTech.
Mark Kaufmann, CFO	Mr. Kaufmann has served as CFO of ARDX since May 2014, having previously served as the company's Chief Business Officer since 2011. Mr. Kaufmann has over 20 years of business and corporate development experience in the biopharma industry. This experience includes serving as President and CEO of Allostera Pharma and President and CEO of Celmed BioSciences. Mr. Kaufmann has a B.A. in Biochemical Sciences from Harvard University and a M.B.A. from the University of Michigan.

Source: Company data, Wedbush Securities, Inc.

Financial Model

ARDX raised approximately $60.8M in its June 19 IPO after deducting discounts and expenses. This figure includes proceeds from the underwriter's option, which has been exercised. We expect ARDX has $98M in cash and equivalents currently and 18.5M common shares outstanding.

With partners funding the development of its lead programs, and assuming consistent achievement of milestones under its partnership agreements, we forecast ARDX to have little cash burn going forward. Although it is conceivable for ARDX to avoid further capital raises going forward, we include a financing event in 2017/2018 to fund expanded clinical activities. As of the end of Q1:14, ARDX had 37 full-time employees, including 30 in R&D.

Figure 14: Financial Forecast to 2022

7/13/2014
Ticker: (ARDX:Nasdaq)
Ardelyx, Inc

Wedbush PacGrow Life Sciences
David M. Nierengarten, Ph.D.
415-274-6862

	2012	2013	Q1	Q2	Q3	Q4	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E
Revenues:															
US Product Sales	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$10,264	$119,751	$277,496	$517,752	$800,125
ex-US royalties	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$5,482	$26,086	$52,235	$87,696
Licensing and other revenue	$3,182	$8,063	$3,236	$5,609	$5,609	$5,609	$20,063	$39,578	$84,720	$52,284	$52,284	$66,000	$66,000	$42,000	$42,000
Collaborative development revenue	$2,228	$20,865	$5,314	$5,580	$5,859	$6,152	$22,904	$42,606	$65,305	$79,379	$89,630	$97,018	$105,015	$113,672	$123,042
Total Revenues	**5,410**	**28,928**	**8,550**	**11,189**	**11,468**	**11,761**	**42,967**	**82,184**	**150,025**	**131,663**	**152,178**	**288,251**	**474,598**	**725,659**	**1,052,863**
Cost and Expenses:															
Cost of Sales	0	0	0	0	0	0	0	0	0	0	1,026	11,975	27,750	51,775	80,012
R&D	10,184	28,093	7,637	8,042	8,469	8,918	33,066	56,436	101,988	154,283	192,248	226,571	268,573	320,160	383,729
SG&A	4,031	3,700	1,377	1,460	1,547	1,640	6,024	7,605	9,601	12,121	17,869	58,483	97,919	157,983	228,576
Total Operating Expenses	**14,215**	**31,793**	**9,014**	**9,502**	**10,016**	**10,558**	**39,090**	**64,041**	**111,589**	**166,404**	**211,143**	**297,029**	**394,242**	**529,918**	**692,317**
Operating Income (Loss)	(8,805)	(2,865)	(464)	1,687	1,452	1,202	3,877	18,143	38,436	(34,741)	(58,965)	(8,778)	80,356	195,741	360,545
Net Interest Income (Expense)	(30)	(52)	(4)	249	736	752	1,734	3,219	4,235	4,840	4,941	3,485	3,808	5,999	10,572
Other non-operating Income (Expense)	(950)	(3,506)	(2,603)	9,059	0	0	0	0	0	0	0	0	0	0	0
Income Before Income Taxes	(9,785)	(6,423)	(3,071)	10,995	2,188	1,955	5,611	21,363	42,671	(29,901)	(54,025)	(5,293)	84,163	201,740	371,117
Provision for Income Taxes	0	141	0	583	116	104	802	6,229	14,935	0	0	484	14,141	70,609	129,891
Net Income (Loss)	(9,785)	(6,564)	(3,071)	10,412	2,072	1,851	4,808	15,134	27,736	(29,901)	(54,025)	(5,777)	70,022	131,131	241,226
GAAP EPS	**(11.32)**	**(5.82)**	**(2.44)**	**3.86**	**0.11**	**0.10**	**1.06**	**0.81**	**1.48**	**(1.51)**	**(2.71)**	**(0.29)**	**3.48**	**6.48**	**11.87**
Total Shares Outstanding	864	1,128	1,256	18,529	18,529	18,529	18,529	18,629	18,729	19,829	19,929	20,029	20,129	20,229	20,329
Cash Burn	0	0	0	0	0	0	0	0	0	(12,271)	(51,270)	(16,607)	0	0	0
Cash Balance	32,903	34,435	33,221	98,141	100,326	101,980	101,980	116,717	143,565	168,495	117,225	100,617	151,967	252,732	457,410

Source: Wedbush Securities, Inc.

Covered Companies Mentioned

COMPANY	TICKER	RATING	PRICE TARGET	PRICE
Ironwood Pharmaceuticals, Inc.	IRWD	N	$11	$14.47
NPS Pharmaceuticals, Inc.	NPSP	O	$44	$30.53
Relypsa, Inc.	RLYP	O	$57	$23.15

RATING SCALE / DEFINITION

O = Outperform
N = Neutral
U = Underperform

Analyst Biography

David Nierengarten, Ph.D.

David is an Analyst covering stocks in the Biotechnology/Biopharmaceuticals/BioDefense sector. His prior sell-side research experience at Robert W. Baird & Co. covered biotechnology companies of all market capitalizations, with a focus on oncology and rare diseases.

David received his B.S. (Biochemistry) from the University of Wisconsin-Madison and Ph.D. (Molecular and Cell Biology) from the University of California-Berkeley.

David's Edge: David's early stage venture capital investing experience gives him a balanced perspective on developmental-stage biotechnology companies and their ultimate risk/reward potential. His experience on the other side of that equation in a clinical-stage, venture backed biotechnology company provides him with insights into corporate operations. The combination of experiences creates a focus on value creation in this event-driven space.

Analyst Certification
I, David M. Nierengarten, Ph.D., Dilip Joseph, Liana Moussatos, Ph.D., certify that the views expressed in this report accurately reflect my personal opinion and that I have not and will not, directly or indirectly, receive compensation or other payments in connection with my specific recommendations or views contained in this report.

Disclosure information regarding historical ratings and price targets is available at http://www.wedbush.com/ResearchDisclosure/DisclosureQ114.pdf

Investment Rating System:
Outperform: Expect the total return of the stock to outperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Neutral: Expect the total return of the stock to perform in-line with the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.
Underperform: Expect the total return of the stock to underperform relative to the median total return of the analyst's (or the analyst's team) coverage universe over the next 6-12 months.

The Investment Ratings are based on the expected performance of a stock (based on anticipated total return to price target) relative to the other stocks in the analyst's coverage universe (or the analyst's team coverage).*

Rating Distribution (as of March 31, 2014)	**Investment Banking Relationships (as of March 31, 2014)**
Outperform:54% Neutral: 43% Underperform: 3%	Outperform:22% Neutral: 2% Underperform: 0%

The Distribution of Ratings is required by FINRA rules; however, WS' stock ratings of Outperform, Neutral, and Underperform most closely conform to Buy, Hold, and Sell, respectively. Please note, however, the definitions are not the same as WS' stock ratings are on a relative basis.

The analysts responsible for preparing research reports do not receive compensation based on specific investment banking activity. The analysts receive compensation that is based upon various factors including WS' total revenues, a portion of which are generated by WS' investment banking activities.

Wedbush Equity Research Disclosures as of July 14, 2014

Company	Disclosure
Ardelyx Inc.	1,3,5,7
Ironwood Pharmaceuticals	1
NPS Pharmaceuticals Inc.	1,3,4,5
Relypsa	1,3,4,5,7

Research Disclosure Legend
1. WS makes a market in the securities of the subject company.
2. WS managed a public offering of securities within the last 12 months.
3. WS co-managed a public offering of securities within the last 12 months.
4. WS has received compensation for investment banking services within the last 12 months.
5. WS provided investment banking services within the last 12 months.
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7. WS expects to receive compensation for investment banking services within the next 3 months.
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9. WS has received compensation for products and services other than investment banking services within the past 12 months.
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12. The analyst maintains Contingent Value Rights that enables him/her to receive payments of cash upon the company's meeting certain clinical and regulatory milestones.

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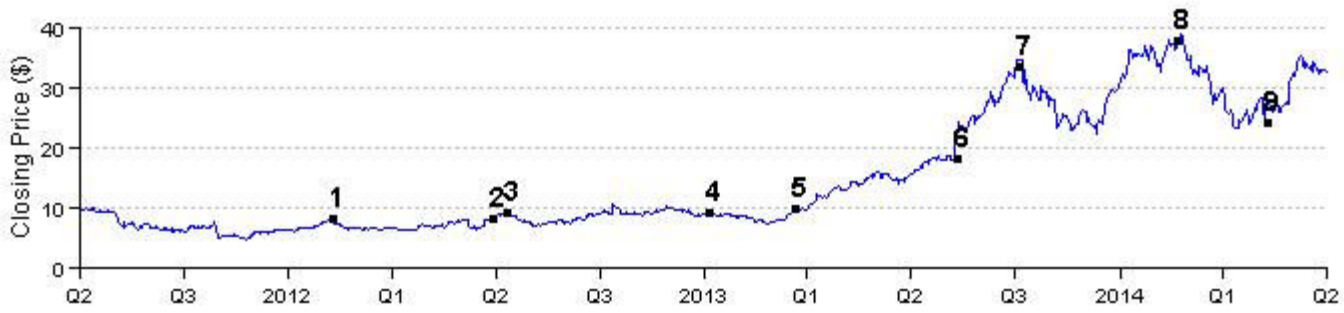
Wedbush disclosure price charts are updated within the first fifteen days of each new calendar quarter per FINRA regulations. Price charts for companies initiated upon in the current quarter, and rating and target price changes occurring in the current quarter, will not be displayed until the following quarter. Additional information on recommended securities is available on request.

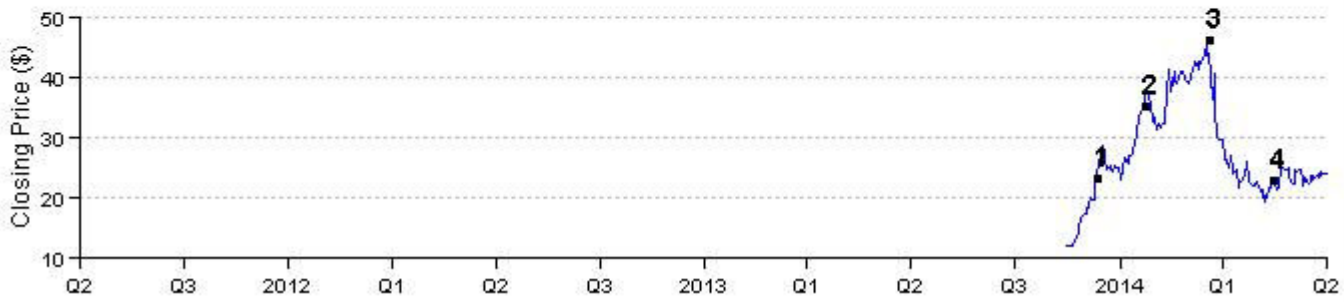
NPSP

1) 02/06/12 OUTPERFORM $14	2) 06/27/12 OUTPERFORM $17	3) 07/09/12 OUTPERFORM $18	4) 01/02/13 OUTPERFORM $19	5) 03/19/13 OUTPERFORM $22	6) 08/08/13 OUTPERFORM $29
7) 10/02/13 OUTPERFORM $43	8) 02/18/14 OUTPERFORM $47	9) 05/08/14 OUTPERFORM $44			



RLYP

1) 12/10/13 OUTPERFORM $34	2) 01/21/14 OUTPERFORM $46	3) 03/18/14 OUTPERFORM $56	4) 05/13/14 OUTPERFORM $57



* WS changed its rating system from (Strong Buy/Buy/Hold/Sell) to (Outperform/ Neutral/Underperform) on July 14, 2009.
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