Achaogen (AKAO)

November 3, 2014

Price
$10.50

Rating
NEUTRAL

12-Month Price Target
$9

Initiating Coverage with NEUTRAL Rating; Focus on Patients Most in Need

- **Achaogen is focused on developing antibiotics to treat patients with no other options**; its first candidate, plazomicin, is in development for patients with infections resistant to most classes of antibiotics. Plazomicin is being tested in infections where mortality rates hover around 30-50%.
- **Plazomicin being tested for superiority (mortality endpoint) in its pivotal study** compared to colistin, a "last resort" drug that was disregarded for years due to its tolerability. Colistin is generally dosed sub-optimally due to toxicity; *in vitro* and in animal models, plazomicin works faster and is more efficacious at relevant doses.
- **Strong scientific rationale, but questions remain**. In our view, the Phase III study may reach its superiority endpoint; we believe plazomicin has a superior profile to colistin. However, we believe plazomicin is paving new ground in its study, with clinical risk for it to achieve the high bar of superiority.
- **Superiority could lead to premium pricing for a niche population**. If plazomicin is found superior in its pivotal study, we believe Achaogen can command a premium price of $15,000 per course of therapy. We believe the cost is in line with treatment of a niche population; in our view, plazomicin will be reserved as drug of last resort.
- **Quiet 12-18 months expected for Achaogen as it executes**. Achaogen began enrollment in its pivotal study in September, interim analyses are planned; however, data isn't expected until 2017. We do not see much room for upside for shares in the near term.
- **We are initiating coverage with a NEUTRAL rating and $9 price target**. Our price target is achieved by applying a 5x multiple on plazomicin peak US sales of ~$225M and a 15x multiple on plazomicin peak royalty revenue from EU sales. We apply a discount rate of 35% due to what we perceive as a high degree of clinical risk for the program.

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Company Information	
Shares Outst (M)	17.7
Market Cap (M)	$186.0
52-Wk Range	$7.72 - $19.69
Book Value/sh	$4.28
Cash/sh	$4.21
Enterprise Value (M)	$111.5
LT Debt/Cap %	0%
Cash Burn (M)	$11.2

Company Description

Achaogen is a biopharmaceutical company based in South San Francisco, California, focused on antibiotics for multi-drug resistant infections.

FYE Dec	2013A	2014E			2015E		
REV	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	$3.5A	$6.0A		$6.0A	$4.0E		$5.8E
Q2 Jun	$4.5A	$5.2A		5.2A	$4.0E		5.8E
Q3 Sep	$5.3A	$6.0E		5.9E	$4.0E		5.8E
Q4 Dec	$5.2A	$6.0E		5.9E	$4.0E		5.8E
Year*	**$18.5A**	**$23.2E**		**$22.6E**	**$16.0E**		**$24.2E**
Change	-90%	25%			-31%		
	2013A	**2014E**			**2015E**		
EPS	ACTUAL	CURR.	PREV.	CONS.	CURR.	PREV.	CONS.
Q1 Mar	($10.00)A	($1.00)A		($1.00)A	($0.36)E		($0.93)E
Q2 Jun	($11.09)A	($0.20)A		(0.20)A	($0.37)E		(1.30)E
Q3 Sep	($0.38)A	($0.16)E		(0.27)E	($0.38)E		(1.14)E
Q4 Dec	($0.54)A	($0.21)E		(0.26)E	($0.39)E		(1.33)E
Year*	**($33.83)A**	**($1.57)E**		**($1.24)E**	**($1.51)E**		**($1.08)E**
P/E	--	--			--		
Change	-5222%	95%			4%		

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

Source: Thomson Reuters

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Investment thesis

Achaogen is a biopharmaceutical company based in South San Francisco, California, focused on antibiotics for multi-drug resistant infections. Its lead candidate plazomicin is a next-generation aminoglycoside in a pivotal study for patients with carbapenem-resistant (CRE) infections. The study is a superiority study against colistin, a drug of "last resort;" although we believe the rationale behind the study is sound, we believe there are various unknowns that add clinical risk to the trial. We believe the stock is fairly valued at these levels, we see little room for upside in the next 12-18 months with little news flow.

Valuation. We derive our $9 price target by applying a 5x multiple to potential ~$225M in US sales of plazomicin and a 15x multiple on royalties for plazomicin in the EU, discounted by 35%; we assume an ex-US partnership for plazomicin with tiered royalties up to 22%. We use a diluted share count of 19.5M, including options and warrants. We believe Achaogen is well capitalized to execute on the pivotal study of plazomicin; the company ended 2Q with $74M in cash. As a reminder, Achaogen has a partnership with BARDA that covers many costs of plazomicin development; we anticipate this contract will be extended next year. Beyond plazomicin, Achaogen has a pipeline of agents targeting *pseudomonas;* the compounds are in preclinical development and are not included in our valuation.

Risks to the attainment of our price target. The key risk to Achaogen is the failure of plazomicin to reach superiority in its pivotal study. Other risks include failure to enroll patients in its study or potential lack of uptake of plazomicin commercially due to increased competition expected for gram-negative infections in the coming years. There is also risk Achaogen's other programs will not reach human development.

Key points:

- **Achaogen focuses on patients in most dire need.** Achaogen's lead compound plazomicin is in development for patients with pneumonia or bloodstream infections who are resistant to most classes of antibiotics; the mortality in this population is 30-50%. We believe the need for new agents for these patients is clear.
- **Sub-optimal dosing of colistin opens the window for superiority, but risks remain.** Colistin is a drug of "last resort" due to its safety profile, but has been gaining use due to lack of other options. *In vitro,* the compound works against most multi-resistant strains; however, the compound is not dosed optimally in humans due to toxicity. In animal models plazomicin rapidly kills multi-resistant bacteria at doses used in humans; we believe there is strong scientific rationale to believe plazomicin will outperform colistin in the pivotal study. However, we believe there is still a high degree of clinical risk to the study as 1) plazomicin has not been tested before in this resistant population, 2) plazomicin levels have to be closely monitored to manage toxicity, which may limit efficacious exposure and 3) meropenem, a drug available for use in the pivotal study, has not been studied prospectively at high doses in this resistant population.
- **Quiet 12-18 months ahead as Achaogen gets its Phase III study up and running.** We believe there is not much news flow in the coming year to move Achaogen shares. We anticipate an interim look at the pivotal study for efficacy/futility in 2015 after about 95 patients have been enrolled; however, we believe it is likely the study will be continued as planned. There would be significant upside to shares if plazomicin could demonstrate superiority with such as small sample size. We see some downside risk if the interim analysis takes longer than expected.
- **Clear need for plazomicin, but reach likely limited.** In our view, if plazomicin can achieve superiority in its pivotal study, it should demand premium pricing. We believe the target population for plazomicin will be relatively small; the aminoglycoside class comes with toxicities that need to be monitored and managed; therefore, we believe the drug will be used as a last resort, as colistin is being used now. We believe the influx of new gram negative agents in the coming years will improve empiric therapy, narrowing plazomicin use to the most severe cases.

Figure 1: Upcoming catalysts

Timing	Event	Program
H2:15	Phase III Interim Analysis #1	Plazomicin (CRE)
Q4:15	Supportive efficacy trial top-line data (sep trial)	Plazomicin (CRE)
2015	IND for LpxC inhibitor or antimicrobial antibody	Pseudomonas Aeruginosa
H2:16	Phase III Interim Analysis #2	Plazomicin (CRE)
H1:17	Phase III top-line	Plazomicin (CRE)

Source: Company data, Wedbush Securities, Inc.

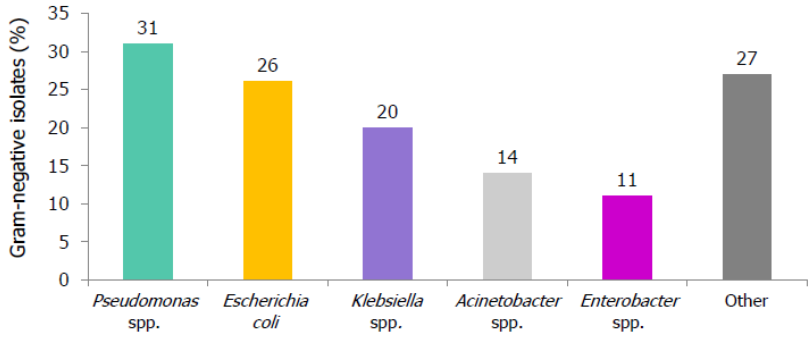
Gram-negative (-) antibacterial resistance an "URGENT" need

Gram-negative bacteria are found in various hospital-acquired infections including abdominal, urinary, skin and lung infections, with *pseudomonas, e. coli and klebsiella* the most prevalent bugs (Figure 2). Resistance is growing against antibiotics to treat these infections and there is a dearth of new drugs to treat these "superbugs." In 2008, the Infectious Disease Society of America coined the acronym "ESKAPE" to represent the six pathogens seen as the greatest threat in hospital infections. Two are gram-positive; in our view, the influx of new agents for gram-positive infections in the past year has turned focus to the rest of the list.

- *Enterococcus faecium* (E): A gram-positive anaerobic pathogen with inherent resistance against β-lactamase antibiotics including imipenem, a carbapenem. Isolates are found in a majority of vancomycin-resistant enterococci (VRE) in the US.
- *Staphylococcus aureus* (S): Gram-positive strain known for its resistant form (MRSA).
- *Klebsiella pneumoniae* (K): Gram-negative strain, part of the *enterobacteriaceae* family, resistant to various cephalosporins and carbapenems. Presence of extended spectrum β-lactamase (ESBL) containing *klebsiella* is a predictor of prolonged hospital stays and increased mortality. In the US, presence of *K. pneumoniae carbapenemase* (KPC), a serine carbapenemase leading to carbapenem resistance has led to epidemics in various hospitals. Carbapenems are generally drugs of last resort and resistance to the class has led to use of older, toxic antibiotics due to lack of other options. *E. coli*, another member of the *enterobacteriaceae* family, has also become more carbapenem-resistant.
- *Acinetobacter baumannii* (A). An opportunistic gram-negative pathogen with a high level of environmental persistence (up to 5 months), opening up the potential for contamination. *Acinetobacter* is inherently resistant to various antibiotics by possessing efflux pumps and expressing low numbers of pores to allow antibiotics in. The pathogen also has various β-lactamases including metallo- β-lactamases and carbapenemases.
- *Pseudomonas aeruginosa* (P). A gram-negative pathogen common in cystic fibrosis patients; it is the leading cause of gram-negative hospital-acquired infections.
- *Enterobacter cloacae* (E). A gram-negative pathogen found most often in urinary and respiratory infections; pathogens can be carbapenem-resistant.

There are a reported 2M cases of illness caused by antibiotic resistance in the US each year and ~23,000 deaths. The go-to class of antibiotics for multi-drug resistant (MDR) bacteria, carbapenems, is decreasing in efficacy due to resistance – spurring the CDC to categorize carbapenem-resistant enterobacteriaceae (CRE - a large class of gram-negative-resistant bacteria, including *e. coli* and *klebsiella*) as an "urgent" health threat. Although at the moment, there are only ~9,000 CRE infections a year in the US, mortality is high in patients with these infections due to a lack of treatment options. Other MDR bugs such as *acinetobacter*, *pseudomonas* and ESBL producing *enterobacteriacease* have been classified at a threat level of "serious".

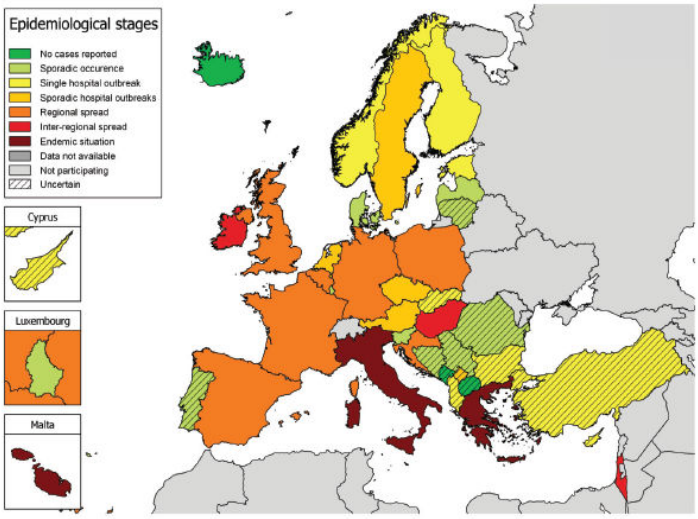
Figure 2: Pathogens found in the ICU, 2007



Source: Company data, Wedbush Securities, Inc.

In Europe, a recent report demonstrated the growing occurrence of carbapenemase-producing *enterobacteriaceae* (Figure 3); prevalence of these pathogens has increased since last surveyed in 2010. The state of carbapenem-resistant *a. baumannii* appears to be more dire (Figure 4). Resistance rates are higher in Europe than the US, likely due to greater carbapenem use.

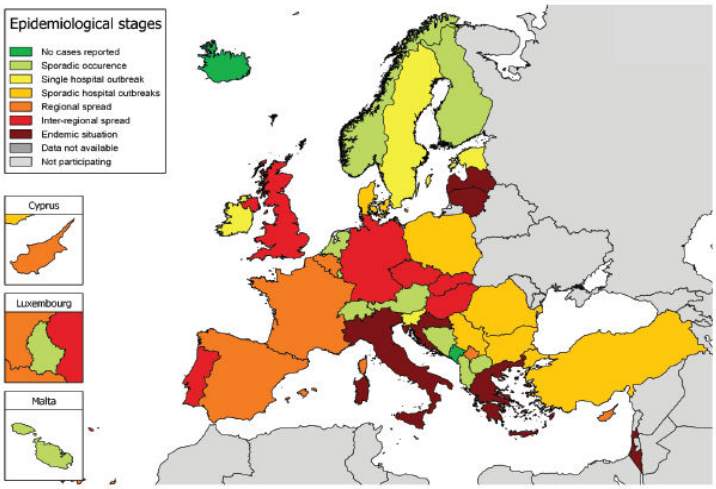
Figure 3: CRE prevalence



In some countries, the epidemiological stage might not represent the exact extent of the spread of CPE as it is a subjective judgment by national experts. Results presented here reflect the uncertainty at the time of the survey.

Source: Company data, Wedbush Securities, Inc.

Figure 4: *Acinetobacter baumannii prevalence*



The stage designations for CRAb should be taken with caution for all 38 participating countries. Most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country, because at the time of the survey, surveillance and reporting of CRAb are not performed routinely in their country, and because fewer national reference laboratory structures for CRAb exist in European countries.

Source: Company data, Wedbush Securities, Inc.

Treatment paradigm. The treatment of infections associated with gram-negative pathogens varies from hospital to hospital; however, overall, patients are treated empirically, without identification of specific pathogens. On average, empiric therapy is successful in about 75% of patients, with the remainder failing first-line therapy. Choice of empiric therapy is determined by local susceptibility data and previous experience. Type of infection also determines who treats the patient, which also influences choice of therapy. Generally, within the first 48 hours of treating with an antibiotic, it is known whether or not a patient in responding to therapy.

Different indications present different opportunities. Each infection type, in our view, presents different opportunities in the gram-negative space, as each indication involves varying seriousness of infection, types of pathogens present and different treatment paradigms. We review five of the major gram negative indications and unmet needs for each; we focus on the US opportunity, although we believe the EU opportunity is about the same in size with higher resistance rates.

Figure 5: Overview of some gram-negative infections

	Complicated intra-abdominal infections (cIAI)	Complicated urinary tract infections (cUTI)	Skin infections (ABSSSI)	Lung infections/pneumonia (HAP/VAP)	Bacteremia (Blood stream infections)
Patient/year (US)	1.7M	4M	3M	1.1M	1.2M
Treated empirically for gram negative infection:	70%	78%	20%	78%	30%
Gram positive pathogens	38%	n/a	80%	24%	65%
First line failures:	27%	24%		*pseudomonas* 20-30%	*staphylococcal* 50%
Most prevalent pathogens:	*e. coli* 45%-60%	*e. coli* 45%	*MRSA* 60%	*acinetobacter baumannii* 5-15%	*enterococcus spp* 9%
	klebsiella 22-25%	*klebsiella* 19%	*e. coli* 4%	*enterobacteriaceae* 15-25%	*e. coli* 6%
		pseudomonas 19%	*k. pneumoniae* 4%	*e. coli* 11%	*klebsiella spp* 5%
				MRSA 5-20%	*pseudomonas* 4%
Treatment paradigm:	In hospital only	In hospital/outpatient	In hospital/outpatient	IV only; combination therapy	Combination therapy
Days of therapy:	6-9 days	10-14 days	7-14 days	10-14 days	7-14 days
Drugs used:	cephalosporins	cephalosporins	glycopeptides	antipseudomonal cephalosporin or carbapenem	vancomycin, cepholasporins
	carbapenems	quinolones	oxazolidinones	oxazolidinones	carbapenems
			cephalosporins	piperacillin/tazobactam + fluoroquinolone	tigecycline, colistin, amikacin

Source: Company data, Wedbush Securities, Inc.

Complicated intra-abdominal infection (cIAI). cIAIs are defined as infection that extends into the peritoneal space with associated abscess formation or peritonitis (inflammation of the abdominal cavity). There are about 1.7M patients in the US with cIAI each year. Generally, cIAI is defined by its severity and usually observed in the emergency room, general ward of the hospital or in the ICU. Infections can be post-surgery (hospital acquired) or community acquired; hospital-acquired infections have higher mortality rates.

Over a third of infections are caused by a mix of gram-positive and gram-negative bacteria; gram-positive content increases when the infection is community-acquired. Infections are usually treated in the hospital with surgery/containment procedure; treatment time with antibiotics corresponds to time spent in recovery in the hospital.

A recent observational study confirmed expected pathogens for cIAI, with ESBL producing pathogens the most commonly found drug-resistant strains. Carbapenem-resistant *klebsiella pneumonia* and *pseudomonas* strains were also isolated, but less prevalent. ESBL-containing bacteria were more prevalent in samples taken after surgery, suggesting that antibiotics used first line likely knock out many of the non-ESBL pathogens.

Generally, surgeons are the decision makers for antibiotic use in cIAI. Their choice is driven by knowledge of pathogen profiles in the hospital and what has worked in their hands previously; cost appears to be less of a factor in this setting.

Unmet needs:

- cIAIs are the second-leading cause of infectious mortality in the ICU
- ESBL-containing species appear to be transmitted in the gut, making many cIAI infections resistant to third- and fourth-generation cephalosporins; new antibiotics are needed to combat ESBLs.

Complicated urinary tract infection (cUTI). cUTIs are the most prevalent gram-negative infections found, with an estimated 150M in the world each year, including uncomplicated cases. For complicated cases in the hospital setting, 4M patients per year present in the US for treatment. Complicated infections are often associated with foreign bodies such as catheters, pyelonephritis, inflammation in the pelvis, or other pathologies. There has been a shift towards outpatient therapy over time, limiting hospital stays with the use of fluoroquinolone therapy; however, resistance to this class is approaching 25-30%. Drugs available to treat quinolone-resistant strains are available as IV only, most being administered multiple times a day, leading to increased hospital stays. We believe an oral compound that treats resistant strains could make inroads into the multi-billion dollar opportunity defined by the branded quinolones.

Generally patients are seen in the hospital and treated by someone in the ER, a hospitalist or internist with an infectious disease physician or urologist called in for a consult.

Unmet needs:

- Drugs to treat quinolone-resistant patients
- An option for outpatient therapy for patients with MDR pathogens

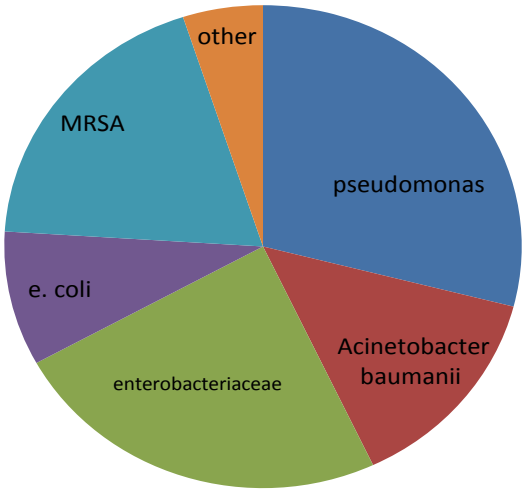
Skin infections. Skin infections are a large market, with about 3M cases in the US each year. The large majority of complicated skin infections (ABSSSI) are gram-positive. Pathogens vary by wound type, with burn wounds more likely to harbor gram-negative bugs. The rise of MRSA to about 60% in most hospitals has led to agents against MRSA being used as empiric therapy. Skin infections are treated both in and outpatient, depending on severity of disease and co-morbidities; step-down therapy is preferred when possible.

Lung infections. There are about 1.1M patients treated each year for lung infections – community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP). Mortality rates for HAP/VAP are high (20-50%) and infections account for 25% of all ICU infections. The most prevalent pathogen is *staphylococcus aureus*, followed *by pseudomonas aeruginosa* (Figure 6). Most patients are treated in the ICU by critical care physicians. Generally the origin of infection can help a physician know if the infection is gram-positive or gram-negative; combination therapy is standard to cover all of the prevalent pathogens.

Unmet needs:

- Drugs to combat resistant pathogens such as MRSA, pseudomonas and acinetobacter

Figure 6: Pathogens common in HAP/VAP



Source: Company data, Wedbush Securities, Inc.

Bloodstream infections. There are about 1.2M patients treated in the US for bloodstream infections each year. About 65% of these infections are caused by gram-positive organisms; however, if an infection begins as a cUTI or cIAI, it is likely caused by gram negative pathogens. Patients with extended hospital stays or ICU stays are at higher risk for carbapenemase producing gram-negative *klebsiella pneumonia* (KPCs); mortality rates are high in this population. Resistant cases are generally treated with combination therapy including a carbapenem with colistin or tigecycline.

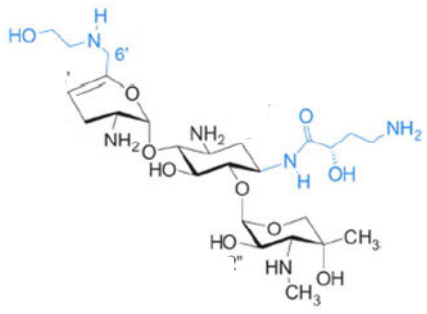
Unmet needs:

- Drugs to treat the growing number of resistant infections.

Plazomicin: Laser focus on CRE infections

Plazomicin is a next-generation aminoglycoside active against strains of bacteria with enzymes that deactivate other members of the aminoglycoside class such as amikacin (Figure 7). Aminoglycoside resistance is driven by aminoglycoside-modifying enzymes (AMEs); plazomicin is designed to sterically block AME sites of action.

Figure 7: Plazomicin (left) compared to the aminoglycoside class against CRE pathogens



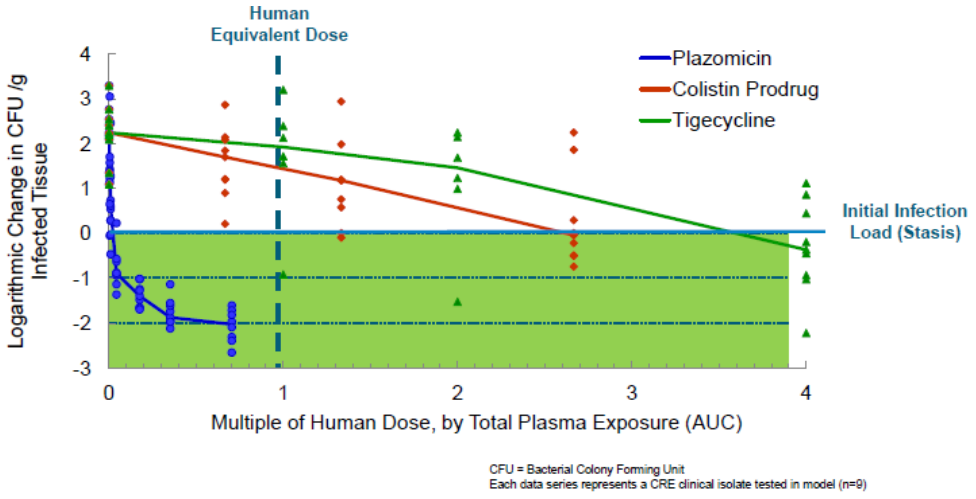
Compound	Class	N	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Plazomicin	**Aminoglycoside**	**807**	**0.5**	**2**
Gentamicin	Aminoglycoside	807	4	128
Amikacin	Aminoglycoside	806	32	64
Ciprofloxacin	Fluoroquinolone	767	8	8
Ceftazidime	Cephalosporin	510	64	>128
Piperacillin/tazobactam	Penicillin/Beta-lactamase inhibitor	731	>128	>128
Tigecycline	Glycycline	723	1	2
Colistin/polymyxin B	Polymyxin	692	1	4

Source: Company data, Wedbush Securities, Inc.

Drugs of last resort – more is needed. Increasing resistance, specifically carbapenem-resistant *enterobacteriaceae* (CRE) has led to increasing mortality from hospital-acquired bacterial infections, especially for serious bloodstream infections (bacteremia) and pneumonia. When patients are carbapenem-resistant, combinations of drugs are typically used - either meropenem or tigecycline are dosed in combination with colistin. However, mortality can be as high as 40-50% in patients with CRE bacteria not susceptible to carbapenem therapy.

Colistin fell out of use due to nephrotoxicity issues; it has returned to favor only due to lack of other options. Colistin is bactericidal with high efficacy *in vitro*; however, this does not translate to the clinic. One reason for this is that colistin is dosed as a pro-drug, colistin methanesulfonate (CMS); colistin is the active form. CMS is safer, but it does not have anti-bacterial activity; the compound must be hydrolyzed to be active; high doses are needed to gain target attainment at the site of infection with the active drug. However, this is often not achievable due to toxicity. Therefore, there is a need for therapy that can kill CRE pathogens and rapidly get to the site of infection at efficacious levels. Achaogen has demonstrated *in vivo* in a murine model that at the dose used in humans, colistin does not reach bactericidal levels (Figure 8). In contrast, plazomicin appears to be rapidly bactericidal and reduce levels of bacteria in this model.

Figure 8: Murine model of CRE infection



Source: Company data, Wedbush Securities, Inc.

Pivotal study looks for superiority

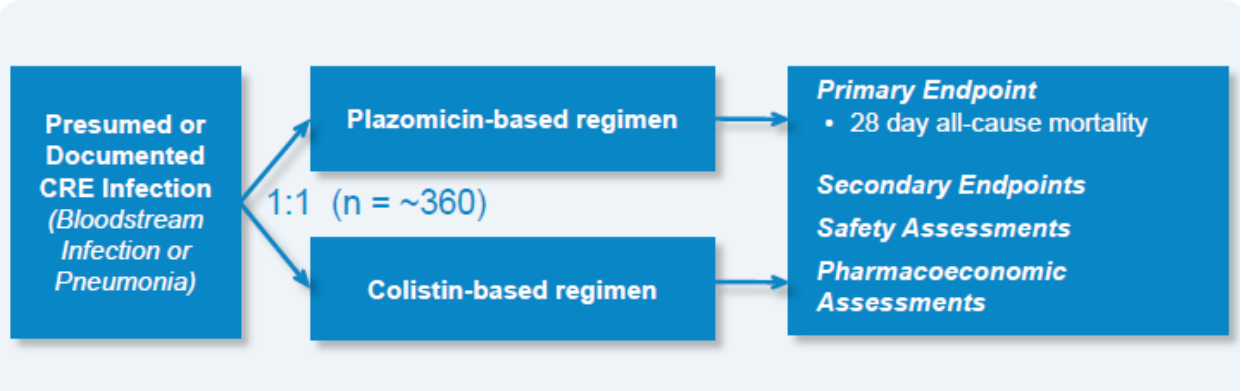
Achaogen believes the sub-optimal dosing and efficacy of colistin sets up the opportunity for plazomicin to significantly improve outcomes in patients with CRE infection. The company is running a superiority study of plazomicin versus colistin in patients with CRE bloodstream or pneumonia infections; drugs will be used in combination with meropenem or tigecycline (Figure 9); the trial is being conducted under a special protocol assessment (SPA) with the FDA. The primary endpoint is superiority for all-cause mortality at day 28 with secondary endpoints such as time to death, mortality at 14 days, and clinical response at end of treatment or test of cure. The study will enroll 286 patients with confirmed CRE infection defined as pathogens non-susceptible to meropenem (MIC ≥ 4ug/mL). Patients will be enrolled if they have a previously confirmed case of CRE; this will then be validated in a central laboratory. Patients can also be admitted to the study if they test positive for a case of presumed CRE based on a rapid test (12-36 hour turnaround) for carbapenemase production; about 80% of these patients will be confirmed as CRE. Patients enrolled but not meeting CRE criteria will be evaluated for safety, but will not count in the primary endpoint analysis. The company believes it will have to enroll about ~360 patients to get 286 confirmed CRE cases, mirroring the ~80% accuracy of the rapid diagnostic.

The study will have two interim analyses for efficacy and futility expected in mid-15 and mid-16, when one third and two thirds of confirmed CRE patients hit the end of study on day 28, respectively. Patient numbers will not be adjusted at the time of interim analyses. The study is powered at 70% assuming 35% mortality on the colistin arm with an absolute reduction of 12% in the plazomicin arm; if there is a 14% reduction, the study would be powered at 80%. These parameters are based on a meta-analysis of mortality in

bloodstream infections where individuals with pathogens not carbapenem susceptible (MIC ≥ 4ug/mL) had an increase in mortality of 21% compared to patients with bacteria that are carbapenem susceptible.

Patients will be stratified by severity (APACHE score) and infection type; only those with an APACHE score of 15-30 will be enrolled – a sick population with mortality rates in the ICU of ~30-50%, in line with Achaogen's assumptions for the study. Patients with colistin-resistant infections will be excluded; these patients cannot be randomized to colistin and would disrupt the blinding of the study.

Figure 9: Pivotal trial design



Source: Company data, Wedbush Securities, Inc.

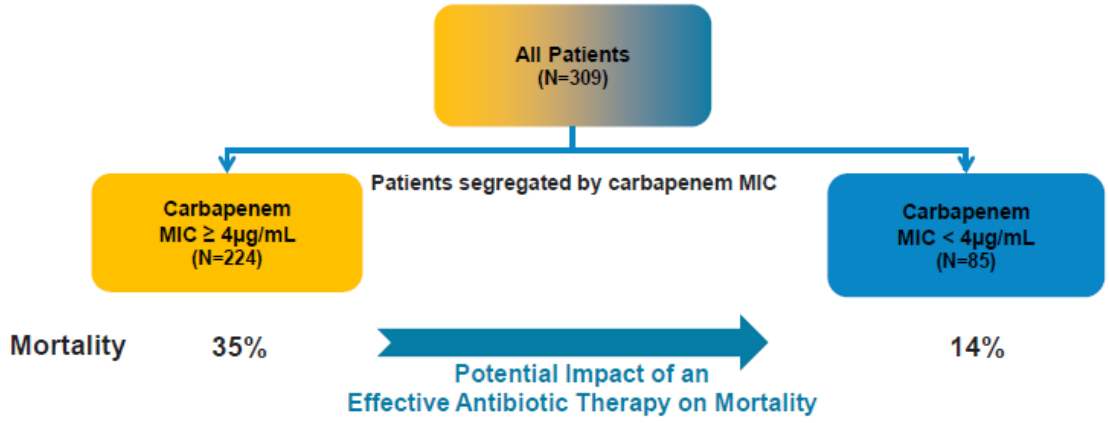
Beyond efficacy endpoints, plazomicin levels will also be monitored; plazomicin is an aminoglycoside; side effects expected with its class include nephrotoxicity, ototoxicity and less often, neuromuscular blockage. Achaogen is developing an assay for the pivotal study to allow for safe dosing of the drug; this assay will be a companion diagnostic for the drug is it is approved.

Plazomicin will be dosed first at 15mg/kg over a 30 minute infusion; renal function will be monitored and dosing adjusted after the first dose with a therapeutic drug management (TDM) strategy. Meropenem will be dosed every eight hours with either 1g or 2g; in practice the high dose is generally used in resistant patients. Dose adjustments will be allowed for varying renal function per the meropenem label.

Risks to superiority. In our view, there is good scientific rationale to support plazomicin's superiority to colistin. However, we believe there are unknowns to the study that in our view make the trial high risk.

- **Mortality rates overall**. The pivotal study is powered for 35% mortality in the colistin arm – if mortality rates are lower than anticipated, it could make it difficult to see a statistically superior effect of plazomicin. However, our analysis of the literature suggests that 35% mortality is in line with what has been observed across various hospitals for patients with CRE pathogens. Therefore, we believe there is a low chance this would derail the study.
- **Meropenem effectiveness**. In the pivotal study, physicians can use meropenem in combination with either colistin or plazomicin. All patients counted towards the primary endpoint will have pathogens with a meropenem MIC value of ≥ 4ug/mL, a threshold that appears to delineate effectiveness (Figure 10). Achaogen has used this metric to help power its pivotal study. That being said, this hypothesis has never been tested in a randomized prospective controlled study; therefore, it is difficult to predict response to meropenem in the study and we believe it is possible responses could vary. We note that there are literature reports that using a high dose (2g) of meropenem and long infusion times may increase success of meropenem to 60% in patients with MIC values of 8ug/mL; bactericidal target attainment may be reached with high probability. If meropenem outperforms expectations in this resistant population, it may obscure the benefit of plazomicin.
- **Plazomicin effectiveness**. In our view, *in vitro* and animal data suggest plazomicin should be rapidly bactericidal in patients with CRE pathogens. However, the extent of this effect and how it translates into an outcome such as mortality is unknown. In our view, this adds risk to the study. We believe the supportive efficacy study scheduled to report data in 2015/2016 may help to de-risk the pivotal trial from this perspective.

Figure 10: Meta-analysis of mortality in patients with CRE bloodstream infections



Source: Company data, Wedbush Securities, Inc.

Supportive efficacy study to build safety database and potentially de-risk the pivotal study. Achaogen is planning to begin a supportive study for plazomicin; the FDA has required 300-350 patients to be dosed with plazomicin prior to approval. The study will be an open-label single-arm study of about 50 patients. The details on the study are not finalized; the study will likely look at populations with the highest need, such as colistin-resistant patients. As a reminder, due to blinding of the pivotal study colistin-resistant patients are excluded from enrollment. However, rates of colistin resistance are low, therefore, we believe this population will only account for a subset of the study to allow for rapid enrollment. We anticipate greater clarity on a trial design after Achaogen speaks with FDA and EMA this quarter.

In our view, data from this study, expected in late 2015/early 2016, may de-risk the pivotal study; it will be the first look at plazomicin efficacy in a highly resistant population.

Phase 2 study established clinical efficacy in a different population. Achaogen conducted a study of plazomicin against levofloxacin in cUTI infections. Patients were randomized to 10mg/kg or 15mg/kg a day of plazomicin versus levofloxacin in the first part of the study; the second part of the study only administered plazomicin at 15mg/kg. Efficacy was determined by clinical and microbiological results at test of cure (TOC) in the modified intent to treat (mITT) population (all patients with at least one pathogen) and microbiologically evaluable (ME) population (patients matching inclusion criteria with a sample at the TOC time point). The cure rates in the two populations differ due to lack of samples at the TOC visit; however, we believe overall the drugs seem similar. Most of the isolates were not multi-drug resistant (MDR); we believe this may be due to 54% of patients coming from the US where resistance is lower than other geographies.

Side effects were similar between arms overall (Figure 12); AEs of specific interest for plazomicin, such as oto- and nephrotoxicity were monitored. One patient had mild transient vertigo and one had irreversible unilateral tinnitus (mild). There were two adverse events of mild renal function impairment, including increases in serum creatinine that returned to baseline after treatment; two other increases in creatine for patients on plazomicin were not considered adverse events.

Figure 11: Phase II cUTI trial data

By-Patient Microbiological Response	Plazomicin 10 mg/kg	Plazomicin 15 mg/kg	Levofloxacin 750 mg
Microbiologically Evaluable (ME)			
N	7	35	21
Eradication, n (%)	6 (86%)	31 (89%)	17 (81%)
Modified Intent-to-Treat (MITT)**			
N	12	51	29
Eradication, n (%)	6 (50%)	31 (61%)	17 (59%)

Source: Company data, Wedbush Securities, Inc.

Figure 12: Adverse events from the Phase II cUTI trial

Adverse Event, number of patients (%)	Plazomicin 10 mg/kg (22 patients)	Plazomicin 15 mg/kg (74 patients)	Levofloxacin 750 mg (44 patients)
Headache	2 (9.1%)	6 (8.1%)	3 (6.8%)
Diarrhoea	0 (0.0%)	4 (5.4%)	2 (4.5%)
Dizziness	0 (0.0%)	4 (5.4%)	0 (0.0%)
Nausea	0 (0.0%)	4 (5.4%)	0 (0.0%)
Vomiting	0 (0.0%)	4 (5.4%)	1 (2.3%)
Gastritis	1 (4.5%)	2 (2.7%)	0 (0.0%)
Abdominal pain upper	0 (0.0%)	1 (1.4%)	1 (2.3%)
Cough	1 (4.5%)	1 (1.4%)	1 (2.3%)
Dyspepsia	1 (4.5%)	1 (1.4%)	1 (2.3%)
Dyspnoea	1 (4.5%)	1 (1.4%)	0 (0.0%)
Hypokalaemia	0 (0.0%)	1 (1.4%)	2 (4.5%)
Insomnia	0 (0.0%)	1 (1.4%)	1 (2.3%)
Dysgeusia	0 (0.0%)	0 (0.0%)	2 (4.5%)
Hypertension	1 (4.5%)	0 (0.0%)	1 (2.3%)
Pruritus	1 (4.5%)	0 (0.0%)	2 (4.5%)
Tachycardia	1 (4.5%)	0 (0.0%)	1 (2.3%)
Upper respiratory tract infection	0 (0.0%)	0 (0.0%)	2 (4.5%)

Source: Company data, Wedbush Securities, Inc.

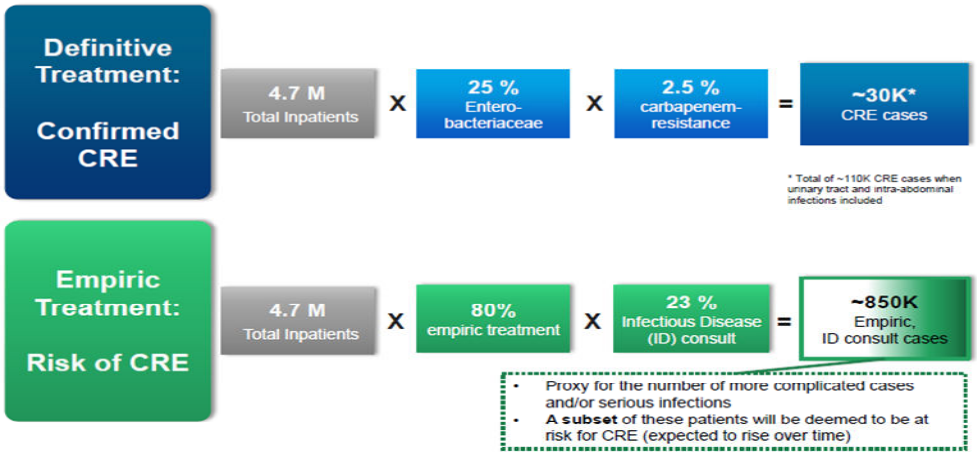
Path to market and commercialization

Achaogen anticipates interim analyses from its Phase III study in 2015 and 2016 with final data in 2017. We believe there is some risk to these timelines depending on rates of CRE infection and enrollment rates. In our view, approval of gram-negative compounds such as Cubist's Zerbaxa and Astra Zeneca's/Actavis's CAZ AVI in the US in December 2014 and 1Q15, respectively, may decrease the number of patients eligible for enrollment in the plazomicin pivotal study.

If the study reaches superiority, we believe the regulatory path should be straightforward. There is also potential room for upside if the company were to receive breakthrough designation based on supportive efficacy data such as efficacy in colistin resistant patients – the drug may see early use in that instance. We do not include this possibility in our valuation at this time.

Achaogen believes it can treat patients with confirmed CRE or those at risk of CRE (Figure 13). In our view, faster diagnostic tests are needed to identify CRE patients; even Achaogen's rapid test has a 12- to 36-hour turnaround. We believe there is potential for such diagnostics to be developed by the time plazomicin hits the market in late 2018.

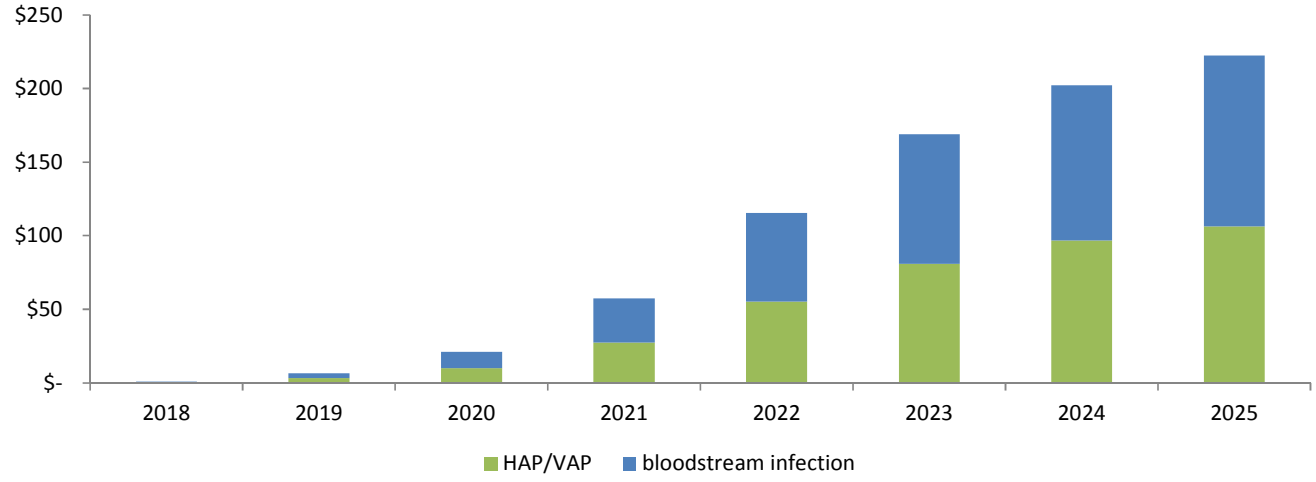
Figure 13: Patients with bloodstream infections and pneumonia; potential patient populations



Source: Company data, Wedbush Securities, Inc.

In our view, the safety profile of plazomicin and the monitoring needed to ensure safe dosing of the drug will keep it as a last resort; we believe the company will price the drug accordingly. We assume a gross price of $15,000 in the US with a 15% gross to net adjustment, assuming a hit on superiority in the Phase III study. We believe the influx of new agents for gram-negative infections will keep plazomicin as a last resort drug, limiting its use. We currently include only confirmed CRE cases as the potential market for plazomicin. We estimate close to half of these patients will be treated with plazomicin, although without clinical data it is hard to understand how the compound will fit into the treatment paradigm. We currently estimate peak revenue of ~$225M in the US in 2025 and ~$100M in the EU in 2026; we assume an ex-US partnership with a 22% royalty to Achaogen.

Figure 14: Revenue estimates for plazomicin US



Source: Company data, Wedbush Securities, Inc.

Beyond plazomicin

Achaogen suffered a setback in 2013 when its Phase I multiple ascending dose study for *pseudomonas, LpxC* inhibitor ACHN-975, was terminated due to inflammation at the injection site. The compound is from a new class of antibiotics inhibiting LpxC, an enzyme

needed in the outer membrane synthesis of gram negative bacteria (Figure 15). Achaogen believes the adverse events were likely due to distribution of charge across the molecule, leading to aggravation of the infusion site. It is working on a backup compounds with the same scaffold, but different charge distribution. Achaogen plans to file an IND in 2015 with human development to begin in 2016. The company is also working on an anti-*pseudomonas* antibody that may require only one injection for efficacy. Due to the early stage of these programs, we do not include them in our valuation.

Figure 15: In vitro profile of ACHN-975, LpxC inhibitor, against *pseudomonas*

Compound	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
ACHN-975	**0.25**	**1**
Tobramycin	1	>32
Ciprofloxacin	0.5	>4
Ceftazidime	8	>32
Imipenem	2	>16
Colistin	1	4

Susceptible
Non-Susceptible

Source: Company data, Wedbush Securities, Inc.

Intellectual property

Achaogen has not yet applied for QIDP status for plazomicin; however, the company intends to and will likely be granted QIDP status, giving it 10 years of US market exclusivity. Beyond QIDP, plazomicin is covered by one granted patent which will expire in 2031 before extensions. There is one US patent and various ex-US patents pending that should cover plazomicin through 2028 at least. As a reminder, Achaogen has a license agreement with Isis (ISIS, not covered) for plazomicin; we model a low-single-digit royalty of sales to ISIS in our model.

Management

Achaogen's management has experience in development and commercialization of various anti-infective products.

Figure 16: Management team

	Position	Prior experience
Kenneth Hillan, MB ChB	CEO	Genentech, Roche
Derek Bertocci	CFO	Accuray, Bioform, Visx
Ian Friedland MD	CMO	Cubist, Calixa, JNJ

Source: Company data, Wedbush Securities, Inc.

Figure 17: Board of directors

	Prior/current experience
Bryan E Roberts PhD	Venrock, Zeltiq Aesthetics, Ironwood
Chris Boerner PhD	Seattle Genetics, Dendreon, Genetech
John C Doyle	Castlight Health, Genentech
Kenneth Hillan, MB ChB	Genentech, Roche
Scott M Rocklage PhD	5AM Ventures, Cubist
Camille D. Samuels	Venrock, Versant Ventures
John W Smither	Kythera, Amgen
Christopher T Walsh PhD	Harvard Medical School

Source: Company data, Wedbush Securities, Inc.

Figure 18: Projected income statement for Achaogen

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Heather Behanna, Ph.D.

11/3/2014

Achaogen
Annual Financial Results & Projections
($ in thousands except per share data)

	FY:13A	Q1	Q2	Q3	Q4	FY:14E	FY:15E	FY:16E	FY:17E	FY:18E	FY:19E	FY:20E
REVENUES												
Plazomicin US	0	0	0	0	0	0	0	0	0	899	6,543	21,112
Collaborations, contract revenue, royalties	18,512	5,988	5,203	6,000	6,000	23,191	16,000	12,000	0	0	0	0
TOTAL	**18,512**	**5,988**	**5,203**	**6,000**	**6,000**	**23,191**	**16,000**	**12,000**	**0**	**899**	**6,543**	**3,368**
EXPENSES												
COGS	0	0	0	0	0	0	0	0	0	0	796	1,915
R&D expense	23,484	6,605	6,195	6,300	7,000	26,100	32,283	35,446	36,000	32,000	32,000	32,000
SG&A	6,992	2,617	2,346	2,381	2,417	9,761	9,912	10,314	12,500	32,500	67,016	76,477
TOTAL	30,476	9,222	8,541	8,681	9,417	35,861	42,195	45,760	48,500	64,500	99,812	110,392
Operating Income	(11,964)	(3,234)	(3,338)	(2,681)	(3,417)	(12,670)	(26,195)	(33,760)	(48,500)	(63,601)	(93,269)	(89,110)
Interest (expense) and other, net	(1,341)	(221)	(217)	(201)	(240)	(879)	(879)	0	0	0	0	0
PRETAX INCOME	(13,112)	(3,455)	(3,507)	(2,882)	(3,657)	(13,549)	(27,074)	(33,760)	(48,500)	(63,601)	(93,269)	(89,110)
Taxes	0	0	0	0	0	0	0	0	0	0	0	0
NET INCOME	(13,112)	(3,455)	(3,507)	(2,882)	(3,657)	(13,501)	(27,074)	(33,760)	(48,500)	(63,601)	(93,269)	(89,110)
GAAP EPS (fully taxed)	**(33.83)**	**(1.00)**	**(0.20)**	**(0.16)**	**(0.21)**	**(1.57)**	**(1.37)**	**(1.69)**	**(2.05)**	**(2.62)**	**(3.77)**	**(3.23)**
Diluted Shares Outstanding	388	3,456	17,691	17,741	17,791	14,170	19,753	19,953	23,903	24,306	24,756	27,581
Cash Burn	(10,864)	(2,867)	(2,796)	(2,381)	(3,117)	(11,161)	(24,595)	(31,760)	(45,500)	(59,601)	(83,269)	(79,110)
Cash Balance	83,182	84,937	74,496	72,115	68,998	68,998	44,403	46,483	57,383	82,381	100,632	139,023

Source: Company data, Wedbush Securities, Inc.

Figure 19: Other covered companies mentioned

Company	Ticker	Rating	Price Target	Current Price
Tetraphase Pharmceuticals	TTPH	Outperform	$31	$23.65
Cubist Pharmaceuticals	CBST	Neutral	$70	$73.88

Source: Company data, Wedbush Securities, Inc.

Analyst Biography

Heather Behanna, Ph.D. is an Analyst covering stocks in the Biotechnology/Biodefence sector. Her prior sell-side research experience at JMP Securities focused on anti-infective, orphan and oncology companies of various market caps.

Heather received her Ph.D.(Chemistry) at Northwestern University, M.Sc. (Organic Chemistry) from the Weizmann Institute of Science and B.S. (Biopsychology) from Tufts University. She also completed a postdoctoral fellowship at the Feinberg Medical School in CNS Drug Discovery.

Heather's Edge: Heather's experience working at a global pharmaceutical company as a medicinal chemist gives her a novel perspective for evaluating developmental stage biotech companies. Her experience in various therapeutic areas on the science and corporate side gives her focus on value creation.

Analyst Certification
I, Heather Behanna, Ph.D., David M. Nierengarten, Ph.D., Dilip Joseph, 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.

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Investment Rating System:
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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.
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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).*

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Outperform:54% Neutral: 43% Underperform: 3%	Outperform:23% Neutral: 1% Underperform: 0%

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Wedbush Equity Research Disclosures as of November 3, 2014

Company	Disclosure
Achaogen	1
Cubist Pharmaceuticals	1
Tetraphase Pharmaceuticals	1

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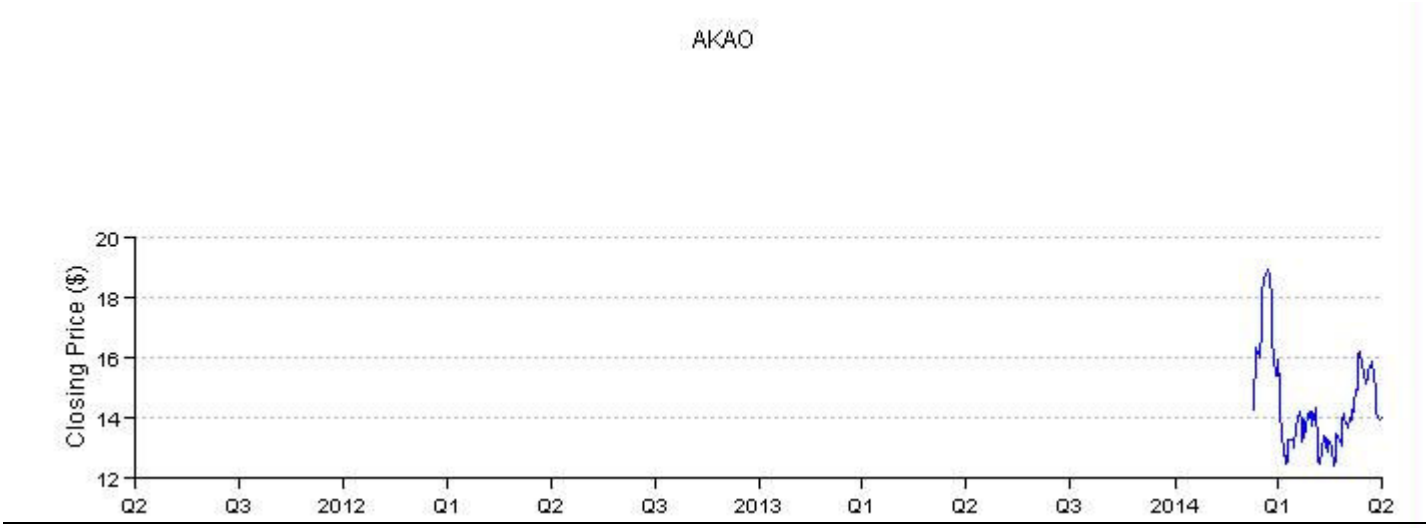

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